Clinical trial results:
RAMSES / FLOT7
Perioperative RAMucirumab in combination with FLOT versus FLOT alone for reSEctable eSophagogastric adenocarcinoma
RAMSES - a phase II/III trial of the AIO

Summary

EudraCT number	2015-003118-26
Trial protocol	DE IT
Global end of trial date	20 June 2022
Results information	
Result version number	v1 (current)
This version publication date	23 September 2023
First version publication date	23 September 2023

Trial information

Trial identification	
Sponsor protocol code	RAMSES/FLOT7
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02661971
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest
Sponsor organisation address	Steinbacher Hohl 2-26, Frankfurt am Main Mitte-West, Frankfurt am Main, Germany, 60488
Public contact	Dr. Claudia Pauligk, Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest, info@ikf-khnw.de
Scientific contact	Dr. Claudia Pauligk, Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest, info@ikf-khnw.de

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	22 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this trial was to evaluate the efficacy and safety of the combination of perioperative FLOT with the anti-VEGFR antibody ramucirumab in patients with resectable esophagogastric adenocarcinoma.

Protection of trial subjects:

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the AMG (Arzneimittelgesetz), the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. The trial was authorized/approved by the competent authority (Paul-Ehrlich-Institut, PEI) and the competent ethics committee responsible for the trial ("federführende Ethikkommission"). Before recruitment into the clinical trial, each patient was informed that participation in the study is completely voluntary, and that he or she may withdraw his or her participation in the trial at any time without any declaration of reasons, which will not lead to any disadvantage for the respective patient. The eligibility of a new patient was determined by the local investigator during regular clinical visits. The examinations for the study and the inclusion of the patient were done after detailed written and oral education about aims, methods, anticipated benefits and potential hazards of the study by use of the informed consent forms and after given written consent of the patient. Safety of FLOT/Ramucirumab was monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported. An independent data safety and monitoring board (DSMB) was responsible for assessment of reports summarizing safety data or study results and gave recommendations for planned protocol amendments.

Background therapy: -

Evidence for comparator:

FLOT, a docetaxel-based triple combination consisting of 5-FU, leucovorin, oxaliplatin and docetaxel, is one of the most intensively evaluated regimen for gastric and GEJ cancer. It has been evaluated in the perooperative setting, the metastatic and limited metastatic settings, in elderly and in operable patients. FLOT is regarded as a standard chemotherapy regimen for gastric cancer in Germany.

Ramucirumab is a human monoclonal antibody that specifically binds VEGF-R2. The binding of ramucirumab to VEGF-R2 prevents its interaction with the activating ligands VEGF-A, VEGF-C, and VEGF-D. Ramucirumab was approved for advanced or metastatic esophagogastric adenocarcinoma after previous chemotherapy.

Actual start date of recruitment	12 July 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	Germany: 170
Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	180
EEA total number of subjects	180

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)	130
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 180 patients for enrolled the phase II part between JULY 2016 and NOV 2019 in 50 centres in Germany and 10 centres in Italy. Approx. 758 additional patients were planned for phase III. However, the trial was terminated after phase II part and not transitioned into phase III.

Pre-assignment

Screening details:

Patients with locally advanced adenocarcinoma of the stomach and gastroesophageal junction type I-III (i.e. cT2 any N or any T N-positive) with exclusion of distant metastases were included in this trial.
Due to safety concerns, patients with GEJ type I as well as with planned transthoracic esophagectomy at study entry were excluded after NOV2017

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - FLOT

Arm description:

4 pre-operative treatments of FLOT (docetaxel, oxaliplatin, leucovorin & 5-fluorouracil) on d1, d15, d29 and d43, plus additional 4 post-operative FLOT treatments after surgery (start 6 to 8 weeks after surgery) on d1, d15, d29, d43 of the post-operative treatment phase

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Administration 50 mg/m², iv over 1 h d1, d15, d29, d43 pre- and post-operative

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Infusion , Injection

Dosage and administration details:

85 mg/m² in 500 ml 5% Glucose, iv over 2h

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	folinic acid
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion , Injection

Dosage and administration details:

200 mg/m² in 250 ml NaCl 0.9%, iv over 30 min

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Injection , Infusion

Dosage and administration details:

2600 mg/m², iv over 24 h

Arm title	Arm B - FLOT/Ramucirumab

Arm description:

Patients received Ramucirumab at indicated days as well as the FLOT regimen, which was administered identical to Arm A as described above. Surgery in Arm B was planned to occur 4 to 6 weeks after d1 of last FLOT/ramucirumab dose (but never earlier than 4 weeks after d1 of last FLOT/ramucirumab dose). Patients received FLOT + Ramucirumab for 8 weeks in the post-operative treatment phase followed by 16 additional doses of Ramucirumab as a monotherapy every 2 weeks.

Arm type	Experimental
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Administration 50 mg/m², iv over 1 h d1, d15, d29, d43 pre- and post-operative

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Infusion , Injection

Dosage and administration details:

85 mg/m² in 500 ml 5% Glucose, iv over 2h

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	folinic acid
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion , Injection

Dosage and administration details:

200 mg/m² in 250 ml NaCl 0.9%, iv over 30 min

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion , Injection

Dosage and administration details:

2600 mg/m², iv over 24 h

Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	SUB32795
Other name	Cyramza
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:
8mg/kg, iv over 1 h, d1

Number of subjects in period 1	Arm A - FLOT	Arm B - FLOT/Ramucirumab
Started	91	89
started pre-OP treatment	90	88
underwent surgery	85	87
started post-OP treatment	57	64
started maintenance	0 [1]	43
Completed	46	24
Not completed	45	65
Consent withdrawn by subject	13	18
Physician decision	1	3
death	3	9
Adverse event, non-fatal	14	19
unplanned hospitalization	-	1
histological report from 26.09.2017 declared no ca	1	-
Lost to follow-up	1	-
Sponsor decision	-	4
Lack of efficacy	12	11

Notes:
[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: No maintenance phase was planned in Arm A

Baseline characteristics

Reporting groups	
Reporting group title	Arm A - FLOT

Reporting group description:

4 pre-operative treatments of FLOT (docetaxel, oxaliplatin, leucovorin & 5-fluorouracil) on d1, d15, d29 and d43, plus additional 4 post-operative FLOT treatments after surgery (start 6 to 8 weeks after surgery) on d1, d15, d29, d43 of the post-operative treatment phase

Reporting group title	Arm B - FLOT/Ramucirumab

Reporting group description:

Patients received Ramucirumab at indicated days as well as the FLOT regimen, which was administered identical to Arm A as described above. Surgery in Arm B was planned to occur 4 to 6 weeks after d1 of last FLOT/ramucirumab dose (but never earlier than 4 weeks after d1 of last FLOT/ramucirumab dose). Patients received FLOT + Ramucirumab for 8 weeks in the post-operative treatment phase followed by 16 additional doses of Ramucirumab as a monotherapy every 2 weeks.

Reporting group values	Arm A - FLOT	Arm B - FLOT/Ramucirumab	Total
Number of subjects	91	89	180
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	51	60	
full range (min-max)	35 to 70	36 to 70	-
Gender categorical Units: Subjects			
Female	24	24	48
Male	67	65	132
ECOG Units: Subjects			
ECOG 0	73	59	132
ECOG 1	18	30	48
Primary localisation			
Adenocarcinomas of the gastro-esophageal junction were classified according to the Siewert classification as tumors having their center 5 cm proximal or distal of the anatomical cardia			
Units: Subjects			
GEJ type I	12	16	28
GEJ type II	29	24	53
GEJ type III	7	8	15

Stomach, corpus or antrum	43	41	84
cT stage			
Clinical tumor stage (cT) and clinical nodal (cN) stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumor–node–metastasis classification			
Units: Subjects			
T1	0	1	1
T2	17	13	30
T3	70	67	137
T4	2	2	4
T4a	2	6	8
cN stage			
Clinical tumor stage (cT) and clinical nodal (cN) stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumor–node–metastasis classification.			
Units: Subjects			
N-	23	17	40
N+	68	72	140
Barrett's carcinoma			
Barrett's carcinoma was defined as the presence of Barrett's mucosa in tumors of the gastro-esophageal junction as assessed by either baseline endoscopy or pathological examination. Stomach tumors were automatically regarded non-Barrett			
Units: Subjects			
Yes	10	8	18
No	72	77	149
Unclear	6	4	10
Missing	3	0	3
Lauren's type Units: Subjects			
Diffuse	36	30	66
Intestinal	31	33	64
Mixed	11	9	20
Not evaluable acc. to Lauren	8	14	22
Missing	5	3	8
Signet-ring cells			
Defined as the presence of any signet-ring cells.			
Units: Subjects			
Yes	39	33	72
No	50	54	104
Missing	2	2	4
Grading according to WHO			
WHO grading increases with the lack of cellular differentiation, reflecting how much the tumor cells differ from the cells of the normal tissue they have originated from			
Units: Subjects			
G1	4	3	7
G2	22	27	49
G3	58	54	112
Missing	7	5	12
HER2 status Units: Subjects			
HER2 positive	2	0	2
HER2 negative	87	85	172

Missing	2	4	6

Subject analysis sets

Subject analysis set title	mITT Arm A
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

includes all patients in Arm A who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

Subject analysis set title	mITT Arm B
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

includes all patients in Arm B who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

Reporting group values	mITT Arm A	mITT Arm B	
Number of subjects	79	73	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	59	61	
full range (min-max)	35 to 70	36 to 70	
Gender categorical			
Units: Subjects			
Female	23	23	
Male	56	50	
ECOG			
Units: Subjects			
ECOG 0	63	50	
ECOG 1	16	23	
Primary localisation			
Adenocarcinomas of the gastro-esophageal junction were classified according to the Siewert classification as tumors having their center 5 cm proximal or distal of the anatomical cardia			
Units: Subjects			
GEJ type I	0	0	
GEJ type II	29	24	
GEJ type III	7	8	
Stomach, corpus or antrum	43	41	

cT stage			
Clinical tumor stage (cT) and clinical nodal (cN) stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumor–node–metastasis classification			
Units: Subjects			
T1	0	1	
T2	15	12	
T3	60	54	
T4	2	1	
T4a	2	5	
cN stage			
Clinical tumor stage (cT) and clinical nodal (cN) stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumor–node–metastasis classification.			
Units: Subjects			
N-	20	15	
N+	59	58	
Barrett's carcinoma			
Barrett's carcinoma was defined as the presence of Barrett's mucosa in tumors of the gastro-esophageal junction as assessed by either baseline endoscopy or pathological examination. Stomach tumors were automatically regarded non-Barrett			
Units: Subjects			
Yes	2	4	
No	68	67	
Unclear	6	2	
Missing	3	0	
Lauren's type Units: Subjects			
Diffuse	36	28	
Intestinal	24	24	
Mixed	9	8	
Not evaluable acc. to Lauren	7	11	
Missing	3	2	
Signet-ring cells			
Defined as the presence of any signet-ring cells.			
Units: Subjects			
Yes	37	31	
No	40	41	
Missing	2	1	
Grading according to WHO			
WHO grading increases with the lack of cellular differentiation, reflecting how much the tumor cells differ from the cells of the normal tissue they have originated from			
Units: Subjects			
G1	2	3	
G2	17	17	
G3	53	49	
Missing	7	4	
HER2 status Units: Subjects			
HER2 positive	0	0	
HER2 negative	77	69	
Missing	2	4	

End points

End points reporting groups

Reporting group title	Arm A - FLOT

Reporting group description:

4 pre-operative treatments of FLOT (docetaxel, oxaliplatin, leucovorin & 5-fluorouracil) on d1, d15, d29 and d43, plus additional 4 post-operative FLOT treatments after surgery (start 6 to 8 weeks after surgery) on d1, d15, d29, d43 of the post-operative treatment phase

Reporting group title	Arm B - FLOT/Ramucirumab

Reporting group description:

Patients received Ramucirumab at indicated days as well as the FLOT regimen, which was administered identical to Arm A as described above. Surgery in Arm B was planned to occur 4 to 6 weeks after d1 of last FLOT/ramucirumab dose (but never earlier than 4 weeks after d1 of last FLOT/ramucirumab dose). Patients received FLOT + Ramucirumab for 8 weeks in the post-operative treatment phase followed by 16 additional doses of Ramucirumab as a monotherapy every 2 weeks.

Subject analysis set title	mITT Arm A
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

includes all patients in Arm A who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

Subject analysis set title	mITT Arm B
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

includes all patients in Arm B who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.

Primary: Pathological complete and subtotal response

End point title	Pathological complete and subtotal response

End point description:

The pathological complete response (pCR) and subtotal response (pSR) rate was chosen as primary endpoint for the phase II part of
the trial and was defined as the proportion of patients with pCR as evaluated blinded by central pathologist referring to the total number of patients of the

End point type	Primary

End point timeframe:

The relevant time point for the primary study endpoint was reached upon completion of surgery. Patients with a pCR or pSR at this timepoint added to
the rate of the primary endpoint.

End point values	Arm A - FLOT	Arm B - FLOT/Ramucirumab	mITT Arm A	mITT Arm B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	91	89	79	73
Units: Subjects				
Yes	28	24	23	19
No	63	65	56	54

Statistical analyses

Statistical analysis title	Fisher Exact Test
Comparison groups	mITT Arm A v mITT Arm B
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.719
Method	Fisher exact

Secondary: Margin-free (R0) resection

End point title	Margin-free (R0) resection

End point description:

R0 resection rate was defined as the percentage of patients achieving a R0 (margin-free) resection referring to the total number of patients randomized into the respective treatment arm

End point type	Secondary

End point timeframe:

The relevant time point was reached upon completion of surgery

End point values	Arm A - FLOT	Arm B - FLOT/Ramucirumab	mITT Arm A	mITT Arm B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	91	89	79	73
Units: Subjects				
Yes	75	86	65	70
No	16	3	14	3

Statistical analyses

Statistical analysis title	Fisher Exact Test
Comparison groups	mITT Arm A v mITT Arm B
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	Fisher exact

Secondary: Disease-free survival

End point title	Disease-free survival

End point description:

End point type	Secondary

End point timeframe:

defined as time from randomization to disease progression, relapse or death

End point values	Arm A - FLOT	Arm B - FLOT/Ramucirumab	mITT Arm A	mITT Arm B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	91	89	79	73
Units: month				
median (confidence interval 95%)	20.5 (15.0 to 38.7)	31.3 (22.4 to 46)	20.5 (12.7 to 42.7)	31.9 (23.9 to 999999999)

Attachments (see zip file)	DFS mITT/RAMSES Final analysis_ITT_22.07.2022_DFS.bmp

Statistical analyses

Statistical analysis title	Log Rank Test
Comparison groups	mITT Arm B v mITT Arm A
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.248
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.765
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.21

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

OS defined as time from randomization to death;

End point values	Arm A - FLOT	Arm B - FLOT/Ramucirumab	mITT Arm A	mITT Arm B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	91	89	79	73
Units: month				
median (confidence interval 95%)	45.2 (24.9 to 9999999)	45.8 (26.8 to 9999999)	45.2 (24.9 to 9999999)	45.8 (26.7 to 999999999)

Attachments (see zip file)	OS mITT/RAMSES Final analysis_ITT_22.07.2022_OS.bmp

Statistical analyses

Statistical analysis title	Log Rank Test
Comparison groups	mITT Arm A v mITT Arm B
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.749
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.923
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.565
upper limit	1.509

Secondary: Surigcal morbidity

End point title	Surigcal morbidity

End point description:

End point type	Secondary

End point timeframe:

upto 60 days from surgery

End point values	Arm A - FLOT	Arm B - FLOT/Ramucirumab	mITT Arm A	mITT Arm B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	85	87	74	71
Units: subjects				
Any surgical or medical complication	30	39	24	29

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical mortality

End point title	Surgical mortality

End point description:

End point type	Secondary

End point timeframe:

upto 60 days from surgery

End point values	Arm A - FLOT	Arm B - FLOT/Ramucirumab	mITT Arm A	mITT Arm B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	85	87	74	71
Units: Subjects				
Mortality at 30 days post OP	1	3	1	2
Mortality at 60 dyas post OP	3	4	3	2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: after patient has given written informed consent until at least 30 days after the last dose of study treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups	
Reporting group title	Arm A safety population
Reporting group description: include all patients in Arm A who received at least one dose of study treatment	
Reporting group title	Arm B safety population
Reporting group description: included all patients in Arm B who received at least one dose of study treatment	
Reporting group title	Arm A safety population excluding GEJ I
Reporting group description: includes all patients in Arm A who received at least one dose of study treatment except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.	
Reporting group title	Arm B safety population excluding GEJ I
Reporting group description: includes all patients in Arm B who were randomized except for those with GEJ type I or in whom transthoracic esophagectomy was planned at study entry.	

Serious adverse events	Arm A safety population	Arm B safety population	Arm A safety population excluding GEJ I
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 90 (50.00%)	67 / 88 (76.14%)	40 / 79 (50.63%)
number of deaths (all causes)	40	39	34
number of deaths resulting from adverse events	4	12	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leptomeningeal spread			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertension			
subjects affected / exposed	1 / 90 (1.11%)	2 / 88 (2.27%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thromboembolic event			
subjects affected / exposed	2 / 90 (2.22%)	2 / 88 (2.27%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Visceral arterial ischemia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abcess after surgery			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prolonged hospitalisation after surgery			
subjects affected / exposed	2 / 90 (2.22%)	0 / 88 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 90 (1.11%)	2 / 88 (2.27%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	6 / 90 (6.67%)	7 / 88 (7.95%)	6 / 79 (7.59%)
occurrences causally related to treatment / all	3 / 6	3 / 7	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flu like symptoms			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess on the pancreatic upper margin			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Collaps event			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
obstruction of implanted port	Additional description: haematoma, fever		
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain exacerbation			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Port obstruction			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	2 / 90 (2.22%)	2 / 88 (2.27%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	1 / 2	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion site extravasation			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ disorder			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pain			
subjects affected / exposed	1 / 90 (1.11%)	1 / 88 (1.14%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial fistula			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Chylothorax			
subjects affected / exposed	1 / 90 (1.11%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pleural effusion			

subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural haemorrhage			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	3 / 90 (3.33%)	1 / 88 (1.14%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diaphragmatic hernia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic empyema			

subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 90 (1.11%)	1 / 88 (1.14%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	4 / 4	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight loss			
subjects affected / exposed	2 / 90 (2.22%)	0 / 88 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	6 / 90 (6.67%)	10 / 88 (11.36%)	5 / 79 (6.33%)
occurrences causally related to treatment / all	0 / 7	3 / 10	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 1
Postoperative lymphatic fistula			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

postoperative haemorrhage			
subjects affected / exposed	0 / 90 (0.00%)	2 / 88 (2.27%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Circulatory dysregulation			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
malignant cardiac arrhythmias			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Heart failure			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Palpitations			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular dysfunction			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			

subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epileptical attack			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal epilepsy			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 90 (0.00%)	2 / 88 (2.27%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Extraocular muscle paresis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Retinal detachment			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 90 (2.22%)	2 / 88 (2.27%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 90 (3.33%)	4 / 88 (4.55%)	3 / 79 (3.80%)
occurrences causally related to treatment / all	2 / 3	3 / 4	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	2 / 90 (2.22%)	5 / 88 (5.68%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 2	1 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	2 / 90 (2.22%)	0 / 88 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	2 / 88 (2.27%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			

subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 90 (2.22%)	1 / 88 (1.14%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jejunal stenosis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucositis oral			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	3 / 90 (3.33%)	2 / 88 (2.27%)	3 / 79 (3.80%)
occurrences causally related to treatment / all	4 / 4	1 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal mucositis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toothache			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 90 (1.11%)	5 / 88 (5.68%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abcess left hepatic lobe			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			

subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 90 (0.00%)	3 / 88 (3.41%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bladder stone			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spondylolisthesis cervical			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 90 (1.11%)	1 / 88 (1.14%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Catheter related infection			
subjects affected / exposed	2 / 90 (2.22%)	4 / 88 (4.55%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 90 (0.00%)	2 / 88 (2.27%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	2 / 90 (2.22%)	0 / 88 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising pancreatitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Port infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis transient			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 90 (0.00%)	2 / 88 (2.27%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
infection unknown origin			
subjects affected / exposed	1 / 90 (1.11%)	2 / 88 (2.27%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			

subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	3 / 90 (3.33%)	3 / 88 (3.41%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	2 / 3	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mucosal infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 90 (1.11%)	3 / 88 (3.41%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	1 / 3	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Skin infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 88 (1.14%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 90 (1.11%)	5 / 88 (5.68%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	1 / 6	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 90 (1.11%)	0 / 88 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm B safety population excluding GEJ I		
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 72 (75.00%)		
number of deaths (all causes)	30		
number of deaths resulting from adverse events	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leptomeningeal spread			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			

subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thromboembolic event				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Visceral arterial ischemia				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Abcess after surgery				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prolonged hospitalisation after surgery				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chills				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Fever				
subjects affected / exposed	7 / 72 (9.72%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Flu like symptoms				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess on the pancreatic upper margin				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Collaps event				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
obstruction of implanted port	Additional description: haematoma, fever			
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain exacerbation				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Port obstruction				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Infusion site extravasation				

subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ disorder				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pain				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Aspiration				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchial fistula				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chylothorax				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pleural effusion				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural haemorrhage				

subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary fibrosis				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diaphragmatic hernia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic empyema				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Weight loss			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 1		
Postoperative lymphatic fistula			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
postoperative haemorrhage			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Wound complication				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Circulatory dysregulation				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
malignant cardiac arrhythmias				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Heart failure				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Right ventricular dysfunction				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				

Dizziness				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epileptical attack				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Grand mal epilepsy				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stroke				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Extraocular muscle paresis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal detachment				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 72 (4.17%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal stenosis			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric perforation			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Volvulus				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Jejunal stenosis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mucositis oral				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal mucositis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Toothache			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abcess left hepatic lobe			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury				
subjects affected / exposed	2 / 72 (2.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Bladder stone				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Spondylolisthesis cervical				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal infection				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchial infection				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Catheter related infection				
subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Device related infection			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Necrotising pancreatitis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Port infection			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis transient			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
infection unknown origin			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			

subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal infection				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peritoneal infection				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 72 (4.17%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 72 (4.17%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm A safety population	Arm B safety population	Arm A safety population excluding GEJ I
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 90 (97.78%)	88 / 88 (100.00%)	77 / 79 (97.47%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 90 (4.44%)	11 / 88 (12.50%)	4 / 79 (5.06%)
occurrences (all)	4	16	4
Thromboembolic event			
subjects affected / exposed	6 / 90 (6.67%)	6 / 88 (6.82%)	5 / 79 (6.33%)
occurrences (all)	6	8	5
General disorders and administration site conditions			
Chills			
subjects affected / exposed	5 / 90 (5.56%)	8 / 88 (9.09%)	5 / 79 (6.33%)
occurrences (all)	5	8	5
Edema limbs			
subjects affected / exposed	6 / 90 (6.67%)	16 / 88 (18.18%)	4 / 79 (5.06%)
occurrences (all)	6	25	4
Fatigue			

subjects affected / exposed	52 / 90 (57.78%)	48 / 88 (54.55%)	44 / 79 (55.70%)
occurrences (all)	111	109	87
Fever			
subjects affected / exposed	23 / 90 (25.56%)	24 / 88 (27.27%)	19 / 79 (24.05%)
occurrences (all)	28	29	24
Pain			
subjects affected / exposed	21 / 90 (23.33%)	30 / 88 (34.09%)	15 / 79 (18.99%)
occurrences (all)	34	52	26
Immune system disorders			
Allergic reaction			
subjects affected / exposed	4 / 90 (4.44%)	7 / 88 (7.95%)	4 / 79 (5.06%)
occurrences (all)	4	9	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 90 (8.89%)	7 / 88 (7.95%)	4 / 79 (5.06%)
occurrences (all)	8	8	4
Dyspnoea			
subjects affected / exposed	4 / 90 (4.44%)	8 / 88 (9.09%)	2 / 79 (2.53%)
occurrences (all)	6	14	2
Epistaxis			
subjects affected / exposed	8 / 90 (8.89%)	20 / 88 (22.73%)	5 / 79 (6.33%)
occurrences (all)	9	24	5
Pleural effusion			
subjects affected / exposed	6 / 90 (6.67%)	18 / 88 (20.45%)	2 / 79 (2.53%)
occurrences (all)	7	24	2
Pneumonitis			
subjects affected / exposed	3 / 90 (3.33%)	2 / 88 (2.27%)	3 / 79 (3.80%)
occurrences (all)	3	2	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 90 (4.44%)	5 / 88 (5.68%)	2 / 79 (2.53%)
occurrences (all)	5	7	2
Investigations			
Neutrophil count decreased			
subjects affected / exposed	36 / 90 (40.00%)	44 / 88 (50.00%)	28 / 79 (35.44%)
occurrences (all)	72	84	57

Platelet count decreased			
subjects affected / exposed	6 / 90 (6.67%)	9 / 88 (10.23%)	4 / 79 (5.06%)
occurrences (all)	9	13	7
Weight loss			
subjects affected / exposed	16 / 90 (17.78%)	17 / 88 (19.32%)	15 / 79 (18.99%)
occurrences (all)	18	23	17
White blood cell count decreased			
subjects affected / exposed	36 / 90 (40.00%)	33 / 88 (37.50%)	29 / 79 (36.71%)
occurrences (all)	87	53	74
Injury, poisoning and procedural complications			
Wound complication			
subjects affected / exposed	1 / 90 (1.11%)	5 / 88 (5.68%)	1 / 79 (1.27%)
occurrences (all)	1	7	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 90 (4.44%)	10 / 88 (11.36%)	4 / 79 (5.06%)
occurrences (all)	5	12	5
Dysgeusia			
subjects affected / exposed	14 / 90 (15.56%)	12 / 88 (13.64%)	11 / 79 (13.92%)
occurrences (all)	15	15	12
Headache			
subjects affected / exposed	5 / 90 (5.56%)	8 / 88 (9.09%)	3 / 79 (3.80%)
occurrences (all)	5	10	3
Paraesthesia			
subjects affected / exposed	21 / 90 (23.33%)	22 / 88 (25.00%)	18 / 79 (22.78%)
occurrences (all)	40	46	34
Peripheral sensory neuropathy			
subjects affected / exposed	36 / 90 (40.00%)	37 / 88 (42.05%)	29 / 79 (36.71%)
occurrences (all)	71	74	55
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 90 (22.22%)	10 / 88 (11.36%)	19 / 79 (24.05%)
occurrences (all)	25	11	19
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	5 / 90 (5.56%)	3 / 88 (3.41%)	4 / 79 (5.06%)
occurrences (all)	9	4	7
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	17 / 90 (18.89%)	16 / 88 (18.18%)	14 / 79 (17.72%)
occurrences (all)	23	24	22
Ascites			
subjects affected / exposed	0 / 90 (0.00%)	5 / 88 (5.68%)	0 / 79 (0.00%)
occurrences (all)	0	5	0
Constipation			
subjects affected / exposed	19 / 90 (21.11%)	19 / 88 (21.59%)	15 / 79 (18.99%)
occurrences (all)	20	22	16
Diarrhoea			
subjects affected / exposed	58 / 90 (64.44%)	52 / 88 (59.09%)	52 / 79 (65.82%)
occurrences (all)	121	152	99
Dyspepsia			
subjects affected / exposed	5 / 90 (5.56%)	3 / 88 (3.41%)	4 / 79 (5.06%)
occurrences (all)	5	3	4
Dysphagia			
subjects affected / exposed	9 / 90 (10.00%)	7 / 88 (7.95%)	10 / 79 (12.66%)
occurrences (all)	11	10	10
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 90 (5.56%)	6 / 88 (6.82%)	5 / 79 (6.33%)
occurrences (all)	8	7	7
Mucositis oral			
subjects affected / exposed	27 / 90 (30.00%)	29 / 88 (32.95%)	25 / 79 (31.65%)
occurrences (all)	45	50	36
Nausea			
subjects affected / exposed	55 / 90 (61.11%)	56 / 88 (63.64%)	46 / 79 (58.23%)
occurrences (all)	128	142	107
Vomiting			
subjects affected / exposed	22 / 90 (24.44%)	33 / 88 (37.50%)	15 / 79 (18.99%)
occurrences (all)	39	65	28
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	47 / 90 (52.22%)	39 / 88 (44.32%)	36 / 79 (45.57%)
occurrences (all)	57	49	43
Dry skin			
subjects affected / exposed	5 / 90 (5.56%)	4 / 88 (4.55%)	5 / 79 (6.33%)
occurrences (all)	5	4	5
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	18 / 90 (20.00%)	14 / 88 (15.91%)	13 / 79 (16.46%)
occurrences (all)	24	24	17
Rash acneiform			
subjects affected / exposed	4 / 90 (4.44%)	6 / 88 (6.82%)	4 / 79 (5.06%)
occurrences (all)	4	6	4
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 90 (0.00%)	8 / 88 (9.09%)	0 / 79 (0.00%)
occurrences (all)	0	16	0
Infections and infestations			
Catheter related infection			
subjects affected / exposed	1 / 90 (1.11%)	2 / 88 (2.27%)	0 / 79 (0.00%)
occurrences (all)	1	2	0
Device related infection			
subjects affected / exposed	1 / 90 (1.11%)	4 / 88 (4.55%)	1 / 79 (1.27%)
occurrences (all)	1	4	1
Lung infection			
subjects affected / exposed	3 / 90 (3.33%)	2 / 88 (2.27%)	2 / 79 (2.53%)
occurrences (all)	3	2	2
Sepsis			
subjects affected / exposed	2 / 90 (2.22%)	3 / 88 (3.41%)	2 / 79 (2.53%)
occurrences (all)	2	3	2
Urinary tract infection			
subjects affected / exposed	2 / 90 (2.22%)	7 / 88 (7.95%)	0 / 79 (0.00%)
occurrences (all)	2	8	0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	21 / 90 (23.33%)	13 / 88 (14.77%)	19 / 79 (24.05%)
occurrences (all)	27	28	19

Non-serious adverse events	Arm B safety population excluding GEJ I		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 72 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 72 (15.28%)		
occurrences (all)	16		
Thromboembolic event			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	8		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	8		
Edema limbs			
subjects affected / exposed	15 / 72 (20.83%)		
occurrences (all)	24		
Fatigue			
subjects affected / exposed	42 / 72 (58.33%)		
occurrences (all)	96		
Fever			
subjects affected / exposed	20 / 72 (27.78%)		
occurrences (all)	25		
Pain			
subjects affected / exposed	27 / 72 (37.50%)		
occurrences (all)	46		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	6		
Dyspnoea			

subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Pneumonitis subjects affected / exposed occurrences (all)	6 / 72 (8.33%) 6 15 / 72 (20.83%) 19 13 / 72 (18.06%) 20 1 / 72 (1.39%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 4		
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Weight loss subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all)	34 / 72 (47.22%) 61 7 / 72 (9.72%) 12 14 / 72 (19.44%) 20 25 / 72 (34.72%) 40		
Injury, poisoning and procedural complications Wound complication subjects affected / exposed occurrences (all)	5 / 72 (6.94%) 7		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	9 / 72 (12.50%) 12		

Dysgeusia subjects affected / exposed occurrences (all)	12 / 72 (16.67%) 15		
Headache subjects affected / exposed occurrences (all)	7 / 72 (9.72%) 8		
Paraesthesia subjects affected / exposed occurrences (all)	15 / 72 (20.83%) 38		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	29 / 72 (40.28%) 66		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	10 / 72 (13.89%) 10		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 3		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	15 / 72 (20.83%) 24		
Ascites subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 0		
Constipation subjects affected / exposed occurrences (all)	14 / 72 (19.44%) 17		
Diarrhoea subjects affected / exposed occurrences (all)	42 / 72 (58.33%) 128		
Dyspepsia subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2		
Dysphagia			

subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	9		
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	6		
Mucositis oral			
subjects affected / exposed	25 / 72 (34.72%)		
occurrences (all)	47		
Nausea			
subjects affected / exposed	51 / 72 (70.83%)		
occurrences (all)	132		
Vomiting			
subjects affected / exposed	34 / 72 (47.22%)		
occurrences (all)	61		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	33 / 72 (45.83%)		
occurrences (all)	43		
Dry skin			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	22		
Rash acneiform			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	16		
Infections and infestations			
Catheter related infection			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Device related infection			

subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Lung infection			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		
Sepsis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2017	- Patients with esophageal cancer and those with adenocarcinoma of GEJ type I and all patients who are planned to have transthoracic esophagectomy must no longer be included - Patients with severe, especially vascular, concomitant diseases (e.g., pAVK, chronic nicotine and/or previous alcohol abuse) are no longer included - Handling instructions for patients with GEJ type I and II who were already enrolled have been added
08 March 2018	1) After exclusion of AEG/GEJ type I tumors in the 1st amendment of the study, it was decided to replace the 28 affected patients with an enrollment of 30 additional patients, increasing the total sample size to 180 patients 2) Extension of the study to Italy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 October 2017	An interim safety analysis, examining six deaths which occurred during the study after nearly 40 patients in each arm underwent surgery, revealed that almost all of these died from anastomotic leakage (in some cases months after surgery), received FLOT/ramucirumab, had GEJ type I adenocarcinomas undergoing transthoracic esophagectomy and had in mean three relevant comorbidities predominantly cardiovascular disease like peripheral arterial occlusive disease (PAOD) and chronic heart failure as well as diabetes mellitus, chronic nicotine and/or previous alcohol abuse. Based on these findings, the study protocol was amended in November 2017 to exclude patients with potential increased risk including patients with GEJ type I and planned transthoracic esophagectomy from further enrolment	30 November 2017

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36883420