Clinical trial results:
An open-label, randomised, non-comparative phase 2 study evaluating S 95005 (TAS-102) plus bevacizumab to capecitabine plus bevacizumab in patients with previously untreated metastatic colorectal cancer who are non-eligible for intensive therapy.

Summary

EudraCT number	2015-004544-18
Trial protocol	GB DE DK NL BE ES FR IT
Global end of trial date	01 September 2020

Results information

Result version number	v1 (current)
This version publication date	21 August 2021
First version publication date	21 August 2021

Trial information

Trial identification

Sponsor protocol code	CL2-95005-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02743221
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, 33 155724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, 33 155724366, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2020
Global end of trial reached?	Yes
Global end of trial date	01 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the progression-free survival (PFS) based on investigator assessment following RECIST 1.1 in patients receiving S 95005 + bevacizumab (experimental arm) or capecitabine + bevacizumab (control arm) as first-line treatment for metastatic colorectal cancer in patients non-eligible for intensive therapy.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Netherlands: 29
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	154
EEA total number of subjects	104

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	36
From 65 to 84 years	111
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Investigators were oncologists.

Pre-assignment

Screening details:

Male or female patients aged ≥18 years old, with histological or cytological confirmation of adenocarcinoma of the colon or rectum, RAS status determined on tumour biopsy, with at least one measurable metastatic lesion (RECIST criteria), unresectable metastatic disease diagnosed within 6 months prior to the first study drug intake.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	S95005 + bevacizumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S95005
Investigational medicinal product code	
Other name	Trifluridine-tipiracil
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

S95005 was administered orally twice a day (35 mg/m²/dose), within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest; with bevacizumab (5 mg/kg, intravenously) administered every 2 weeks (Day 1 and Day 15).

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously at 5 mg/kg at Day 1 and Day 15 of each cycle in combination with S95005.

Arm title	Capecitabine + bevacizumab

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was administered orally twice daily (1250 mg/m²) on Days 1–14 of each cycle, with bevacizumab (7.5 mg/kg, IV) administered on Day 1 of each cycle. This treatment cycle was repeated every 3 weeks. The starting dose of capecitabine could be 1000mg/m² according to local clinical practice.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously at 7.5 mg/kg on Day 1 of each cycle in combination with capecitabine.

Number of subjects in period 1	S95005 + bevacizumab	Capecitabine + bevacizumab
Started	77	77
Completed	0	0
Not completed	77	77
Physician decision	3	6
non-medical reason	8	3
Adverse event, non-fatal	18	17
Randomised (enrolled) but not treated	-	1
Progressive disease	47	50
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	S95005 + bevacizumab
Reporting group description: -	
Reporting group title	Capecitabine + bevacizumab
Reporting group description: -	

Reporting group values	S95005 + bevacizumab	Capecitabine + bevacizumab	Total
Number of subjects	77	77	154
Age categorical Units: Subjects			
Adults (18-64 years)	20	16	36
From 65-84 years	57	54	111
85 years and over	0	7	7
Age continuous Units: years			
arithmetic mean	69.8	72.8	
standard deviation	± 10.2	± 11.0	-
Gender categorical Units: Subjects			
Female	37	29	66
Male	40	48	88

End points

End points reporting groups

Reporting group title	S95005 + bevacizumab
Reporting group description: -	
Reporting group title	Capecitabine + bevacizumab
Reporting group description: -	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
Tumour assessments were performed by the investigator based on Response Evaluation Criteria in Solid Tumours (RECIST version 1.1, 2009) every 8 weeks until the progression of the disease, death or initiation of new anticancer treatment (whichever occurred first).	
End point type	Primary
End point timeframe:	
PFS was defined as the time from the date of randomisation until the date of PFS event i.e. radiological disease progression or death due to any cause.	

End point values	S95005 + bevacizumab	Capecitabine + bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	76		
Units: Number of PFS events	48	52		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
The primary analysis was conducted after having reached 100 PFS events.	
Comparison groups	S95005 + bevacizumab v Capecitabine + bevacizumab
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.06

Notes:

[1] - This study was a non-comparative study in order to optimize the design of the Phase 3 confirmatory study. The PFS hazard ratio was estimated using the Cox proportional hazard model adjusting for the stratification factors (RAS status, ECOG status).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened or became serious between the first or bevacizumab intake and the last IMP intake + 35 days (both included).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	S 95005 + bevacizumab
Reporting group description: -	
Reporting group title	Capecitabine + bevacizumab

Reporting group description: -

Serious adverse events	S 95005 + bevacizumab	Capecitabine + bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 77 (66.23%)	45 / 76 (59.21%)	
number of deaths (all causes)	66	66	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	13 / 77 (16.88%)	16 / 76 (21.05%)	
occurrences causally related to treatment / all	0 / 13	0 / 16	
deaths causally related to treatment / all	0 / 12	0 / 16	
Metastases to peritoneum			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to spine			

subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 77 (0.00%)	4 / 76 (5.26%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	3 / 77 (3.90%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 77 (1.30%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 77 (0.00%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
General physical health deterioration			
subjects affected / exposed	0 / 77 (0.00%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Influenza like illness			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal dryness			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 77 (3.90%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood bilirubin increased			
subjects affected / exposed	0 / 77 (0.00%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood calcium decreased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood magnesium decreased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood phosphorus decreased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			

subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 77 (2.60%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mitral valve incompetence			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 77 (2.60%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 77 (1.30%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 77 (5.19%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 77 (3.90%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	3 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 77 (5.19%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Ascites			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 77 (2.60%)	6 / 76 (7.89%)	
occurrences causally related to treatment / all	2 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			

subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	3 / 77 (3.90%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Malignant gastrointestinal obstruction			
subjects affected / exposed	0 / 77 (0.00%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			

subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 77 (2.60%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	3 / 77 (3.90%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal failure			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			

subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 77 (2.60%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	2 / 77 (2.60%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 77 (2.60%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	3 / 77 (3.90%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 77 (5.19%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia toxoplasmal			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 77 (1.30%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 77 (3.90%)	5 / 76 (6.58%)	
occurrences causally related to treatment / all	2 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	1 / 77 (1.30%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	S 95005 + bevacizumab	Capecitabine + bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 77 (97.40%)	69 / 76 (90.79%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	7 / 77 (9.09%)	4 / 76 (5.26%)	
occurrences (all)	7	4	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 77 (12.99%)	9 / 76 (11.84%)	
occurrences (all)	12	11	
Hypotension			
subjects affected / exposed	4 / 77 (5.19%)	1 / 76 (1.32%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 77 (18.18%)	18 / 76 (23.68%)	
occurrences (all)	20	23	
Fatigue			
subjects affected / exposed	30 / 77 (38.96%)	23 / 76 (30.26%)	
occurrences (all)	51	34	
Influenza like illness			
subjects affected / exposed	6 / 77 (7.79%)	3 / 76 (3.95%)	
occurrences (all)	6	4	
Pyrexia			

subjects affected / exposed	5 / 77 (6.49%)	4 / 76 (5.26%)	
occurrences (all)	5	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 77 (3.90%)	8 / 76 (10.53%)	
occurrences (all)	3	9	
Dysphonia			
subjects affected / exposed	4 / 77 (5.19%)	1 / 76 (1.32%)	
occurrences (all)	6	1	
Dyspnoea			
subjects affected / exposed	6 / 77 (7.79%)	8 / 76 (10.53%)	
occurrences (all)	6	13	
Epistaxis			
subjects affected / exposed	4 / 77 (5.19%)	4 / 76 (5.26%)	
occurrences (all)	7	6	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 77 (7.79%)	2 / 76 (2.63%)	
occurrences (all)	6	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 77 (11.69%)	2 / 76 (2.63%)	
occurrences (all)	11	2	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 77 (10.39%)	3 / 76 (3.95%)	
occurrences (all)	9	3	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 77 (6.49%)	2 / 76 (2.63%)	
occurrences (all)	7	2	
Blood bilirubin increased			
subjects affected / exposed	6 / 77 (7.79%)	10 / 76 (13.16%)	
occurrences (all)	21	27	
Blood creatinine increased			
subjects affected / exposed	5 / 77 (6.49%)	1 / 76 (1.32%)	
occurrences (all)	6	1	
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	1 / 77 (1.30%)	4 / 76 (5.26%)	
occurrences (all)	8	5	
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 77 (7.79%)	1 / 76 (1.32%)	
occurrences (all)	7	1	
Lymphocyte count decreased			
subjects affected / exposed	5 / 77 (6.49%)	1 / 76 (1.32%)	
occurrences (all)	8	2	
Neutrophil count decreased			
subjects affected / exposed	19 / 77 (24.68%)	1 / 76 (1.32%)	
occurrences (all)	131	1	
Platelet count decreased			
subjects affected / exposed	7 / 77 (9.09%)	4 / 76 (5.26%)	
occurrences (all)	30	6	
Weight decreased			
subjects affected / exposed	13 / 77 (16.88%)	7 / 76 (9.21%)	
occurrences (all)	16	8	
White blood cell count decreased			
subjects affected / exposed	15 / 77 (19.48%)	1 / 76 (1.32%)	
occurrences (all)	39	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 77 (7.79%)	5 / 76 (6.58%)	
occurrences (all)	6	9	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 77 (9.09%)	9 / 76 (11.84%)	
occurrences (all)	9	11	
Dysgeusia			
subjects affected / exposed	6 / 77 (7.79%)	6 / 76 (7.89%)	
occurrences (all)	7	6	
Headache			
subjects affected / exposed	7 / 77 (9.09%)	4 / 76 (5.26%)	
occurrences (all)	13	4	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	23 / 77 (29.87%)	5 / 76 (6.58%)	
occurrences (all)	36	7	
Anaemia of malignant disease			
subjects affected / exposed	5 / 77 (6.49%)	1 / 76 (1.32%)	
occurrences (all)	5	2	
Leukopenia			
subjects affected / exposed	6 / 77 (7.79%)	2 / 76 (2.63%)	
occurrences (all)	9	7	
Neutropenia			
subjects affected / exposed	41 / 77 (53.25%)	6 / 76 (7.89%)	
occurrences (all)	253	11	
Thrombocytopenia			
subjects affected / exposed	12 / 77 (15.58%)	4 / 76 (5.26%)	
occurrences (all)	25	5	
Thrombocytosis			
subjects affected / exposed	4 / 77 (5.19%)	0 / 76 (0.00%)	
occurrences (all)	8	0	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 77 (0.00%)	4 / 76 (5.26%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 77 (14.29%)	6 / 76 (7.89%)	
occurrences (all)	22	7	
Constipation			
subjects affected / exposed	13 / 77 (16.88%)	15 / 76 (19.74%)	
occurrences (all)	22	17	
Diarrhoea			
subjects affected / exposed	41 / 77 (53.25%)	32 / 76 (42.11%)	
occurrences (all)	95	65	
Dry mouth			
subjects affected / exposed	2 / 77 (2.60%)	6 / 76 (7.89%)	
occurrences (all)	2	7	
Dyspepsia			

subjects affected / exposed	6 / 77 (7.79%)	2 / 76 (2.63%)	
occurrences (all)	7	2	
Nausea			
subjects affected / exposed	38 / 77 (49.35%)	13 / 76 (17.11%)	
occurrences (all)	127	23	
Proctalgia			
subjects affected / exposed	4 / 77 (5.19%)	4 / 76 (5.26%)	
occurrences (all)	7	4	
Stomatitis			
subjects affected / exposed	14 / 77 (18.18%)	16 / 76 (21.05%)	
occurrences (all)	19	30	
Vomiting			
subjects affected / exposed	23 / 77 (29.87%)	9 / 76 (11.84%)	
occurrences (all)	84	9	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 77 (2.60%)	6 / 76 (7.89%)	
occurrences (all)	3	11	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	18 / 77 (23.38%)	0 / 76 (0.00%)	
occurrences (all)	18	0	
Dry skin			
subjects affected / exposed	4 / 77 (5.19%)	4 / 76 (5.26%)	
occurrences (all)	4	4	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 77 (3.90%)	39 / 76 (51.32%)	
occurrences (all)	4	54	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	5 / 77 (6.49%)	7 / 76 (9.21%)	
occurrences (all)	6	12	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 77 (9.09%)	3 / 76 (3.95%)	
occurrences (all)	9	4	

Back pain			
subjects affected / exposed	7 / 77 (9.09%)	6 / 76 (7.89%)	
occurrences (all)	10	6	
Myalgia			
subjects affected / exposed	1 / 77 (1.30%)	4 / 76 (5.26%)	
occurrences (all)	2	5	
Pain in extremity			
subjects affected / exposed	4 / 77 (5.19%)	1 / 76 (1.32%)	
occurrences (all)	4	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 77 (10.39%)	5 / 76 (6.58%)	
occurrences (all)	10	5	
Oral herpes			
subjects affected / exposed	1 / 77 (1.30%)	4 / 76 (5.26%)	
occurrences (all)	1	4	
Rhinitis			
subjects affected / exposed	4 / 77 (5.19%)	1 / 76 (1.32%)	
occurrences (all)	4	1	
Upper respiratory tract infection			
subjects affected / exposed	8 / 77 (10.39%)	3 / 76 (3.95%)	
occurrences (all)	13	3	
Urinary tract infection			
subjects affected / exposed	10 / 77 (12.99%)	5 / 76 (6.58%)	
occurrences (all)	15	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	29 / 77 (37.66%)	15 / 76 (19.74%)	
occurrences (all)	49	23	
Hyperkalaemia			
subjects affected / exposed	5 / 77 (6.49%)	0 / 76 (0.00%)	
occurrences (all)	7	0	
Hypoalbuminaemia			
subjects affected / exposed	4 / 77 (5.19%)	2 / 76 (2.63%)	
occurrences (all)	4	2	
Hypomagnesaemia			

subjects affected / exposed occurrences (all)	4 / 77 (5.19%) 4	2 / 76 (2.63%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2016	-Update of study duration: selection stopped after the primary endpoint has been reached (100 PFS event) or after the randomization of 150 patients. Update of inclusion/non-inclusion criteria. Update of prohibited medications (sorivudine or its analogues) and therapies (palliative radiotherapy allowed).
25 January 2017	The main objective of this amendment was to implement the urgent safety measures which aimed to revise the instructions given in the study protocol for the dose modifications for S95005 in case of febrile neutropenia to be in line with the European SmPCs of Lonsurf® which had been approved by the European Commission at the time of medicine registration in the European Union on 25 April 2016.
29 January 2019	The definition of end of study was revised as last treatment withdrawal visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the exceptional circumstances in relation to the COVID-19 pandemic, the Sponsor decided in accordance with competent regulatory authorities' guidelines to implement some precautionary measures in order to mitigate the risk of infection.

Notes: