Clinical trial results:
A randomised phase II trial assessing REGorafenib combined with IRInotecan as second-line treatment in patients with metastatic gastro-oesophageal adenocarcinomas.

Summary

EudraCT number	2018-002374-46
Trial protocol	FR
Global end of trial date	19 May 2022

Results information

Result version number	v1 (current)
This version publication date	06 July 2023
First version publication date	06 July 2023

Trial information

Trial identification

Sponsor protocol code	UC-0110/1807

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03722108
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
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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	24 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of regorafenib combined with irinotecan (REGIRI), compared to irinotecan (IRI) alone, as second-line treatment in patients with metastatic gastro-oesophageal adenocarcinomas. The efficacy will be evaluated in terms of overall survival (OS).

Protection of trial subjects:

An Independent Ethics Committees reviewed and gave a favorable opinion to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.
This study was conducted in accordance with:
-Declaration of Helsinki, as modified in 2008,
-Loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine, as modifed in 2016
-Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation)
-Amended Loi Informatique et Libertés n°78-17 du 6 janvier 1978, relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel,
-Amended Loi n° 2004-800 du 6 août 2004, relative à la bioéthique,
-Décision du 24 novembre 2006 fixant les règles de Bonnes Pratiques Cliniques pour les recherches biomédicales portant sur des médicaments à usage humain
-Arrêté du 24 mai 2006 relatif au contenu et aux modalités de présentation d’un protocole de recherche biomédicale portant sur un médicament à usage humain-Good Manufacturing Practices, in particular, Annex 13 on investigational medicinal products.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	25 February 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 89
Worldwide total number of subjects	89
EEA total number of subjects	89

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)	53
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

89 subjects were randomized from 25/02/2019 to 21/09/2021 by 22 participating centers.
Recruitment only in France.

Pre-assignment

Screening details:

The study population is composed of patients aged ≥18 years old, with metastatic gastrooesophageal adenocarcinomas after failure of first-line fluoropyrimidine and platinum-based chemotherapies.
The trial consisted of a screening phase before randomization to establish eligibility: 108 patients was assessed for eligibility.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	REGIRI arm

Arm description:

regorafenib combined with irinotecan:
During the 4-week treatment cycle, irinotecan (180 mg/m2) will be infused intravenously over 90 min on day D1 and D15 of each cycle. Oral regorafenib (160 mg/day [4 x 40 mg tablets/day]) will be taken daily from D2-8 and D16-22 of each cycle.
The patients will be treated until disease progression or until discontinuations of treatment for other reasons. Dose interruptions and modifications may be required depending on the individual patient's treatment tolerance.

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

Dosage and administration details:

Oral regorafenib (160 mg/day [4 x 40 mg tablets/day]) will be taken daily from D2-8 and D16-22 of each cycle.

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

Dosage and administration details:

During the 4-week treatment cycle, irinotecan (180 mg/m2) will be infused intravenously over 90 min on day D1 and D15 of each cycle.

Arm title	IRI arm

Arm description:

Irinotecan alone:
During the 4-week treatment cycle, irinotecan (180 mg/m2) will be infused intravenously over 90 min on D1 and D15 of each cycle.
The patients will be treated until disease progression or until discontinuations of treatment for other reasons. Dose interruptions and modifications may be required depending on the individual patient's treatment tolerance.

Arm type	Control
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the 4-week treatment cycle, irinotecan (180 mg/m2) will be infused intravenously over 90 min on D1 and D15 of each cycle.

Number of subjects in period 1	REGIRI arm	IRI arm
Started	44	45
Completed	0	2
Not completed	44	43
Physician decision	-	2
Death	2	1
Other	-	2
Adverse event	9	5
Progressive disease	31	30
Biological progression	-	2
Withdrawal by subject	2	1

Baseline characteristics

Reporting groups	
Reporting group title	REGIRI arm

Reporting group description:

regorafenib combined with irinotecan:
During the 4-week treatment cycle, irinotecan (180 mg/m2) will be infused intravenously over 90 min on day D1 and D15 of each cycle. Oral regorafenib (160 mg/day [4 x 40 mg tablets/day]) will be taken daily from D2-8 and D16-22 of each cycle.
The patients will be treated until disease progression or until discontinuations of treatment for other reasons. Dose interruptions and modifications may be required depending on the individual patient's treatment tolerance.

Reporting group title	IRI arm

Reporting group description:

Irinotecan alone:
During the 4-week treatment cycle, irinotecan (180 mg/m2) will be infused intravenously over 90 min on D1 and D15 of each cycle.
The patients will be treated until disease progression or until discontinuations of treatment for other reasons. Dose interruptions and modifications may be required depending on the individual patient's treatment tolerance.

Reporting group values	REGIRI arm	IRI arm	Total
Number of subjects	44	45	89
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	26	27	53
From 65-84 years	18	18	36
85 years and over	0	0	0
Age continuous Units: years			
median	62	60	
full range (min-max)	34 to 82	28 to 80	-
Gender categorical Units: Subjects			
Female	40	37	77
Male	4	8	12
Patient contraception? Units: Subjects			
Missing	4	5	9
NO	0	3	3
YES	40	37	77
Location of tumour Units: Subjects			

GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA	30	30	60
GASTRIC ADENOCARCINOMA	14	15	29
Histological type Units: Subjects			
OTHER	2	4	6
LIEBERKUHNIEN ADENOCARCINOMA	22	27	49
MUCINOUS ADENOCARCINOMA	1	1	2
DUCTAL ADENOCARCINOMA	7	4	11
PAPILLARY ADENOCARCINOMA	2	1	3
INDEPENDENT CELLS ADENOCARCINOMA	7	7	14
MIXED ADENOCARCINOMA	3	1	4
HER2 STATUS Units: Subjects			
Missing	6	4	10
HER2+	9	9	18
HER2-	29	32	61
Synchronous metastases Units: Subjects			
NO	16	19	35
YES	28	26	54
Previous chemotherapy Units: Subjects			
YES	44	45	89
Previous radiotherapy Units: Subjects			
NO	35	39	74
YES	9	6	15
Previous surgery Units: Subjects			
NO	27	27	54
YES	17	18	35
Previous other cancer therapy Units: Subjects			
NO	38	36	74
YES	6	9	15

End points

End points reporting groups

Reporting group title	REGIRI arm

Reporting group description:

regorafenib combined with irinotecan:
During the 4-week treatment cycle, irinotecan (180 mg/m2) will be infused intravenously over 90 min on day D1 and D15 of each cycle. Oral regorafenib (160 mg/day [4 x 40 mg tablets/day]) will be taken daily from D2-8 and D16-22 of each cycle.
The patients will be treated until disease progression or until discontinuations of treatment for other reasons. Dose interruptions and modifications may be required depending on the individual patient's treatment tolerance.

Reporting group title	IRI arm

Reporting group description:

Irinotecan alone:
During the 4-week treatment cycle, irinotecan (180 mg/m2) will be infused intravenously over 90 min on D1 and D15 of each cycle.
The patients will be treated until disease progression or until discontinuations of treatment for other reasons. Dose interruptions and modifications may be required depending on the individual patient's treatment tolerance.

Primary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Survival rates will be estimated according to Kaplan-Meier. If a patient is alive at the database cut-off date, then the patient will be censored at the last date of follow-up.

End point type	Primary

End point timeframe:

The primary endpoint was OS, defined as the time from the date of randomisation until death of any cause.

End point values	REGIRI arm	IRI arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	45		
Units: Months				
median (confidence interval 95%)	6.3 (5.2 to 7.1)	8.2 (5.4 to 9.7)		

Statistical analyses

Statistical analysis title	OS analysis
Comparison groups	REGIRI arm v IRI arm

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.74

Secondary: Overall survival rates

End point title	Overall survival rates
End point description: OS rates at 6 and 12 months were estimated by the Kaplan-Meier method	
End point type	Secondary
End point timeframe: at 6 and 12 months	

End point values	REGIRI arm	IRI arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	45		
Units: percent				
median (confidence interval 95%)				
6 months	54.6 (38.8 to 67.8)	60.0 (44.3 to 72.6)		
12 months	25.0 (13.5 to 38.4)	23.5 (12.3 to 36.7)		

Statistical analyses

Statistical analysis title	OS analysis
Comparison groups	REGIRI arm v IRI arm
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.74

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression free survival (PFS) was defined as the time from the date of randomization to the date of disease progression (radiological or clinical) or death of any cause, whichever occured first. Patients without tumour progression or alive at the time of analysis were censored at the date of their last tumour assessment.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of disease progression (radiological or clinical) or death of any cause, whichever occured first.

End point values	REGIRI arm	IRI arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	45		
Units: Months				
median (confidence interval 95%)	2.2 (1.8 to 3.6)	1.9 (1.7 to 2.1)		

Statistical analyses

Statistical analysis title	PFS analysis
Comparison groups	REGIRI arm v IRI arm
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	Log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.45

Secondary: PFS rates at 3 and 6 months

End point title	PFS rates at 3 and 6 months

End point description:

End point type	Secondary

End point timeframe:

At 3-month and 6-month after randomization.

End point values	REGIRI arm	IRI arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	45		
Units: Months				
median (confidence interval 95%)				
3 months	40.9 (26.5 to 54.8)	33.3 (20.2 to 47.0)		
6 months	18.2 (8.5 to 30.7)	20.0 (9.9 to 32.7)		

Statistical analyses

Statistical analysis title	PFS analysis
Comparison groups	REGIRI arm v IRI arm
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	Log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.45

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

DCR will be compared between treatment groups using the Cochran-Mantel-Haenszel test.

End point type	Secondary

End point timeframe:

Disease control rate (DCR) was defined as the percentage of patients with complete response (CR), partial response (PR), or stable disease (SD) as best response at the database cut-off date.

End point values	REGIRI arm	IRI arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	45		
Units: percent				
number (not applicable)	45.5	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

Objective response rate will be compared between treatment groups using the Cochran-Mantel-Haenszel test.

End point type	Secondary

End point timeframe:

Objective response rate (ORR)was defined as the percentage of patients with CR or PR. Patients who discontinued their treatment without a tumour assessment were considered nonresponders for the analysis.

End point values	REGIRI arm	IRI arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	45		
Units: percent				
number (not applicable)	15.9	13.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From randomization until 30 days after end of treatment (up to 5 years).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	REGIRI arm
Reporting group description: -	
Reporting group title	IRI arm
Reporting group description: -	

Serious adverse events	REGIRI arm	IRI arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 44 (50.00%)	17 / 43 (39.53%)	
number of deaths (all causes)	39	40	
number of deaths resulting from adverse events	4	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Peritoneal carcinosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour perforation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Malignant neoplasm progression			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
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			
Anaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (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	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 44 (4.55%)	4 / 43 (9.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 4	
Pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 44 (6.82%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 44 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stenosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Catheter site infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (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			
Anorexia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	REGIRI arm	IRI arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 44 (100.00%)	43 / 43 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to peritoneum			

subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Tumour perforation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 44 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	4	
HYPERTENSION			
subjects affected / exposed	10 / 44 (22.73%)	0 / 43 (0.00%)	
occurrences (all)	25	0	
Hypotension			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Pulmonary embolism			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Raynaud's phenomenon			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Venous thrombosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 44 (68.18%)	25 / 43 (58.14%)	
occurrences (all)	151	93	
Chest discomfort			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	5 / 44 (11.36%)	1 / 43 (2.33%)	
occurrences (all)	11	1	
Chills			

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Disease progression			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Early satiety			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	7 / 44 (15.91%)	4 / 43 (9.30%)	
occurrences (all)	20	16	
General physical health deterioration			
subjects affected / exposed	5 / 44 (11.36%)	7 / 43 (16.28%)	
occurrences (all)	6	13	
Generalised oedema			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Hypothermia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	8 / 44 (18.18%)	4 / 43 (9.30%)	
occurrences (all)	15	6	
Mucosal toxicity			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	3 / 44 (6.82%)	3 / 43 (6.98%)	
occurrences (all)	4	4	
Pain			
subjects affected / exposed	3 / 44 (6.82%)	4 / 43 (9.30%)	
occurrences (all)	3	10	
Peripheral swelling			

subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 44 (2.27%)	4 / 43 (9.30%)	
occurrences (all)	1	8	
Xerosis			
subjects affected / exposed	3 / 44 (6.82%)	1 / 43 (2.33%)	
occurrences (all)	4	2	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Intermenstrual bleeding			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	3	
Pelvic pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	2	
Dysphonia			
subjects affected / exposed	8 / 44 (18.18%)	1 / 43 (2.33%)	
occurrences (all)	15	1	
Dyspnoea			
subjects affected / exposed	7 / 44 (15.91%)	2 / 43 (4.65%)	
occurrences (all)	12	2	
Dyspnoea exertional			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Hiccups			
subjects affected / exposed	6 / 44 (13.64%)	0 / 43 (0.00%)	
occurrences (all)	9	0	
Laryngeal pain			

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Lung disorder			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Pneumonia aspiration			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Rales			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	7 / 44 (15.91%)	0 / 43 (0.00%)	
occurrences (all)	18	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 44 (11.36%)	1 / 43 (2.33%)	
occurrences (all)	18	1	
Confusional state			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Insomnia			
subjects affected / exposed	3 / 44 (6.82%)	1 / 43 (2.33%)	
occurrences (all)	6	6	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 44 (4.55%)	2 / 43 (4.65%)	
occurrences (all)	8	9	
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 44 (4.55%)	2 / 43 (4.65%)	
occurrences (all)	6	5	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 44 (4.55%)	3 / 43 (6.98%)	
occurrences (all)	2	5	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 44 (6.82%)	5 / 43 (11.63%)	
occurrences (all)	3	7	
Intestinal transit time increased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Lipase increased			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Platelet count decreased			
subjects affected / exposed	3 / 44 (6.82%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Weight decreased			
subjects affected / exposed	16 / 44 (36.36%)	3 / 43 (6.98%)	
occurrences (all)	32	4	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Overdose			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Radiation oesophagitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Cardiac disorders			

Cardiac failure			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Anosmia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Cholinergic syndrome			
subjects affected / exposed	2 / 44 (4.55%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Dizziness			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Dysarthria			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	4	0	
Headache			
subjects affected / exposed	3 / 44 (6.82%)	2 / 43 (4.65%)	
occurrences (all)	5	2	
Memory impairment			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Neuralgia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	12 / 44 (27.27%)	5 / 43 (11.63%)	
occurrences (all)	42	22	
Neurotoxicity			

subjects affected / exposed	1 / 44 (2.27%)	3 / 43 (6.98%)	
occurrences (all)	1	8	
Paraesthesia			
subjects affected / exposed	3 / 44 (6.82%)	0 / 43 (0.00%)	
occurrences (all)	6	0	
Retinal migraine			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	4	
Speech disorder			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 44 (40.91%)	16 / 43 (37.21%)	
occurrences (all)	48	55	
Febrile neutropenia			
subjects affected / exposed	5 / 44 (11.36%)	0 / 43 (0.00%)	
occurrences (all)	6	0	
Leukopenia			
subjects affected / exposed	3 / 44 (6.82%)	1 / 43 (2.33%)	
occurrences (all)	4	1	
Lymphopenia			
subjects affected / exposed	3 / 44 (6.82%)	3 / 43 (6.98%)	
occurrences (all)	7	7	
Neutropenia			
subjects affected / exposed	14 / 44 (31.82%)	8 / 43 (18.60%)	
occurrences (all)	39	17	
Thrombocytopenia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	6	0	

Thrombotic microangiopathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Strabismus			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	2	
Abdominal hernia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	14 / 44 (31.82%)	14 / 43 (32.56%)	
occurrences (all)	28	31	
Abdominal pain lower			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	7 / 44 (15.91%)	3 / 43 (6.98%)	
occurrences (all)	10	4	
Anal inflammation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Ascites			

subjects affected / exposed	0 / 44 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	12 / 44 (27.27%)	12 / 43 (27.91%)	
occurrences (all)	20	25	
Diarrhoea			
subjects affected / exposed	35 / 44 (79.55%)	25 / 43 (58.14%)	
occurrences (all)	137	72	
Dry mouth			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	2 / 44 (4.55%)	2 / 43 (4.65%)	
occurrences (all)	4	3	
Dysphagia			
subjects affected / exposed	8 / 44 (18.18%)	6 / 43 (13.95%)	
occurrences (all)	21	8	
Enterocolitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Gastric perforation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 44 (6.82%)	3 / 43 (6.98%)	
occurrences (all)	5	8	
Haematemesis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	2	
Haemorrhoids			
subjects affected / exposed	4 / 44 (9.09%)	0 / 43 (0.00%)	
occurrences (all)	9	0	
Inguinal hernia			

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Intestinal obstruction			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Melaena			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	23 / 44 (52.27%)	25 / 43 (58.14%)	
occurrences (all)	80	99	
Oesophageal pain			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Oesophageal stenosis			
subjects affected / exposed	2 / 44 (4.55%)	1 / 43 (2.33%)	
occurrences (all)	3	2	
Rectal haemorrhage			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Salivary hypersecretion			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Subileus			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	20 / 44 (45.45%)	16 / 43 (37.21%)	
occurrences (all)	34	43	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	

Cholestasis			
subjects affected / exposed	2 / 44 (4.55%)	2 / 43 (4.65%)	
occurrences (all)	2	4	
Hepatic cytolysis			
subjects affected / exposed	4 / 44 (9.09%)	0 / 43 (0.00%)	
occurrences (all)	11	0	
Hepatic pain			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Hepatomegaly			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	15 / 44 (34.09%)	4 / 43 (9.30%)	
occurrences (all)	55	22	
Dry skin			
subjects affected / exposed	3 / 44 (6.82%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Erythema			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Hyperkeratosis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Mucocutaneous rash			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	4 / 44 (9.09%)	0 / 43 (0.00%)	
occurrences (all)	8	0	
Rash			

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Skin fissures			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
SKIN TOXICITY			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	1	2	
Urticaria			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	1	2	
Dysuria			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Oliguria			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Urinary tract disorder			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Amyotrophy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	3 / 44 (6.82%)	7 / 43 (16.28%)	
occurrences (all)	4	9	
Bone pain			
subjects affected / exposed	2 / 44 (4.55%)	2 / 43 (4.65%)	
occurrences (all)	5	3	
Muscle spasms			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	4	0	
Spinal pain			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Tumour pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
COVID-19			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Diverticulitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	3 / 44 (6.82%)	0 / 43 (0.00%)	
occurrences (all)	5	0	
Fungal infection			

subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Groin infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	2 / 44 (4.55%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Oral herpes			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	1	2	
Urosepsis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Nerve injury			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	3 / 44 (6.82%)	1 / 43 (2.33%)	
occurrences (all)	7	1	
Decreased appetite			
subjects affected / exposed	16 / 44 (36.36%)	16 / 43 (37.21%)	
occurrences (all)	36	29	

Dehydration			
subjects affected / exposed	2 / 44 (4.55%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Diabetes mellitus			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Hyperkalaemia			
subjects affected / exposed	0 / 44 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	3	
Hypoalbuminaemia			
subjects affected / exposed	4 / 44 (9.09%)	1 / 43 (2.33%)	
occurrences (all)	5	1	
Hypokalaemia			
subjects affected / exposed	3 / 44 (6.82%)	2 / 43 (4.65%)	
occurrences (all)	3	2	
Hyponatraemia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Hypophosphataemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Hypoproteinaemia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Malnutrition			
subjects affected / exposed	0 / 44 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2020	-Some exemple are given to illustrate the inclusion critéria #4 (Asymptomatic primary tumour (e.g. no dysphagia leading to trouble swallowing tablets, no bleeding requiring repeated blood transfusion) -Clarification regarding the previous lines of treatment for the inclusion criterion #7 (Disease progression after a first line fluoropyrimidine and platinum agent-based chemotherapy or early recurrent disease after surgery with neo-adjuvant and/or adjuvant platinum-based chemotherapy (within 6 months of the end of chemotherapy) or progression during neo-adjuvant and/or adjuvant platinum-based chemotherapy (5-FU or 5-FU prodrugs combined with cisplatin or oxaliplatin). For example, docetaxel combined with FOLFOX, PD-L1/PD1 inhibitors combined with FOLFOX or LV5-FU2-cisplatin or 5-FU-cisplatin are acceptable prior therapies.) -Modification of the inclusion criterion #10 (Lipase ≤1.5 x ULN) -Precision of the non-inclusion criteria #27 (Participation in another clinical trial with investigational product within the 30 days before inclusion) -Modification of the investigators list -Declaration of new recruitment centers -Modification (by Bayer) of the regorafenib IB (safety) -Modification of the patient informed consent following diffusion the new regorafenib IB
15 October 2021	-End of inclusion of new patients -Regorafenib was removed from the treatment regimen of the last 3 patients in the REGIRI arm

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported