An open-label, randomised, phase III Study cOmparing trifLuridine/tipiracil (S 95005) in combination with bevacizumab to capecitabine in combination with bevacizumab in firST-line treatment of patients with metastatIC colorectal cancer who are not candidatE for intensive therapy

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To demonstrate the superiority of S 95005 + bevacizumab over capecitabine + bevacizumab in terms of Progression-free survival (PFS) based on Investigator assessment in first-line treatment of patients with unresectable metastatic colorectal cancer...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52901

Source
ToetsingOnline

Brief title
SOLSTICE study

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastatic colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Servier R&D Benelux
Source(s) of monetary or material Support: Institut de Recherches Internationales Servier

Intervention

Keyword: cancer, colorectal, metastatic

Outcome measures

Primary outcome

Progression-free survival (PFS) based on Investigator assessment .

Secondary outcome

Key secondary endpoint: Overall survival (OS)

Other secondary endpoints :

Overall response rate (ORR)

Disease control rate (DCR)

Duration of response (DoR)

Time to treatment failure (TTF)

Safety and tolerability

Quality of life (Qol) (EORTC QLQ-C30 and EQ-5D-5L)

Study description

Background summary

Very few clinical trials have been conducted in frail, elderly patients and/or unfit patients to standard full dose irinotecan or oxaliplatin combination chemotherapy. Therefore there is a high need to perform trials in this specific population of patients to provide them with a new therapeutic option.
S 95005 is an oral administered combination of an antineoplastic thymidine-based nucleoside analogue (trifluridine [FTD]) and a thymidine phosphorylase inhibitor (tipiracil hydrochloride [TPI]).
Co-administration of TPI with FTD prevents the rapid degradation of FTD, resulting in a significant increase in systemic exposure to FTD. Following uptake into cancer cells, FTD is phosphorylated by thymidine kinase, further metabolized in cells to a deoxyribonucleic acid (DNA) substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation.
FTD incorporation into DNA is markedly higher than that of other nucleoside analogues.
FTD also exhibits thymidylate synthase inhibition (TSI). However, results of in vivo studies show FTD incorporation into DNA to be the primary mechanism of antitumour activity with oral administration.
This mechanism of action of S 95005 differentiates it from conventional fluoropyrimidines, which are uracil-based, and for which the primary mode of action is TSI.
In non clinical studies ,S 95005 demonstrated antitumor activity against both 5 FU sensitive and resistant colorectal cancer cell lines.
S95005 is approved as monotherapy for the treatment of adult patients with advanced mCRC in different countries.
Non clinical research shows that combined S 95005 and bevacizumab treatment had superior antitumor activity compared to either drug alone
The clinical rationale of the development in this indication is based on the results of an Investigator Initiated phase I/II study of trifluridine/tipiracil in combination with bevacizumab for mCRC refractory to standard therapies (C-TASK FORCE) conducted in Japanese patients .
There is a similar ongoing phase 2 study (CI2-95005-002). The analysis of the primary endpoint (100 PFS) showed a median PFS of 9.23 months (95% CI 7.59-11.56) for trifluridine/tipiracil-bevacizumab and 7.82 months (95% CI 5.55-10.15) for capecitabine-bevacizumab. The Hazard Ratio adjusted on stratification covariates was 0.71 (95% CI 0.48-1.06). The secondary endpoint of OS was immature but followed a
positive trend with 18.00 months for trifluridine/tipiracil-bevacizumab and 16.16 months for capecitabine+bevacizumab.

Study objective

To demonstrate the superiority of S 95005 + bevacizumab over capecitabine + bevacizumab in terms of Progression-free survival (PFS) based on Investigator assessment in first-line treatment of patients with unresectable metastatic colorectal cancer who are not candidate for intensive therapy.

Study design

International, open-label, controlled two-arm, randomised phase III study comparing S 95005 in combination with bevacizumab versus capecitabine in combination with bevacizumab in the first-line treatment of patients with unresectable metastatic colorectal cancer (mCRC) who are not candidate for intensive therapy.
854 patients will be randomised in a (1:1) ratio. The stratification factors will be ECOG performance status (0 vs. 1 vs. 2), tumour localisation (right vs. left) and reason why the patient is not candidate to intensive therapy (clinical condition reason vs. non-clinical condition reason).
S 95005 + bevacizumab = 4 weeks cycle
or capecitabine + bevacizumab = 3 weeks cycle study scheme:
screening, inclusion, randomisation, visit on D1 + D15 each cycle in the S95005+beva arm, and first cycle of cape+beva. In that arm afterwards only on D1. Tumor measurements every 8 weeks. QoL questionnaires every 6 weeks.

Intervention

Blood and urine sampling, contrast enhanced CT, Qol questionnaires.

Study burden and risks

Cfr adverse events of medication and procedures described in patient information.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Written informed consent obtained
- Male or female participant aged >=18 years old at the time of ICF signature (or legal age depending on local country regulation).
- Has definitive histologically confirmed adenocarcinoma of the colon or rectum.
- Has at least one measurable metastatic lesion.
- RAS status based on local biological assessment of tumour biopsy must be available.
- Patient is not a candidate for standard full dose combination chemotherapy with irinotecan or oxaliplatin according to investigator*s judgment and decision taken during a multidisciplinary meeting (if organised in the centre). Reasons for non-eligibility to these standard treatments could be, but are not limited to, age, performance status, low tumour burden, comorbidities or non-clinical reasons.
- Patient is not a candidate for curative resection of metastatic lesions according to investigator*s judgment and decision taken during a multidisciplinary meeting (if organised in the centre).
- No previous systemic anticancer therapy for unresectable metastatic colorectal cancer. Previous adjuvant or neoadjuvant chemotherapy is allowed only if the patient has been disease free for at least 6 months after the completion of the chemotherapy.
- Ability to swallow oral medication.
- Estimated life expectancy >=12 weeks.
- ECOG (Eastern Cooperative Oncology Group) performance status <=2.
- Adequate haematological, renal, hepatic and coagulation function.
- Women of childbearing potential must have been tested negative in a serum pregnancy test. Within the frame of this study, female participants of childbearing potential and male participants with partner of childbearing potential must use an highly effective method of birth control as well as their partners lasting at least 6 months after the last dose of IMP. Women using

hormonal contraceptive must also use a barrier method.

Exclusion criteria

- Unlikely to cooperate in the study.
- Pregnancy, breastfeeding or possibility of becoming pregnant during the study.
- Participation in another interventional study, major surgery, drainage for ascites, pleural effusion or pericardial fluid, previous radiotherapy, within the specified timeframes prior to the randomisation.
- Patients who have not recovered from clinically relevant non-hematologic CTCAE grade >= 3 toxicity of previous anticancer therapy prior to the randomisation.
- Symptomatic central nervous system metastases.
- Has certain serious illness or serious medical condition(s) described in the protocol.
- Hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
- Other malignancies excluding malignancies that are in remission for more than 5 years, cervix carcinoma-in-situ deemed cured by adequate treatment or basal cell carcinoma.
- Treatment with systemic immunosuppressive therapy (except steroids given in prophylactic setting or at a chronic low dose (<=20mg/day prednisone equivalent)).
- Criteria related to S 95005 administration:
Has previously received S 95005.
History of allergic reactions attributed to compounds of similar composition to S 95005 or any of its excipients.
Any contraindication present in the SmPC of trifluridine/tipiracil.
- Criteria related to bevacizumab administration:
History of allergic reactions or hypersensitivity to bevacizumab or any of its excipients.
History of hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
Serious non-healing wound, non-healing ulcer or non-healing bone fracture.
Deep venous thromboembolic event within 4 weeks prior to randomisation.
Known coagulopathy that increases risk of bleeding, bleeding diatheses. Any other haemorrhage/bleeding event CTCAE grade >= 3 within 4 weeks prior to randomisation.
Any contraindication present in the SmPC of bevacizumab.
- Criteria related to capecitabine administration:
History of allergic reactions or hypersensitivity to capecitabine or any of its excipients or fluorouracil.
History of severe and unexpected reaction to fluoropyrimidine therapy.
Known complete absence of dihydropyrimidine dehydrogenase (DPD) activity or partial deficiency of DPD preventing the administration of the starting dose of

capecitabine as defined per study protocol.
Treatment with sorivudine or its chemical related analogues, such as brivudine, within 4 weeks prior to the randomisation.
Any contraindication present in the SmPC of capecitabine.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-04-2019
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	avastin
Generic name:	bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	lonsurf
Generic name:	trifluridine+tipiracil hydrochloride
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	xeloda
Generic name:	capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-03-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	25-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	29-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-004059-22-NL
CCMO	NL68912.056.19

Study results