Clinical trial results:
Essai de phase II randomisé multicentrique évaluant l'efficacité d'une chimiothérapie seule ou combinée à l'AMG 102 ou au panitumumab en traitement de première ligne chez des patients atteints d' adénocarcinome œsogastrique localement avancé (non résécable) ou métastatique.

Summary

EudraCT number	2009-012797-12
Trial protocol	FR
Global end of trial date	01 September 2018

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	ACCORD 20/0904 - Prodige 17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01443065
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Nourredine AIT-RAHMOUNE, Unicancer, 33 1 71 93 67 04,, n.ait-rahmoune@unicancer.fr
Scientific contact	Laure Monard, Unicancer, 33 1 73 79 73 09, l-monard@unicancer.fr

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	03 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the progression-free survival rate at 4 months.

Protection of trial subjects:

This study was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice (GCP) Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.
Furthermore, independent Ethics Committees reviewed and gave favorable opinions to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.
Written informed consent was obtained from all patients prior to enrollment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2011
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: 162
Worldwide total number of subjects	162
EEA total number of subjects	162

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)	83

From 65 to 84 years	77
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Prodige 17 – Accord 20 was designed as a phase II, randomized, multicentric, open, three-arm study in patients with locally advance (unresectable) or metastatic adenocarcinoma of the stomach, oesphagus, or cadia.

Pre-assignment

Screening details:

The study consisted of a 7-day screening phase to establish patients' eligibility and document baseline measurements, a treatment phase (14-day cycle till disease progression), and a long-term follow-up to monitor the progression-free survival, overall survival, time to progression, overall response rate, tumour control rate, and safety

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	mFOLFOX6

Arm description:

Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.

Arm type	Active comparator
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

85 mg/m² on day 1 every 14 days

Investigational medicinal product name	Folinic acid/Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

400 mg/m² (racemate) or 200 mg/m² (L-folinic acid) on day 1 every 14 days

Investigational medicinal product name	5-fluoro-uracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m² bolus on day 1 then 2400 mg/m² infusion over 46 h every 14 days.

Arm title	mFOLFOX6 + panitumumab

Arm description:

Panitumumab (6 mg/kg) IV over 60 min (±15 min) before Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h,

followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.

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

Dosage and administration details:

85 mg/m² on day 1 every 14 days

Investigational medicinal product name	Folinic acid/Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

400 mg/m² (racemate) or 200 mg/m² (L-folinic acid) on day 1 every 14 days

Investigational medicinal product name	5-fluoro-uracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m² bolus on day 1 then 2400 mg/m² infusion over 46 h every 14 days.

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

Dosage and administration details:

6 mg/kg on day 1 every 14 days

Arm title	mFOLFOX6 + rilotumumab

Arm description:

Rilotumumab (10 mg/kg) IV over 60 min (±15 min) before Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.

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

Dosage and administration details:

85 mg/m² on day 1 every 14 days

Investigational medicinal product name	Folinic acid/Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

400 mg/m² (racemate) or 200 mg/m² (L-folinic acid) on day 1 every 14 days

Investigational medicinal product name	5-fluoro-uracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m² bolus on day 1 then 2400 mg/m² infusion over 46 h every 14 days.

Investigational medicinal product name	Rilotumumab
Investigational medicinal product code	
Other name	AMG 102
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

10 mg/kg on day 1 every 14 days

Number of subjects in period 1	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab
Started	56	49	57
Completed	0	0	1
Not completed	56	49	56
Physician decision	11	6	7
Patient decision	3	4	5
Disease progression	33	21	31
Exceeding the treatment deferral	1	-	-
Adverse event, non-fatal	3	9	4
Death	3	7	7
Surgery	1	1	2
Radiotherapy	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	mFOLFOX6
Reporting group description:	
Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.	
Reporting group title	mFOLFOX6 + panitumumab
Reporting group description:	
Panitumumab (6 mg/kg) IV over 60 min (±15 min) before Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.	
Reporting group title	mFOLFOX6 + rilotumumab
Reporting group description:	
Rilotumumab (10 mg/kg) IV over 60 min (±15 min) before Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.	

Reporting group values	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab
Number of subjects	56	49	57
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	64	64	65
full range (min-max)	38 to 87	23 to 83	32 to 83
Gender categorical Units: Subjects			
Female	17	16	20
Male	39	33	37
ECOG Units: Subjects			
PS 0	20	16	17
PS 1	36	33	39
Missing	0	0	1
Primary tumour localisation Units: Subjects			
Esophagus	12	12	8
Cardia	17	13	19

Stomach	26	24	30
Cardia and Stomach	1	0	0
Disease type			
Units: Subjects			
Locally advanced	3	0	2
Metastatic	53	49	55
Dealy from primary tumour diagnosis to randomisation			
Units: month			
median	1.1	1.0	1.1
full range (min-max)	0.3 to 65.8	0.1 to 46.8	0.1 to 55.4
Delay from diagnosis of metastasis to randomisation			
Units: month			
median	0.9	0.7	0.7
full range (min-max)	0 to 26.1	0 to 2.8	0 to 29.3

Reporting group values	Total		
Number of subjects	162		
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			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	53		
Male	109		
ECOG			
Units: Subjects			
PS 0	53		
PS 1	108		
Missing	1		
Primary tumour localisation			
Units: Subjects			
Esophagus	32		
Cardia	49		
Stomach	80		
Cardia and Stomach	1		
Disease type			
Units: Subjects			

Locally advanced	5		
Metastatic	157		

Dealy from primary tumour diagnosis to randomisation Units: month median full range (min-max)	- -		
Delay from diagnosis of metastasis to randomisation Units: month median full range (min-max)	- -		

End points

End points reporting groups

Reporting group title	mFOLFOX6

Reporting group description:

Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.

Reporting group title	mFOLFOX6 + panitumumab

Reporting group description:

Panitumumab (6 mg/kg) IV over 60 min (±15 min) before Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.

Reporting group title	mFOLFOX6 + rilotumumab

Reporting group description:

Rilotumumab (10 mg/kg) IV over 60 min (±15 min) before Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.

Primary: 4-month PFS

End point title	4-month PFS[1]

End point description:

Progression-free survival (PFS) was evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1). PFS was defined as the time from randomisation to the date of progression or death from any cause, whichever occurred first. The patients alive without progression were censored at the date of the last tumour evaluation and with a maximum of 4 months.

End point type	Primary

End point timeframe:

4 months.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The 4-month PFS rate was the proportion of patients alive without progression at 4 months. In the experimental arms (mFOLFOX6 + panitumumab and mFOLFOX6 + rilotumumab), the decision limits were set at, at least 26 successes observed in 51 patients (4-month PFS ≥51%) to conclude to efficacy, and more than 26 disease progressions or deaths observed in 51 patients (4-month PFS <51%) to conclude to inefficacy. There were no statistical comparisons between groups.

End point values	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	49	57	
Units: percent				
median (confidence interval 95%)	71 (57 to 82)	63 (48 to 77)	63 (48 to 75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival (PFS) was evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1). PFS was defined as the time from randomisation to the date of progression or death from any cause, whichever occurred first. The patients alive without progression were censored at the date of the last tumour evaluation and with a maximum of 5 years.

End point type	Secondary

End point timeframe:

At baseline then every 8 weeks until disease progression, up to 5 years.

End point values	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	49	57	
Units: month				
median (confidence interval 95%)	5.8 (5.2 to 7.3)	5.2 (3.7 to 7.6)	7.6 (4.0 to 9.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

Time to progression was defined as the time from randomisation to disease progression or death from disease progression. The patients alive without disease progression were censored at the date of last tumour evaluation. The patients who died without disease progression were censored at the date of death irrespective of cause.

End point type	Secondary

End point timeframe:

From randomisation to progression or death from diseaase progression, up to 5 years.

End point values	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	49	57	
Units: month				
median (confidence interval 95%)	5.9 (5.3 to 7.3)	5.2 (3.7 to 7.6)	7.6 (4.0 to 9.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was defined as the time from randomisation to death from any cause. The patients alive were censored at the date of last known status.

End point type	Secondary

End point timeframe:

From randomisation to death, up to 5 years.

End point values	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	49	57	
Units: month				
median (confidence interval 95%)	13.1 (8.7 to 16.9)	8.3 (6.2 to 13.2)	11.5 (7.9 to 17.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

The objective response rate is the proportion of patients with a complete response or partial response. The patients with symptoms of disease progression were evaluated at the tumour level at time of occurrence of the symptoms.

End point type	Secondary

End point timeframe:

At baseline then every 8 weeks, up to 5 years.

End point values	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	49	57	
Units: percent				
number (not applicable)	52	43	49	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

The duration of response was the time from objective tumour response to the date of relapse or progression.

End point type	Secondary

End point timeframe:

Every 8 weeks, up to 5 years.

End point values	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	49	57	
Units: percent				
number (not applicable)	73	78	81	

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour control rate

End point title	Tumour control rate

End point description:

The tumour control rate is the proportion of patients with an objective response (complete or partial response) or a stable disease. Dead patients without disease progression were censored at the date of death.

End point type	Secondary

End point timeframe:

At baseline then every 8 weeks, up to 5 years.

End point values	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	49	57	
Units: month				
median (confidence interval 95%)	5.7 (3.8 to 7.8)	6.4 (3.8 to 11.3)	8.0 (3.9 to 10.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion until 30 days after end of treatment (up to 5 years).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	mFOLFOX6

Reporting group description:

Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.

Reporting group title	mFOLFOX6 + panitumumab

Reporting group description:

Panitumumab (6 mg/kg) IV over 60 min (±15 min) before Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.

Reporting group title	mFOLFOX6 + rilotumumab

Reporting group description:

Rilotumumab (10 mg/kg) IV over 60 min (±15 min) before Oxaliplatin (85 mg/m²) IV over 2h, and simultaneous leucovorin/folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-folinic acid]) IV over 2h, followed by 5-FU (400mg/m²) bolus, then 5-FU (2400 mg/m²) by IV perfusion over 46h every 14 days.

Serious adverse events	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 54 (68.52%)	43 / 48 (89.58%)	57 / 57 (100.00%)
number of deaths (all causes)	54	48	57
number of deaths resulting from adverse events	4	11	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplastic meningitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Vascular disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Deep vein thrombosis			

subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic tumor necrosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Hypotension			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolemic shock			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Gastric haemorrhage			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Pulmonary embolism			
subjects affected / exposed	1 / 54 (1.85%)	5 / 48 (10.42%)	6 / 57 (10.53%)
occurrences causally related to treatment / all	0 / 1	0 / 5	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Thrombosis of leg deep venous			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Venous thrombosis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Surgical and medical procedures			
Gastrectomy			

subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Radiofrequency ablation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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 disorders and administration site conditions			
Anasarca			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	3 / 54 (5.56%)	3 / 48 (6.25%)	8 / 57 (14.04%)
occurrences causally related to treatment / all	2 / 3	3 / 3	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema aggravated			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	0 / 54 (0.00%)	2 / 48 (4.17%)	0 / 57 (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
General physical health deterioration			
subjects affected / exposed	4 / 54 (7.41%)	4 / 48 (8.33%)	4 / 57 (7.02%)
occurrences causally related to treatment / all	1 / 4	1 / 4	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Hyperthermia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Unknown cause of death			

subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Immune system disorders			
Localised skin reaction			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Quincke's edema			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Rash urticarial			
subjects affected / exposed	0 / 54 (0.00%)	3 / 48 (6.25%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Specific allergy (drug)			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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, thoracic and mediastinal disorders			
Distress respiratory			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Dyspnoea			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydropneumothorax			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Interstitial pneumonitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung fibrosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Pneumopathy			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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 oedema			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alkaline phosphatase increased			
subjects affected / exposed	0 / 54 (0.00%)	2 / 48 (4.17%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 48 (2.08%)	0 / 57 (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

Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 54 (11.11%)	2 / 48 (4.17%)	3 / 57 (5.26%)
occurrences causally related to treatment / all	2 / 6	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin low			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Hepatic enzymes increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phosphatase alkaline increased			
subjects affected / exposed	2 / 54 (3.70%)	2 / 48 (4.17%)	3 / 57 (5.26%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight loss			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Injury, poisoning and procedural complications			
Movement of device from original site			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Atrial fibrillation			

subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Myocardial infarction acute			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia transient			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy			
subjects affected / exposed	4 / 54 (7.41%)	2 / 48 (4.17%)	6 / 57 (10.53%)
occurrences causally related to treatment / all	1 / 4	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Neurotoxicity			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paresthesia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	4 / 57 (7.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral neuropathy NOS			

subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	3 / 57 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 54 (1.85%)	1 / 48 (2.08%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory neuropathy			
subjects affected / exposed	2 / 54 (3.70%)	0 / 48 (0.00%)	3 / 57 (5.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient hemiparesis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
anaemia			
subjects affected / exposed	1 / 54 (1.85%)	5 / 48 (10.42%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile aplasia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Febrile Neutropenia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobinaemia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			

subjects affected / exposed	2 / 54 (3.70%)	2 / 48 (4.17%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	2 / 2	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytopenia			
subjects affected / exposed	0 / 54 (0.00%)	3 / 48 (6.25%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	14 / 54 (25.93%)	13 / 48 (27.08%)	16 / 57 (28.07%)
occurrences causally related to treatment / all	5 / 19	2 / 16	16 / 21
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombopenia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual field defect			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 48 (2.08%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pancreatitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphagia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Ascites			

subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites infection			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowel obstruction			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Colitis, enteritis, and gastroenteritis of presumed infectious origin			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Constipation			
subjects affected / exposed	0 / 54 (0.00%)	3 / 48 (6.25%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 54 (3.70%)	6 / 48 (12.50%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	1 / 2	7 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	3 / 54 (5.56%)	4 / 48 (8.33%)	4 / 57 (7.02%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Esophageal stenosis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Gastric pain			

subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hematemesis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Intestinal obstruction			
subjects affected / exposed	0 / 54 (0.00%)	4 / 48 (8.33%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Melena			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Mucositis oral			
subjects affected / exposed	0 / 54 (0.00%)	2 / 48 (4.17%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea and vomiting			

subjects affected / exposed	1 / 54 (1.85%)	2 / 48 (4.17%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Pneumoperitoneum			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Prolapsed hemorrhoid			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyloric stenosis nos			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Subocclusive syndrome			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	1 / 57 (1.75%)
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	2 / 54 (3.70%)	1 / 48 (2.08%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Cholecystitis			

subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Hepatic cytolysis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinemia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 48 (2.08%)	0 / 57 (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
Hypoalbuminemia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 48 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Abscesses of skin			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Dry skin			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Facial rash			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Folliculitis			

subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intertrigo			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Rash			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin fissura			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Skin xerosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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 renal insufficiency			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Nephropathy tubular			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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 failure			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal insufficiency			

subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Hyperglycaemia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Intervertebral disc space narrowing			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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			
Ascites infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Catheter infection			
subjects affected / exposed	0 / 54 (0.00%)	4 / 48 (8.33%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Central line infection			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection NOS			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Folliculitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 57 (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
Paronychia			
subjects affected / exposed	0 / 54 (0.00%)	2 / 48 (4.17%)	0 / 57 (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
Pleural infection bacterial			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 57 (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
Septicemia due to escherichia coli (e. Coli)			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary infection			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 54 (5.56%)	2 / 48 (4.17%)	7 / 57 (12.28%)
occurrences causally related to treatment / all	1 / 3	0 / 2	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dehydration			
subjects affected / exposed	0 / 54 (0.00%)	2 / 48 (4.17%)	0 / 57 (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
Hypernatremia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcemia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalemia			
subjects affected / exposed	0 / 54 (0.00%)	4 / 48 (8.33%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 48 (2.08%)	3 / 57 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphatemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 54 (0.00%)	2 / 48 (4.17%)	0 / 57 (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

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

Non-serious adverse events	mFOLFOX6	mFOLFOX6 + panitumumab	mFOLFOX6 + rilotumumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 54 (98.15%)	48 / 48 (100.00%)	57 / 57 (100.00%)
Investigations			
Bilirubin			
subjects affected / exposed	1 / 54 (1.85%)	5 / 48 (10.42%)	8 / 57 (14.04%)
occurrences (all)	2	25	10
Alanine aminotransferase			
subjects affected / exposed	25 / 54 (46.30%)	18 / 48 (37.50%)	37 / 57 (64.91%)
occurrences (all)	74	44	165
Aspartate aminotransferase			
subjects affected / exposed	30 / 54 (55.56%)	22 / 48 (45.83%)	37 / 57 (64.91%)
occurrences (all)	140	67	206
Alkaline phosphatase			
subjects affected / exposed	29 / 54 (53.70%)	28 / 48 (58.33%)	36 / 57 (63.16%)
occurrences (all)	150	110	199
Plasma magnesium			
subjects affected / exposed	4 / 54 (7.41%)	18 / 48 (37.50%)	12 / 57 (21.05%)
occurrences (all)	8	64	19
Plasma calcium			
subjects affected / exposed	13 / 54 (24.07%)	21 / 48 (43.75%)	41 / 57 (71.93%)
occurrences (all)	41	57	210
Uremia			
subjects affected / exposed	9 / 54 (16.67%)	7 / 48 (14.58%)	12 / 57 (21.05%)
occurrences (all)	14	15	30
Creatine			
subjects affected / exposed	6 / 54 (11.11%)	9 / 48 (18.75%)	7 / 57 (12.28%)
occurrences (all)	23	12	18
Gamma-glutamyl transferase			
subjects affected / exposed	19 / 54 (35.19%)	22 / 48 (45.83%)	27 / 57 (47.37%)
occurrences (all)	99	96	93
Hypoalbuminemia			

subjects affected / exposed	18 / 54 (33.33%)	13 / 48 (27.08%)	23 / 57 (40.35%)
occurrences (all)	54	35	91
Hyponatremia			
subjects affected / exposed	10 / 54 (18.52%)	8 / 48 (16.67%)	9 / 57 (15.79%)
occurrences (all)	33	13	14
Hypokalemia			
subjects affected / exposed	7 / 54 (12.96%)	11 / 48 (22.92%)	8 / 57 (14.04%)
occurrences (all)	11	14	10
Lactate dehydrogenase			
subjects affected / exposed	6 / 54 (11.11%)	4 / 48 (8.33%)	5 / 57 (8.77%)
occurrences (all)	8	15	9
Hyperglycaemia			
subjects affected / exposed	2 / 54 (3.70%)	3 / 48 (6.25%)	6 / 57 (10.53%)
occurrences (all)	5	4	17
Cardiac disorders			
Venous thromboembolism			
subjects affected / exposed	5 / 54 (9.26%)	2 / 48 (4.17%)	9 / 57 (15.79%)
occurrences (all)	11	2	22
Nervous system disorders			
Peripheral neuropathy			
subjects affected / exposed	43 / 54 (79.63%)	39 / 48 (81.25%)	49 / 57 (85.96%)
occurrences (all)	320	249	473
Blood and lymphatic system disorders			
Haemoglobin			
subjects affected / exposed	49 / 54 (90.74%)	45 / 48 (93.75%)	49 / 57 (85.96%)
occurrences (all)	290	256	359
Leucophils			
subjects affected / exposed	24 / 54 (44.44%)	16 / 48 (33.33%)	26 / 57 (45.61%)
occurrences (all)	96	65	68
Neutrophils			
subjects affected / exposed	35 / 54 (64.81%)	30 / 48 (62.50%)	38 / 57 (66.67%)
occurrences (all)	117	84	144
Platelets			
subjects affected / exposed	27 / 54 (50.00%)	24 / 48 (50.00%)	42 / 57 (73.68%)
occurrences (all)	131	111	240
Lymphocytes			

subjects affected / exposed	15 / 54 (27.78%)	11 / 48 (22.92%)	9 / 57 (15.79%)
occurrences (all)	51	53	17
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	42 / 54 (77.78%)	39 / 48 (81.25%)	49 / 57 (85.96%)
occurrences (all)	187	153	268
Anorexia			
subjects affected / exposed	23 / 54 (42.59%)	20 / 48 (41.67%)	21 / 57 (36.84%)
occurrences (all)	40	40	56
Weight loss			
subjects affected / exposed	21 / 54 (38.89%)	22 / 48 (45.83%)	17 / 57 (29.82%)
occurrences (all)	32	61	50
Oedema			
subjects affected / exposed	5 / 54 (9.26%)	6 / 48 (12.50%)	22 / 57 (38.60%)
occurrences (all)	8	9	104
Fever without neutropenia			
subjects affected / exposed	6 / 54 (11.11%)	12 / 48 (25.00%)	16 / 57 (28.07%)
occurrences (all)	13	17	25
Dysgeusia			
subjects affected / exposed	6 / 54 (11.11%)	8 / 48 (16.67%)	11 / 57 (19.30%)
occurrences (all)	16	28	39
Dysphagia			
subjects affected / exposed	13 / 54 (24.07%)	10 / 48 (20.83%)	10 / 57 (17.54%)
occurrences (all)	28	22	24
Dyspnoea			
subjects affected / exposed	9 / 54 (16.67%)	5 / 48 (10.42%)	7 / 57 (12.28%)
occurrences (all)	21	8	12
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	23 / 54 (42.59%)	28 / 48 (58.33%)	28 / 57 (49.12%)
occurrences (all)	92	81	64
Nausea			
subjects affected / exposed	32 / 54 (59.26%)	33 / 48 (68.75%)	43 / 57 (75.44%)
occurrences (all)	84	106	167
Vomiting			

subjects affected / exposed	17 / 54 (31.48%)	20 / 48 (41.67%)	26 / 57 (45.61%)
occurrences (all)	33	54	73
Constipation			
subjects affected / exposed	16 / 54 (29.63%)	19 / 48 (39.58%)	26 / 57 (45.61%)
occurrences (all)	35	49	88
Mucositis			
subjects affected / exposed	20 / 54 (37.04%)	21 / 48 (43.75%)	17 / 57 (29.82%)
occurrences (all)	60	43	36
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 54 (11.11%)	5 / 48 (10.42%)	8 / 57 (14.04%)
occurrences (all)	25	17	11
Rash			
subjects affected / exposed	5 / 54 (9.26%)	38 / 48 (79.17%)	15 / 57 (26.32%)
occurrences (all)	6	183	35
Hand-foot syndrome			
subjects affected / exposed	7 / 54 (12.96%)	9 / 48 (18.75%)	6 / 57 (10.53%)
occurrences (all)	13	15	15
Paronychia			
subjects affected / exposed	1 / 54 (1.85%)	9 / 48 (18.75%)	1 / 57 (1.75%)
occurrences (all)	2	19	1
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	0 / 54 (0.00%)	3 / 48 (6.25%)	1 / 57 (1.75%)
occurrences (all)	0	3	1
Infection without neutropenia			
subjects affected / exposed	3 / 54 (5.56%)	4 / 48 (8.33%)	6 / 57 (10.53%)
occurrences (all)	5	4	8
Blood phosphorus			
subjects affected / exposed	5 / 54 (9.26%)	17 / 48 (35.42%)	15 / 57 (26.32%)
occurrences (all)	15	57	31

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2011	The inclusions were suspended from March 2011 till June 2011: UNICANCER was notified by the manufacturer that glass fragments were found in the vials containing rilotumumab (AMG 102). The manufacturer suggested that a filter be used during the administration of the product. At the time of notification, three patients had been included: one patient in Arm AMG 102. UNICANCER decided to suspend inclusions, as well as, the administration of the product to patient N°2 until further information was available.
17 June 2011	Updated the study documents to include the use of a filter during the administration of rilotumumab.
11 September 2013	On the 27 May 2013, the independent data committee (IDMC) concluded that the treatment in Arm mFOLFOX6 + panitumumab was possibly not efficacious. Furthermore, more patients died in this Arm compared to Arms mFOLFOX6 and Arm mFOLFOX6 + rilotumumab. The IDMC recommended that inclusions in Arm mFOLFOX6 + panitumumab be stopped. On the 24 June 2013, UNICANCER decided to stop the inclusions in Arm mFOLFOX6 + panitumumab. At this time, 150 patients had been included: 50 patients in Arm mFOLFOX6, 49 in Arm mFOLFOX6 + panitumumab, and 51 in Arm mFOLFOX6 + rilotumumab. The last patient randomized to Arm mFOLFOX6 + panitumumab was on the 24 May 2013.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 March 2011	The inclusions were suspended from March 2011 till June 2011: UNICANCER was notified by the manufacturer that glass fragments were found in the vials containing rilotumumab (AMG 102). The manufacturer suggested that a filter be used during the administration of the product. At the time of notification, three patients had been included: one in Arm AMG 102. UNICANCER decided to suspend inclusions, as well as, the administration of the product to this patient until further information was available.	17 June 2011

Notes:

Limitations and caveats

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

No standard first-line chemotherapy existed for treating advanced gastric cancers; however, platinum-based combination chemotherapy was frequently used. In this study, mFOLFOX6 was selected due to its known activity and acceptable safety profile.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31129386