Clinical trial results:
An open-label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory metastatic colorectal cancer (SUNLIGHT study)

Summary

EudraCT number	2020-001976-14
Trial protocol	DK FR DE HU BE AT IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	28 July 2023
First version publication date	28 July 2023

Trial information

Trial identification

Sponsor protocol code	CL3-95005-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04737187
WHO universal trial number (UTN)	-
Other trial identifiers	Investigational New Drug Number: 57674

Notes:

Sponsors

Sponsor organisation name	I.R.I.S.
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Sponsor organisation name	Taiho Oncology, Inc.
Sponsor organisation address	101 Carnegie Center, Suite 101 Princeton, New Jersey, Princeton, United States, 08540
Public contact	clinicaltrialinfo@taihooncology.com , Taiho Oncology, Inc. , 1-609 250-7336, clinicaltrialinfo@taihooncology.com
Scientific contact	clinicaltrialinfo@taihooncology.com , Taiho Oncology, Inc. , 1-609 250-7336, clinicaltrialinfo@taihooncology.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	19 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of trifluridine/tipiracil in combination with bevacizumab over trifluridine/tipiracil monotherapy in terms of Overall Survival (OS) in patients with refractory metastatic colorectal cancer (mCRC).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, as revised in 2013, as revised in Fortaleza, 2013 with the GCP and with the applicable regulatory requirements. All the patients were to freely give their written informed consent before their selection in the study.

Background therapy:

-

Evidence for comparator:

Trifluridine/tipiracil as control arm

Actual start date of recruitment	25 November 2020
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	Poland: 34
Country: Number of subjects enrolled	Spain: 115
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 47
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Russian Federation: 77
Country: Number of subjects enrolled	Brazil: 63
Country: Number of subjects enrolled	Ukraine: 21

Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	492
EEA total number of subjects	315

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)	275
From 65 to 84 years	216
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Investigators were oncologists.

Pre-assignment

Screening details:

Patients with histologically confirmed, unresectable adenocarcinoma of the colon or rectum were eligible for participation if they had received no more than two previous chemotherapy regimens for the treatment of advanced colorectal cancer and had had progressive disease or if their last regimen had caused unacceptable adverse effects.

Period 1

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

Blinding implementation details:

This was an open-label study, no IMP blinding was required.

Arms

Are arms mutually exclusive?	Yes
Arm title	FTD/TPI plus Bev

Arm description:

Subjects received trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev)

Arm type	Experimental
Investigational medicinal product name	Trifluridine/Tipiracil (FTD/TPI)
Investigational medicinal product code	S95005
Other name	TAS-102; Lonsurf®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

FTD/TPI + Bevacizumab
FTD/TPI (35 mg/m²/dose) was administered orally twice a day (BID), 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, intravenous [IV]) administered every 2 weeks (Day 1 and Day 15). This treatment cycle was repeated every 4 weeks.

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

Dosage and administration details:

FTD/TPI + Bevacizumab
FTD/TPI (35 mg/m²/dose) was administered orally twice a day (BID), 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, intravenous [IV]) administered every 2 weeks (Day 1 and Day 15). This treatment cycle was repeated every 4 weeks.

Arm title	FTD/TPI

Arm description:

Subjects received trifluridine/tipiracil (FTD/TPI) as monotherapy

Arm type	Active comparator

Investigational medicinal product name	Trifluridine/Tipiracil (FTD/TPI)
Investigational medicinal product code	S95005
Other name	TAS-102; Lonsurf®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

FTD/TPI as monotherapy
FTD/TPI (35 mg/m²/dose) was administered orally BID, 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. This treatment cycle was repeated every 4 weeks.

Number of subjects in period 1	FTD/TPI plus Bev	FTD/TPI
Started	246	246
Completed	0	0
Not completed	246	246
Physician decision	2	-
Radiological Progressive Disease	145	146
Clinical Progressive Disease	20	20
Adverse event, non-fatal	16	16
Withdrawal Non Medical Reason	5	8
Continuing the study on treatment	32	4
Radiological And Clinical Progressive Disease	26	52

Baseline characteristics

Reporting groups	
Reporting group title	FTD/TPI plus Bev
Reporting group description:	
Subjects received trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev)	
Reporting group title	FTD/TPI
Reporting group description:	
Subjects received trifluridine/tipiracil (FTD/TPI) as monotherapy	

Reporting group values	FTD/TPI plus Bev	FTD/TPI	Total
Number of subjects	246	246	492
Age categorical Units: Subjects			
Adults (18-64 years)	146	129	275
From 65-84 years	100	116	216
85 years and over	0	1	1
Age continuous Units: years			
median	62.00	64.00	
full range (min-max)	20.0 to 84.0	24.0 to 90.0	-
Gender categorical Units: Subjects			
Female	124	112	236
Male	122	134	256

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Full Analysis Set (FAS): based on the intention-to-treat principle, all patients to whom a therapeutic unit was randomly assigned using Interactive Web Response System (IWRS). Patients were analysed in the arm they were assigned by randomisation.	

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients having taken at least one dose of FTD/TPI. Patients were analysed according to the treatment actually received.	

Reporting group values	Full Analysis Set	Safety Set	
Number of subjects	492	492	
Age categorical Units: Subjects			
Adults (18-64 years)	275	275	
From 65-84 years	216	216	
85 years and over	1	1	

Age continuous Units: years			
median	63.00	63.00	
full range (min-max)	20.0 to 90.0	20.0 to 90.0	
Gender categorical Units: Subjects			
Female	236	236	
Male	256	256	

End points

End points reporting groups

Reporting group title	FTD/TPI plus Bev
Reporting group description:	
Subjects received trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev)	
Reporting group title	FTD/TPI
Reporting group description:	
Subjects received trifluridine/tipiracil (FTD/TPI) as monotherapy	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Full Analysis Set (FAS): based on the intention-to-treat principle, all patients to whom a therapeutic unit was randomly assigned using Interactive Web Response System (IWRS). Patients were analysed in the arm they were assigned by randomisation.	

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients having taken at least one dose of FTD/TPI. Patients were analysed according to the treatment actually received.	

Primary: Overall survival

End point title	Overall survival
End point description:	
The primary estimand of interest was defined to assess the effect of the randomised treatments on the survival duration in all patients regardless of whether or not intercurrent events had occurred (treatment policy strategy).	

End point type	Primary
End point timeframe:	
Overall survival (OS) was defined as the observed time elapsed between the date of randomisation and the date of death due to any cause.	

End point values	FTD/TPI plus Bev	FTD/TPI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	246		
Units: month				
number (confidence interval 95%)				
Survival Median (months)	10.78 (9.36 to 11.83)	7.46 (6.34 to 8.57)		
Survival probability at 6 months	0.77 (0.72 to 0.82)	0.61 (0.55 to 0.67)		
Survival probability at 12 months	0.43 (0.36 to 0.49)	0.30 (0.24 to 0.36)		
Survival probability at 18 months	0.28 (0.19 to 0.37)	0.15 (0.09 to 0.22)		

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

The primary estimand was defined to assess the effect of the randomised treatments on the survival duration in all patients regardless of whether or not intercurrent events had occurred (treatment policy strategy).

Comparison groups	FTD/TPI plus Bev v FTD/TPI
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.77

Notes:

[1] - One-sided p < 0.001, stratified log-rank test, with a target p-value < 0.025 for level of significance.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened or became serious between the first IMP intake and the last IMP intake+30 days (both included).

Adverse event reporting additional description:

Number of events for each treatment arm were provided for Serious Adverse Events (SAE) over the study period and Emergent Adverse Events (EAEs) on treatment period. Safety analyses were performed in predefined subgroups ECOG PS (0, 1), Age (< 65, ≥ 65 years), Sex and Baseline creatinine clearance (< 60 mL/min, ≥ 60 mL/min).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	FTD/TPI plus Bev

Reporting group description:

Subjects received trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev)

Reporting group title	FTD/TPI

Reporting group description:

Subjects received trifluridine/tipiracil (FTD/TPI) as monotherapy

Serious adverse events	FTD/TPI plus Bev	FTD/TPI	
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 246 (24.80%)	77 / 246 (31.30%)	
number of deaths (all causes)	146	177	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	6 / 246 (2.44%)	11 / 246 (4.47%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 6	0 / 11	
Metastases to meninges			
subjects affected / exposed	2 / 246 (0.81%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			

subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 246 (0.00%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cancer pain			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to ovary			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
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	1 / 246 (0.41%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 246 (0.00%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 246 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pyrexia			
subjects affected / exposed	0 / 246 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General physical health deterioration			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Anaphylactic reaction			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 246 (0.41%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor retardation			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 246 (0.81%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma output decreased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutrophil count increased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
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			
Stoma site haemorrhage			
subjects affected / exposed	2 / 246 (0.81%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 246 (0.41%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 246 (0.41%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 246 (0.41%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 246 (0.41%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diplegia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 246 (0.81%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 246 (0.41%)	8 / 246 (3.25%)	
occurrences causally related to treatment / all	1 / 1	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	1 / 246 (0.41%)	6 / 246 (2.44%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal lymphadenopathy			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	7 / 246 (2.85%)	5 / 246 (2.03%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	2 / 246 (0.81%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 246 (0.81%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	2 / 246 (0.81%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 246 (0.81%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 246 (0.41%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 246 (0.41%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 246 (0.41%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal hernia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal tenderness			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (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	0 / 246 (0.00%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 246 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			

subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ischaemia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal stenosis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	3 / 246 (1.22%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	2 / 246 (0.81%)	5 / 246 (2.03%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholangitis			
subjects affected / exposed	2 / 246 (0.81%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			

subjects affected / exposed	2 / 246 (0.81%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (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 / 246 (0.41%)	0 / 246 (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 / 246 (0.00%)	5 / 246 (2.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Cholestasis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatomegaly			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 246 (0.81%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelocaliectasis			

subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
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	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	5 / 246 (2.03%)	6 / 246 (2.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	2 / 246 (0.81%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	

Pneumonia			
subjects affected / exposed	1 / 246 (0.41%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 246 (0.41%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal sepsis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paracancerous pneumonia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			

subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	0 / 246 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 246 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial prostatitis			

subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 246 (0.41%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	0 / 246 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hyponatraemia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 246 (0.41%)	
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	FTD/TPI plus Bev	FTD/TPI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	241 / 246 (97.97%)	241 / 246 (97.97%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	34 / 246 (13.82%)	17 / 246 (6.91%)	
occurrences (all)	99	28	
Platelet count decreased			
subjects affected / exposed	22 / 246 (8.94%)	5 / 246 (2.03%)	
occurrences (all)	34	7	
Alanine aminotransferase increased			
subjects affected / exposed	21 / 246 (8.54%)	14 / 246 (5.69%)	
occurrences (all)	22	16	
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 246 (8.54%)	14 / 246 (5.69%)	
occurrences (all)	21	16	

Weight decreased			
subjects affected / exposed	20 / 246 (8.13%)	12 / 246 (4.88%)	
occurrences (all)	20	13	
Blood bilirubin increased			
subjects affected / exposed	14 / 246 (5.69%)	14 / 246 (5.69%)	
occurrences (all)	15	15	
Vascular disorders			
Hypertension			
subjects affected / exposed	25 / 246 (10.16%)	5 / 246 (2.03%)	
occurrences (all)	26	5	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 246 (8.13%)	9 / 246 (3.66%)	
occurrences (all)	32	13	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	153 / 246 (62.20%)	126 / 246 (51.22%)	
occurrences (all)	505	268	
Anaemia			
subjects affected / exposed	71 / 246 (28.86%)	78 / 246 (31.71%)	
occurrences (all)	91	88	
Thrombocytopenia			
subjects affected / exposed	42 / 246 (17.07%)	28 / 246 (11.38%)	
occurrences (all)	98	34	
Leukopenia			
subjects affected / exposed	16 / 246 (6.50%)	21 / 246 (8.54%)	
occurrences (all)	37	42	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	60 / 246 (24.39%)	55 / 246 (22.36%)	
occurrences (all)	94	64	
Fatigue			
subjects affected / exposed	53 / 246 (21.54%)	40 / 246 (16.26%)	
occurrences (all)	68	48	
Pyrexia			

subjects affected / exposed	12 / 246 (4.88%)	15 / 246 (6.10%)	
occurrences (all)	15	16	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	91 / 246 (36.99%)	67 / 246 (27.24%)	
occurrences (all)	188	95	
Diarrhoea			
subjects affected / exposed	51 / 246 (20.73%)	46 / 246 (18.70%)	
occurrences (all)	101	71	
Vomiting			
subjects affected / exposed	46 / 246 (18.70%)	36 / 246 (14.63%)	
occurrences (all)	91	44	
Abdominal pain			
subjects affected / exposed	29 / 246 (11.79%)	27 / 246 (10.98%)	
occurrences (all)	43	28	
Constipation			
subjects affected / exposed	27 / 246 (10.98%)	28 / 246 (11.38%)	
occurrences (all)	41	35	
Stomatitis			
subjects affected / exposed	27 / 246 (10.98%)	9 / 246 (3.66%)	
occurrences (all)	42	9	
Abdominal pain upper			
subjects affected / exposed	22 / 246 (8.94%)	10 / 246 (4.07%)	
occurrences (all)	34	11	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	15 / 246 (6.10%)	3 / 246 (1.22%)	
occurrences (all)	21	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 246 (6.91%)	6 / 246 (2.44%)	
occurrences (all)	18	7	
Back pain			
subjects affected / exposed	16 / 246 (6.50%)	13 / 246 (5.28%)	
occurrences (all)	17	16	
Infections and infestations			

COVID-19 subjects affected / exposed occurrences (all)	17 / 246 (6.91%) 17	8 / 246 (3.25%) 8	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	50 / 246 (20.33%) 61	38 / 246 (15.45%) 44	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 December 2020	Amendment No. 1, dated 30 December 2020 was applicable in all countries. It mainly concerned: - New exclusion criteria for patients with uncontrolled hypertension, patients with history of any life-threatening VEGF related adverse event and patients with proteinuria. - Sponsorship of TOI for the investigational sites in USA. - Change of the time window to perform the tumour assessment. - Baseline ECG obtained prior to patient having signed the ICF could be used if the date of ECG was within 28 days of randomisation. - Clarifications were made. They concerned mainly: *Inclusion criterion number 4: to clarify that the considered prior treatment regimens were those for advanced CRC setting. * IMP management. * Definition of the end of study. * Reasons for discontinuation and restart of treatment period, in case of COVID-19 infection. * Follow-up procedures in case of withdrawal of consent. * Certification of the scales to be used during the study. * Definition of overdose. * Definition of Events requiring an immediate notification (ERIN). * All fatal events occurring between ICF signature and IMP administration were to be reported on AE form. * Precisions in statistical and safety parts of the protocol. * Data sharing section. - Modification of archiving patients' data from 15 to 25 years. Addition of US Product Information in appendix of the study protocol. - Inclusion of a local amendment issued for Italy, Denmark and Germany to specify that pregnancy tests were to be performed at each cycle during treatment period for female patients of childbearing potential. - Inclusion of local amendment issued for France to specify that all patients in France should have received an anti-VEGF monoclonal antibody before entry in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported