# **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	\$95005	
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 S 95005.

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

## **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%)	1
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	
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Influenza like illness		1	
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	l	1	1 1

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	
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Blood bilirubin increased	1		
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	İ	i i	
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		l İ	

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	1		
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	i i		
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			

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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	ĺ		
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	ĺ	ĺ	
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			
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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

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	0/0	1 / 1	
treatment / all	0,0	1 / 1	
treatment / all  deaths causally related to treatment / all	0/0	0/0	
deaths causally related to			
deaths causally related to treatment / all			
deaths causally related to treatment / all  Stevens-Johnson syndrome	0/0	0/0	

Acute kidney injury	I		l I
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	0/0	1/1	
treatment / all		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			İ
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	
1	0/0 	I 0/0 I	] 
Biliary sepsis			

1	1		
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		ĺ	

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)			
occurrences (any	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 / /0 (2.03%)	
. ,	, 		
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	1	
subjects affected / exposed	23 / 77 (29.87%)	5 / 76 (6.58%)
occurrences (all)	36	7
Anaemia of malignant disease subjects affected / exposed	E / 77 // 400/ \	1 /7/ /1 220/ \
occurrences (all)	5 / 77 (6.49%)	1 / 76 (1.32%)
occurrences (an)	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
Thursday		
Thrombocytopenia subjects affected / exposed	12 / 77 (15 50%)	1 / 76 (5 26%)
occurrences (all)	12 / 77 (15.58%)	4 / 76 (5.26%) 5
occarrences (an)	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
Diarrhaga		
Diarrhoea subjects affected / exposed	41 / 77 (53.25%)	32 / 76 (42.11%)
occurrences (all)	95	65
	70	00
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 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 / 20/ )	( / 7 / / 7 000/ )	
	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)			
occurrences (un)	4	4	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 77 (3.90%)	39 / 76 (51.32%)	
occurrences (all)	4	54	
	,	<u> </u>	
Renal and urinary disorders			
Proteinuria subjects affected / exposed	F / 77 // 100/	7 / 7 / (0.010)	
	5 / 77 (6.49%)	7 / 76 (9.21%)	
occurrences (all)	6	12	
Musculoskeletal and connective tissue			
disorders			
Arthralgia subjects affected / exposed	7 / 77 / 0 000/ \	2 / 74 /2 OE0/ \	
occurrences (all)	7 / 77 (9.09%)	3 / 76 (3.95%)	
Occurrences (an)	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	4 / 77 (5.19%)	2 / 76 (2.63%)	
occurrences (all)	4	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: