Clinical trial results:
Randomized phase II study to explore the influence of BRAF and PIK3K status on the efficacy of FOLFIRI plus Bevacizumab or Cetuximab, as first line therapy of patients with KRAS wild-type metastatic colorectal carcinoma and < 3 circulating tumor cells.

Summary

EudraCT number	2012-000840-90
Trial protocol	ES
Global end of trial date	04 November 2018

Results information

Result version number	v1 (current)
This version publication date	01 August 2020
First version publication date	01 August 2020

Trial information

Trial identification

Sponsor protocol code	TTD-12-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01640444
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo de Tratamiento de los Tumores Digestivos (TTD)
Sponsor organisation address	C/ Téllez Nº 30 posterior 1º oficina 4.2 28007 – Madrid , Madrid, Spain, 28007
Public contact	Grupo de Tratamiento de los Tumores Digestivos (TTD), Grupo de Tratamiento de los Tumores Digestivos (TTD), +34 913788 275, ttd@ttdgroup.org
Scientific contact	Grupo de Tratamiento de los Tumores Digestivos (TTD), Grupo de Tratamiento de los Tumores Digestivos (TTD), +34 913788 275, ttd@ttdgroup.org

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	17 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2018
Global end of trial reached?	Yes
Global end of trial date	04 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to explore the impact of the status of BRAF and PI3K expression on efficacy, assessed as progression free survival (PFS), of FOLFIRI+Bevacizumab and FOLFIRI+Cetuximab, in quimo-naïve patients with KRAS wild-type metastatic colorectal carcinoma with < 3 circulating tumor cells.

Protection of trial subjects:

all patients have been treated according to GCP criteria.
Patients were entitled to withdraw from the study at any time and for any reason without prejudice of their future medical care on the part of the doctor or the center.

Background therapy:

There has been no restriction on the use of drugs to treat underlying non-malignant diseases diagnosed before or during the study

Evidence for comparator:

At the moment of the design and the study development there were no evidence of superiority of the most used chemotherapy schedule, FOLFOX vs FOLFIRI. And so, there was no evidence about which monoclonal AB is more useful for the combination.

Actual start date of recruitment	10 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 240
Worldwide total number of subjects	240
EEA total number of subjects	240

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)	170
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First consent 10-10-2012
Last consent 03-11-2016
First randomized patient 10-10-2012
Last randomized patient 04-11-2016
First dose administered 11-10-2012
Last dose administered 22-10-2018
Last end-of-study date 04-11-2018
COUNTRY: Spain. Number of hospitals: 44

Pre-assignment

Screening details:

Patients were stratified by center according to the number of metastatic organs affected (1 vs > 1) and the state of BRAF and PI3K:
BRAF and PI3K native vs BRAF and/or PI3K mutated.
Patients were randomized to receive FOLFIRI+bevacizumab) vs FOLFIRI+cetuximab).
Stratification and randomization were centralized and results were faxed.

Pre-assignment period milestones

Number of subjects started	240
Number of subjects completed	

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PI3K/BRAF mutated

Arm description:

Patients with < 3 CTCs, Ras naive, PI3K and/or BRAF mutated

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

Dosage and administration details:

5 mg/kg Iv/ 2 weeks

Investigational medicinal product name	cetuximab
Investigational medicinal product code	
Other name	Erbitux
Pharmaceutical forms	Concentrate for concentrate for solution for infusion, Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

initial dose of 400 mg/m2 i.v. in 120 minutes on day 1, followed by weekly infusions of 250 mg/m2 i.v. in a 60-minute period.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	Fluorouracilo
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 400 mgr/m2	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 5-FU 2,400 mg/m2 IV in continuous infusion of 46 hours	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	Calcic folinate
Pharmaceutical forms	Concentrate and solvent for solution for infusion, Concentrate and solvent for solution for injection/infusion, Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 400 mg/m2 of racemic formulation, in case of levogyre formulation 200 mg/m2 was used.	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	CPT11
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 180 mg/m2	
Arm title	PI3K/BRAF naive
Arm description: Patients with < 3 CTCs, Ras, PI3K and BRAF naive.	
Arm type	Active comparator
Investigational medicinal product name	Bevacizunab
Investigational medicinal product code	
Other name	Aavstin
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intracavernous use
Dosage and administration details: 5 mg/kg Iv/ 2 weeks	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	Fluorouracilo
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 400 mgr/m2	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion

Routes of administration	Intravenous use
Dosage and administration details: 5-FU 2,400 mg/m2 IV in continuous infusion of 46 hours	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	Calcic folinate
Pharmaceutical forms	Concentrate and solvent for solution for infusion, Concentrate and solvent for solution for injection/infusion, Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 400 mg/m2	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	CPT11
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 180 mg/m2	
Investigational medicinal product name	cetuximab
Investigational medicinal product code	
Other name	Erbitux
Pharmaceutical forms	Concentrate for concentrate for solution for infusion, Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: initial dose of 400 mg/m2 i.v. in 120 minutes on day 1, followed by weekly infusions of 250 mg/m2 i.v. in a 60-minute period.	

Number of subjects in period 1	PI3K/BRAF mutated	PI3K/BRAF naive
Started	44	196
Completed	44	196

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	240	240	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	170	170	
From 65-84 years	70	70	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	76	76	
Male	164	164	

Subject analysis sets	
Subject analysis set title	Folfiri+Beva in BRAF or PI3K mutated
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients diagnosed of Ras naïve CRC and < 3 wit mutated BRAF and/or PI3K. First line FOLFIRI + bevacizumab vs FOLFIRI + cetuximab in first line	
Subject analysis set title	Folfiri+Cetuxi in BRAF or PI3K mutated
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients assigned to Folfiri+Cetuxi in the subgroup of Ras wild tipe, muatted BRAF and/or PI3K	
Subject analysis set title	Folfiri+Beva in BRAF and PI3K naive
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients assigned to Folfiri+Bevacizumab in the subgroup of Ras, BRAF and/or PI3K wild tipe	
Subject analysis set title	Folfiri+Cetuxi in BRAF and PI3K naive
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients assigned to Folfiri+Cetuxi in the subgroup of Ras , BRAF and/or PI3K wild tipe	
Subject analysis set title	Folfiri Bevacizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description: patients assigned to Folfiri Bevacizumab regardless of mutations in PI3K and/or BRAF	
Subject analysis set title	Folfiri cetuximab

Subject analysis set type	Intention-to-treat
Subject analysis set description: patients assigned to Folfiri cetuximab regardless of mutations in PI3K and/or BRAF	
Subject analysis set title	PI3K/BRAF naive
Subject analysis set type	Intention-to-treat
Subject analysis set description: CRC, Ras and PI3K/BRAF naive patients	
Subject analysis set title	PI3K and/or BRAF mutated
Subject analysis set type	Intention-to-treat
Subject analysis set description: Ras naïve CRC with mutation in PI3K and/or BRAF	

Reporting group values	Folfiri+Beva in BRAF or PI3K mutated	Folfiri+Cetuxi in BRAF or PI3K mutated	Folfiri+Beva in BRAF and PI3K naive
Number of subjects	24	20	102
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	11	74
From 65-84 years	6	9	28
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female			
Male			

Reporting group values	Folfiri+Cetuxi in BRAF and PI3K naive	Folfiri Bevacizumab	Folfiri cetuximab
Number of subjects	94	126	114
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	67	92	78
From 65-84 years	27	34	36
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female			

Male			

Reporting group values	PI3K/BRAF naive	PI3K and/or BRAF mutated	
Number of subjects	196	44	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	141	29	
From 65-84 years	55	15	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	PI3K/BRAF mutated
Reporting group description: Patients with < 3 CTCs, Ras naive, PI3K and/or BRAF mutated	
Reporting group title	PI3K/BRAF naive
Reporting group description: Patients with < 3 CTCs, Ras, PI3K and BRAF naive.	
Subject analysis set title	Folfiri+Beva in BRAF or PI3K mutated
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients diagnosed of Ras naïve CRC and < 3 wit mutated BRAF and/or PI3K. First line FOLFIRI + bevacizumab vs FOLFIRI + cetuximab in first line	
Subject analysis set title	Folfiri+Cetuxi in BRAF or PI3K mutated
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients assigned to Folfiri+Cetuxi in the subgroup of Ras wild tipe, muatted BRAF and/or PI3K	
Subject analysis set title	Folfiri+Beva in BRAF and PI3K naive
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients assigned to Folfiri+Bevacizumab in the subgroup of Ras, BRAF and/or PI3K wild tipe	
Subject analysis set title	Folfiri+Cetuxi in BRAF and PI3K naive
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients assigned to Folfiri+Cetuxi in the subgroup of Ras , BRAF and/or PI3K wild tipe	
Subject analysis set title	Folfiri Bevacizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description: patients assigned to Folfiri Bevacizumab regardless of mutations in PI3K and/or BRAF	
Subject analysis set title	Folfiri cetuximab
Subject analysis set type	Intention-to-treat
Subject analysis set description: patients assigned to Folfiri cetuximab regardless of mutations in PI3K and/or BRAF	
Subject analysis set title	PI3K/BRAF naive
Subject analysis set type	Intention-to-treat
Subject analysis set description: CRC, Ras and PI3K/BRAF naive patients	
Subject analysis set title	PI3K and/or BRAF mutated
Subject analysis set type	Intention-to-treat
Subject analysis set description: Ras naïve CRC with mutation in PI3K and/or BRAF	

Primary: PFS PI3K naive vs mutated

End point title	PFS PI3K naive vs mutated
End point description:	
End point type	Primary
End point timeframe: 10-10-2012 to 04-11-2018	

End point values	PI3K/BRAF mutated	PI3K/BRAF naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	196		
Units: months				
number (confidence interval 95%)	8.8 (8.2 to 12.4)	12.7 (11.3 to 14.9)		

Statistical analyses

Statistical analysis title	PI3K/BRAF mutated vs Naive
Statistical analysis description: Primary objective	
Comparison groups	PI3K/BRAF mutated v PI3K/BRAF naive
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank

Post-hoc: PFS Folfiri + Bevacizumab vs Folfiri + Cetuximab

End point title	PFS Folfiri + Bevacizumab vs Folfiri + Cetuximab
End point description:	
End point type	Post-hoc
End point timeframe: 10-10-2012 to 04-11-2018	

End point values	Folfiri Bevacizumab	Folfiri cetuximab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126	114[1]		
Units: month				
median (confidence interval 95%)	12.5 (10.0 to 14.1)	11.5 (9.3 to 15.4)		

Notes:

[1] - A patient randomized to Folfiri cetuxi didn't begin the treatment, not included in safety analýsis

Statistical analyses

Statistical analysis title	Log-rank Test
Comparison groups	Folfiri Bevacizumab v Folfiri cetuximab
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank

Post-hoc: PFS Beva vs Cetuxi in mutated BRAF/PI3K

End point title	PFS Beva vs Cetuxi in mutated BRAF/PI3K

End point description:

End point type	Post-hoc

End point timeframe:

10-10-2012 to 04-11-2018

End point values	Folfiri+Beva in BRAF or PI3K mutated	Folfiri+Cetuxi in BRAF or PI3K mutated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	20		
Units: months				
median (confidence interval 95%)	9.3 (3.7 to 15.0)	8.5 (5.3 to 12.4)		

Statistical analyses

Statistical analysis title	Log-rank Test
Comparison groups	Folfiri+Beva in BRAF or PI3K mutated v Folfiri+Cetuxi in BRAF or PI3K mutated
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Logrank

Post-hoc: PFS Bevacizumab vs Cetuximab in wild BRAF/PI3K

End point title	PFS Bevacizumab vs Cetuximab in wild BRAF/PI3K

End point description:

End point type	Post-hoc

End point timeframe:
10-10-2012 to 04-11-2018

End point values	Folfiri+Beva in BRAF and PI3K naive	Folfiri+Cetuxi in BRAF and PI3K naive		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102	94		
Units: month				
number (confidence interval 95%)	12.9 (10.3 to 14.9)	12.5 (10.5 to 16.1)		

Statistical analyses

Statistical analysis title	Naive patients cetuxi vs bevacizumab
Comparison groups	Folfiri+Beva in BRAF and PI3K naive v Folfiri+Cetuxi in BRAF and PI3K naive
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank

Adverse events

Adverse events information	
Timeframe for reporting adverse events: First consent 10-10-2012 Last end-of-study date 04-11-2018	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Folfiri+Bevacizumab
Reporting group description: -	
Reporting group title	Folfiri+Cetuximab
Reporting group description: -	
Reporting group title	Folfiri + Bevacizumab, mutated
Reporting group description: -	
Reporting group title	Folfiri + Bevacizumab naive
Reporting group description: -	
Reporting group title	Folfiri + Cetuxi, mutated
Reporting group description: -	
Reporting group title	Folfiri + Cetuxi, naive
Reporting group description: -	
Reporting group title	PI3K and BRAF naive
Reporting group description: -	
Reporting group title	PI3K or BRAF mutated
Reporting group description: -	

Serious adverse events	Folfiri+Bevacizumab	Folfiri+Cetuximab	Folfiri + Bevacizumab, mutated
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 126 (28.57%)	43 / 113 (38.05%)	10 / 24 (41.67%)
number of deaths (all causes)	77	66	2
number of deaths resulting from adverse events	3	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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			
Venous thrombosis extremities			

subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Vena cava thrombosis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Jugular vein thrombosis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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			
Pyrexia			
subjects affected / exposed	2 / 126 (1.59%)	5 / 113 (4.42%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 2	2 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Urinary retention			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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			
Pulmonary embolism			
subjects affected / exposed	2 / 126 (1.59%)	2 / 113 (1.77%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Product issues			
Thrombosis in device			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Investigations			
Dehydration			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Hip fracture			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Complication of a gastrointestinal stoma			

subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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 flutter			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Congestive heart failure			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 126 (0.79%)	5 / 113 (4.42%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 126 (0.79%)	1 / 113 (0.88%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anaemia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	5 / 126 (3.97%)	3 / 113 (2.65%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	4 / 5	1 / 3	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 126 (0.79%)	3 / 113 (2.65%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 126 (0.79%)	2 / 113 (1.77%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	2 / 126 (1.59%)	0 / 113 (0.00%)	0 / 24 (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
Subileus			
subjects affected / exposed	0 / 126 (0.00%)	3 / 113 (2.65%)	0 / 24 (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
Pancreatic disorder			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Pancreatitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Constipation			

subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Colitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Intestinal ischaemia			
subjects affected / exposed	2 / 126 (1.59%)	1 / 113 (0.88%)	2 / 24 (8.33%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Intestinal fistula infection			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Hepatobiliary disorders			
Diarrhoea			
subjects affected / exposed	7 / 126 (5.56%)	3 / 113 (2.65%)	3 / 24 (12.50%)
occurrences causally related to treatment / all	8 / 9	3 / 3	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Cholecystitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Bile duct obstruction			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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 and subcutaneous tissue disorders			

Dermatitis acneiform			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Toxic skin eruption			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Skin ulcer			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Renal and urinary disorders			
Bleeding urinary bladder			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Hydronephrosis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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 pain			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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			
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Bacteraemia			
subjects affected / exposed	1 / 126 (0.79%)	1 / 113 (0.88%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	1 / 126 (0.79%)	1 / 113 (0.88%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
In-hospital infection			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Escherichia sepsis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Gastroenteritis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Localised infection			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Abdominal wall infection			

subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Post-procedure sepsis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	0 / 24 (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
Serratia bacteraemia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis pseudomonas			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Septic shock			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Anal abscess			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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
Abdominal infection			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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 intestinal			
subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			

subjects affected / exposed	1 / 126 (0.79%)	0 / 113 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 113 (0.88%)	0 / 24 (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

Serious adverse events	Folfiri + Bevacizumab naive	Folfiri + Cetuxi, mutated	Folfiri + Cetuxi, naive
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 102 (26.47%)	4 / 20 (20.00%)	39 / 93 (41.94%)
number of deaths (all causes)	58	14	52
number of deaths resulting from adverse events	4	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 102 (0.00%)	1 / 20 (5.00%)	0 / 93 (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
Vascular disorders			
Venous thrombosis extremities			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Vena cava thrombosis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 102 (0.00%)	1 / 20 (5.00%)	0 / 93 (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			
Pyrexia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	5 / 93 (5.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Urinary retention			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 102 (1.96%)	0 / 20 (0.00%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Thrombosis in device			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Investigations			
Dehydration			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication of a gastrointestinal stoma			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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 flutter			

subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive heart failure			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
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			
Febrile neutropenia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	5 / 93 (5.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	4 / 102 (3.92%)	0 / 20 (0.00%)	3 / 93 (3.23%)
occurrences causally related to treatment / all	3 / 4	0 / 0	1 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Abdominal pain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	3 / 93 (3.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	2 / 102 (1.96%)	0 / 20 (0.00%)	0 / 93 (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
Subileus			
subjects affected / exposed	0 / 102 (0.00%)	1 / 20 (5.00%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic disorder			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Constipation			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Colitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			

subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal fistula infection			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Hepatobiliary disorders			
Diarrhoea			
subjects affected / exposed	4 / 102 (3.92%)	0 / 20 (0.00%)	3 / 93 (3.23%)
occurrences causally related to treatment / all	5 / 5	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Cholecystitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct obstruction			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
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			
Dermatitis acneiform			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			

subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Renal and urinary disorders			
Bleeding urinary bladder			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Hydronephrosis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Subcutaneous abscess			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
In-hospital infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Localised infection			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Abdominal wall infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-procedure sepsis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	0 / 93 (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
Serratia bacteraemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis pseudomonas			

subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 20 (5.00%)	0 / 93 (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 intestinal			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 20 (5.00%)	0 / 93 (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

Serious adverse events	PI3K and BRAF naive	PI3K or BRAF mutated	
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 195 (33.85%)	14 / 44 (31.82%)	
number of deaths (all causes)	110	33	
number of deaths resulting from adverse events	5	3	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 195 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Venous thrombosis extremities			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 195 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 195 (3.08%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	0 / 195 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Urinary retention			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 195 (2.05%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Thrombosis in device			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Dehydration			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Injury, poisoning and procedural complications			
Staphylococcal bacteraemia			

subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication of a gastrointestinal stoma			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive heart failure			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	6 / 195 (3.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 195 (1.03%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	7 / 195 (3.59%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	4 / 7	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 195 (2.05%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 195 (1.54%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	2 / 195 (1.03%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	2 / 195 (1.03%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatic disorder			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 195 (0.51%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal fistula infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Diarrhoea			
subjects affected / exposed	7 / 195 (3.59%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	8 / 8	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 195 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 195 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bleeding urinary bladder			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal pain			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 195 (1.03%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 195 (0.51%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
In-hospital infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-procedure sepsis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia bacteraemia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis pseudomonas			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 195 (0.51%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 195 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			

subjects affected / exposed	0 / 195 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 195 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Folfiri+Bevacizumab	Folfiri+Cetuximab	Folfiri + Bevacizumab, mutated
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 126 (100.00%)	113 / 113 (100.00%)	24 / 24 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 126 (20.63%)	5 / 113 (4.42%)	4 / 24 (16.67%)
occurrences (all)	79	6	7
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	15 / 126 (11.90%)	9 / 113 (7.96%)	4 / 24 (16.67%)
occurrences (all)	32	12	8
Dizziness			
subjects affected / exposed	8 / 126 (6.35%)	5 / 113 (4.42%)	1 / 24 (4.17%)
occurrences (all)	9	6	1
Syncope			
subjects affected / exposed	5 / 126 (3.97%)	1 / 113 (0.88%)	2 / 24 (8.33%)
occurrences (all)	8	1	2
General disorders and administration site conditions			
Mucosal inflammation			

subjects affected / exposed	59 / 126 (46.83%)	45 / 113 (39.82%)	15 / 24 (62.50%)
occurrences (all)	132	97	32
Pyrexia			
subjects affected / exposed	28 / 126 (22.22%)	22 / 113 (19.47%)	6 / 24 (25.00%)
occurrences (all)	40	31	10
Xerosis			
subjects affected / exposed	0 / 126 (0.00%)	10 / 113 (8.85%)	0 / 24 (0.00%)
occurrences (all)	0	12	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	60 / 126 (47.62%)	47 / 113 (41.59%)	11 / 24 (45.83%)
occurrences (all)	183	101	39
Anaemia			
subjects affected / exposed	18 / 126 (14.29%)	22 / 113 (19.47%)	2 / 24 (8.33%)
occurrences (all)	31	37	2
Leukopenia			
subjects affected / exposed	9 / 126 (7.14%)	7 / 113 (6.19%)	1 / 24 (4.17%)
occurrences (all)	21	10	1
Immune system disorders			
Urinary tract infection			
subjects affected / exposed	8 / 126 (6.35%)	11 / 113 (9.73%)	0 / 24 (0.00%)
occurrences (all)	11	12	0
Social circumstances			
Alopecia			
subjects affected / exposed	38 / 126 (30.16%)	18 / 113 (15.93%)	10 / 24 (41.67%)
occurrences (all)	50	22	12
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	49 / 126 (38.89%)	39 / 113 (34.51%)	9 / 24 (37.50%)
occurrences (all)	148	63	31
Vomiting			
subjects affected / exposed	36 / 126 (28.57%)	33 / 113 (29.20%)	9 / 24 (37.50%)
occurrences (all)	69	53	20
Constipation			
subjects affected / exposed	29 / 126 (23.02%)	34 / 113 (30.09%)	7 / 24 (29.17%)
occurrences (all)	48	42	15
Abdominal pain			

subjects affected / exposed	26 / 126 (20.63%)	23 / 113 (20.35%)	9 / 24 (37.50%)
occurrences (all)	46	43	16
Diarrhoea			
subjects affected / exposed	90 / 126 (71.43%)	75 / 113 (66.37%)	18 / 24 (75.00%)
occurrences (all)	294	224	81
Stomatitis			
subjects affected / exposed	9 / 126 (7.14%)	10 / 113 (8.85%)	4 / 24 (16.67%)
occurrences (all)	20	14	9
Rectal Bleeding			
subjects affected / exposed	13 / 126 (10.32%)	12 / 113 (10.62%)	4 / 24 (16.67%)
occurrences (all)	14	22	4
Odynophagia			
subjects affected / exposed	9 / 126 (7.14%)	3 / 113 (2.65%)	3 / 24 (12.50%)
occurrences (all)	11	3	5
Dry mouth			
subjects affected / exposed	8 / 126 (6.35%)	9 / 113 (7.96%)	2 / 24 (8.33%)
occurrences (all)	10	12	2
Dyspepsia			
subjects affected / exposed	9 / 126 (7.14%)	8 / 113 (7.08%)	1 / 24 (4.17%)
occurrences (all)	13	8	3
Pain in upper abdomen			
subjects affected / exposed	9 / 126 (7.14%)	6 / 113 (5.31%)	2 / 24 (8.33%)
occurrences (all)	12	10	3
Rectal tenesmus			
subjects affected / exposed	2 / 126 (1.59%)	1 / 113 (0.88%)	2 / 24 (8.33%)
occurrences (all)	2	1	2
Aphthous ulcer			
subjects affected / exposed	8 / 126 (6.35%)	3 / 113 (2.65%)	2 / 24 (8.33%)
occurrences (all)	8	3	2
Asthenia			
subjects affected / exposed	80 / 126 (63.49%)	62 / 113 (54.87%)	20 / 24 (83.33%)
occurrences (all)	249	150	79
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	33 / 126 (26.19%)	11 / 113 (9.73%)	6 / 24 (25.00%)
occurrences (all)	68	15	13
Rhinorrhoea			
subjects affected / exposed	10 / 126 (7.94%)	6 / 113 (5.31%)	2 / 24 (8.33%)
occurrences (all)	23	9	3
Dyspnoea			
subjects affected / exposed	8 / 126 (6.35%)	5 / 113 (4.42%)	2 / 24 (8.33%)
occurrences (all)	12	6	6
Cold			
subjects affected / exposed	12 / 126 (9.52%)	7 / 113 (6.19%)	3 / 24 (12.50%)
occurrences (all)	17	9	4
Dysphonia			
subjects affected / exposed	7 / 126 (5.56%)	2 / 113 (1.77%)	2 / 24 (8.33%)
occurrences (all)	7	2	2
Cough			
subjects affected / exposed	6 / 126 (4.76%)	1 / 113 (0.88%)	2 / 24 (8.33%)
occurrences (all)	7	1	3
Skin and subcutaneous tissue disorders			
Eruption			
subjects affected / exposed	5 / 126 (3.97%)	67 / 113 (59.29%)	0 / 24 (0.00%)
occurrences (all)	7	176	0
Palmoplantar erythrodysesthesia syndrome			
subjects affected / exposed	8 / 126 (6.35%)	16 / 113 (14.16%)	1 / 24 (4.17%)
occurrences (all)	11	24	1
Skin fissures			
subjects affected / exposed	4 / 126 (3.17%)	25 / 113 (22.12%)	1 / 24 (4.17%)
occurrences (all)	4	46	1
Dry skin			
subjects affected / exposed	6 / 126 (4.76%)	21 / 113 (18.58%)	1 / 24 (4.17%)
occurrences (all)	6	30	1
Acne			
subjects affected / exposed	2 / 126 (1.59%)	21 / 113 (18.58%)	0 / 24 (0.00%)
occurrences (all)	4	43	0
Dermatitis			

subjects affected / exposed	3 / 126 (2.38%)	20 / 113 (17.70%)	0 / 24 (0.00%)
occurrences (all)	4	23	0
Nail disorder			
subjects affected / exposed	3 / 126 (2.38%)	3 / 113 (2.65%)	2 / 24 (8.33%)
occurrences (all)	3	7	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	10 / 126 (7.94%)	7 / 113 (6.19%)	5 / 24 (20.83%)
occurrences (all)	13	7	7
Bone pain			
subjects affected / exposed	3 / 126 (2.38%)	1 / 113 (0.88%)	2 / 24 (8.33%)
occurrences (all)	3	1	2
Infections and infestations			
Paronychia			
subjects affected / exposed	1 / 126 (0.79%)	30 / 113 (26.55%)	0 / 24 (0.00%)
occurrences (all)	2	48	0
Respiratory tract infection			
subjects affected / exposed	7 / 126 (5.56%)	1 / 113 (0.88%)	2 / 24 (8.33%)
occurrences (all)	7	1	2
Gingivitis			
subjects affected / exposed	3 / 126 (2.38%)	2 / 113 (1.77%)	2 / 24 (8.33%)
occurrences (all)	5	2	4
Pharyngitis			
subjects affected / exposed	2 / 126 (1.59%)	1 / 113 (0.88%)	2 / 24 (8.33%)
occurrences (all)	3	1	3
Nasopharyngitis			
subjects affected / exposed	6 / 126 (4.76%)	4 / 113 (3.54%)	2 / 24 (8.33%)
occurrences (all)	7	5	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	29 / 126 (23.02%)	21 / 113 (18.58%)	5 / 24 (20.83%)
occurrences (all)	54	28	13
Hyperglycaemia			
subjects affected / exposed	4 / 126 (3.17%)	0 / 113 (0.00%)	2 / 24 (8.33%)
occurrences (all)	14	0	4

Non-serious adverse events	Folfiri + Bevacizumab naive	Folfiri + Cetuxi, mutated	Folfiri + Cetuxi, naive
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 102 (97.06%)	20 / 20 (100.00%)	93 / 93 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 102 (21.57%)	0 / 20 (0.00%)	5 / 93 (5.38%)
occurrences (all)	72	0	6
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	11 / 102 (10.78%)	2 / 20 (10.00%)	7 / 93 (7.53%)
occurrences (all)	23	5	7
Dizziness			
subjects affected / exposed	7 / 102 (6.86%)	2 / 20 (10.00%)	3 / 93 (3.23%)
occurrences (all)	8	2	4
Syncope			
subjects affected / exposed	3 / 102 (2.94%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences (all)	6	0	1
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	44 / 102 (43.14%)	7 / 20 (35.00%)	38 / 93 (40.86%)
occurrences (all)	100	14	83
Pyrexia			
subjects affected / exposed	22 / 102 (21.57%)	2 / 20 (10.00%)	20 / 93 (21.51%)
occurrences (all)	30	2	29
Xerosis			
subjects affected / exposed	0 / 102 (0.00%)	4 / 20 (20.00%)	6 / 93 (6.45%)
occurrences (all)	0	4	8
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	49 / 102 (48.04%)	7 / 20 (35.00%)	40 / 93 (43.01%)
occurrences (all)	144	10	91
Anaemia			
subjects affected / exposed	16 / 102 (15.69%)	0 / 20 (0.00%)	22 / 93 (23.66%)
occurrences (all)	29	0	37
Leukopenia			

subjects affected / exposed	8 / 102 (7.84%)	1 / 20 (5.00%)	6 / 93 (6.45%)
occurrences (all)	20	2	8
Immune system disorders			
Urinary tract infection			
subjects affected / exposed	8 / 102 (7.84%)	3 / 20 (15.00%)	8 / 93 (8.60%)
occurrences (all)	11	4	8
Social circumstances			
Alopecia			
subjects affected / exposed	28 / 102 (27.45%)	3 / 20 (15.00%)	15 / 93 (16.13%)
occurrences (all)	38	5	17
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	40 / 102 (39.22%)	4 / 20 (20.00%)	30 / 93 (32.26%)
occurrences (all)	117	4	59
Vomiting			
subjects affected / exposed	26 / 102 (25.49%)	2 / 20 (10.00%)	23 / 93 (24.73%)
occurrences (all)	48	2	49
Constipation			
subjects affected / exposed	21 / 102 (20.59%)	4 / 20 (20.00%)	27 / 93 (29.03%)
occurrences (all)	32	8	34
Abdominal pain			
subjects affected / exposed	16 / 102 (15.69%)	1 / 20 (5.00%)	20 / 93 (21.51%)
occurrences (all)	29	2	38
Diarrhoea			
subjects affected / exposed	69 / 102 (67.65%)	12 / 20 (60.00%)	63 / 93 (67.74%)
occurrences (all)	204	23	197
Stomatitis			
subjects affected / exposed	5 / 102 (4.90%)	4 / 20 (20.00%)	7 / 93 (7.53%)
occurrences (all)	11	4	10
Rectal Bleeding			
subjects affected / exposed	9 / 102 (8.82%)	2 / 20 (10.00%)	10 / 93 (10.75%)
occurrences (all)	10	3	19
Odynophagia			
subjects affected / exposed	6 / 102 (5.88%)	2 / 20 (10.00%)	1 / 93 (1.08%)
occurrences (all)	6	2	1
Dry mouth			

subjects affected / exposed	6 / 102 (5.88%)	2 / 20 (10.00%)	7 / 93 (7.53%)
occurrences (all)	8	3	9
Dyspepsia			
subjects affected / exposed	8 / 102 (7.84%)	2 / 20 (10.00%)	6 / 93 (6.45%)
occurrences (all)	10	2	6
Pain in upper abdomen			
subjects affected / exposed	7 / 102 (6.86%)	1 / 20 (5.00%)	5 / 93 (5.38%)
occurrences (all)	9	2	8
Rectal tenesmus			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences (all)	0	0	1
Aphthous ulcer			
subjects affected / exposed	6 / 102 (5.88%)	0 / 20 (0.00%)	3 / 93 (3.23%)
occurrences (all)	6	0	3
Asthenia			
subjects affected / exposed	60 / 102 (58.82%)	12 / 20 (60.00%)	50 / 93 (53.76%)
occurrences (all)	170	22	128
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	27 / 102 (26.47%)	1 / 20 (5.00%)	10 / 93 (10.75%)
occurrences (all)	55	1	14
Rhinorrhoea			
subjects affected / exposed	8 / 102 (7.84%)	1 / 20 (5.00%)	5 / 93 (5.38%)
occurrences (all)	20	1	8
Dyspnoea			
subjects affected / exposed	6 / 102 (5.88%)	1 / 20 (5.00%)	4 / 93 (4.30%)
occurrences (all)	6	1	5
Cold			
subjects affected / exposed	9 / 102 (8.82%)	0 / 20 (0.00%)	7 / 93 (7.53%)
occurrences (all)	11	0	9
Dysphonia			
subjects affected / exposed	5 / 102 (4.90%)	0 / 20 (0.00%)	2 / 93 (2.15%)
occurrences (all)	5	0	2
Cough			

subjects affected / exposed	4 / 102 (3.92%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences (all)	4	0	1
Skin and subcutaneous tissue disorders			
Eruption			
subjects affected / exposed	5 / 102 (4.90%)	11 / 20 (55.00%)	56 / 93 (60.22%)
occurrences (all)	7	30	146
Palmoplantar erythrodysesthesia syndrome			
subjects affected / exposed	7 / 102 (6.86%)	5 / 20 (25.00%)	11 / 93 (11.83%)
occurrences (all)	10	11	13
Skin fissures			
subjects affected / exposed	3 / 102 (2.94%)	4 / 20 (20.00%)	21 / 93 (22.58%)
occurrences (all)	3	8	38
Dry skin			
subjects affected / exposed	5 / 102 (4.90%)	4 / 20 (20.00%)	17 / 93 (18.28%)
occurrences (all)	5	9	21
Acne			
subjects affected / exposed	4 / 102 (3.92%)	5 / 20 (25.00%)	16 / 93 (17.20%)
occurrences (all)	4	11	32
Dermatitis			
subjects affected / exposed	3 / 102 (2.94%)	3 / 20 (15.00%)	17 / 93 (18.28%)
occurrences (all)	4	3	20
Nail disorder			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	3 / 93 (3.23%)
occurrences (all)	1	0	7
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 102 (4.90%)	1 / 20 (5.00%)	6 / 93 (6.45%)
occurrences (all)	6	1	6
Bone pain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences (all)	1	0	1
Infections and infestations			
Paronychia			
subjects affected / exposed	1 / 102 (0.98%)	6 / 20 (30.00%)	24 / 93 (25.81%)
occurrences (all)	2	9	39
Respiratory tract infection			

subjects affected / exposed	5 / 102 (4.90%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences (all)	5	0	1
Gingivitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 20 (0.00%)	2 / 93 (2.15%)
occurrences (all)	1	0	2
Pharyngitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 20 (0.00%)	1 / 93 (1.08%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	4 / 102 (3.92%)	0 / 20 (0.00%)	4 / 93 (4.30%)
occurrences (all)	4	0	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	24 / 102 (23.53%)	3 / 20 (15.00%)	18 / 93 (19.35%)
occurrences (all)	41	3	28
Hyperglycaemia			
subjects affected / exposed	2 / 102 (1.96%)	0 / 20 (0.00%)	0 / 93 (0.00%)
occurrences (all)	10	0	0

Non-serious adverse events	PI3K and BRAF naive	PI3K or BRAF mutated	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	195 / 195 (100.00%)	44 / 44 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 195 (13.85%)	4 / 44 (9.09%)	
occurrences (all)	78	7	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	18 / 195 (9.23%)	6 / 44 (13.64%)	
occurrences (all)	30	13	
Dizziness			
subjects affected / exposed	10 / 195 (5.13%)	3 / 44 (6.82%)	
occurrences (all)	12	3	
Syncope			
subjects affected / exposed	4 / 195 (2.05%)	2 / 44 (4.55%)	
occurrences (all)	7	2	

General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	82 / 195 (42.05%)	22 / 44 (50.00%)	
occurrences (all)	183	46	
Pyrexia			
subjects affected / exposed	42 / 195 (21.54%)	8 / 44 (18.18%)	
occurrences (all)	59	12	
Xerosis			
subjects affected / exposed	6 / 195 (3.08%)	4 / 44 (9.09%)	
occurrences (all)	8	4	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	89 / 195 (45.64%)	18 / 44 (40.91%)	
occurrences (all)	235	49	
Anaemia			
subjects affected / exposed	38 / 195 (19.49%)	2 / 44 (4.55%)	
occurrences (all)	66	2	
Leukopenia			
subjects affected / exposed	14 / 195 (7.18%)	2 / 44 (4.55%)	
occurrences (all)	28	3	
Immune system disorders			
Urinary tract infection			
subjects affected / exposed	16 / 195 (8.21%)	3 / 44 (6.82%)	
occurrences (all)	19	4	
Social circumstances			
Alopecia			
subjects affected / exposed	43 / 195 (22.05%)	13 / 44 (29.55%)	
occurrences (all)	55	17	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	70 / 195 (35.90%)	13 / 44 (29.55%)	
occurrences (all)	176	34	
Vomiting			
subjects affected / exposed	49 / 195 (25.13%)	11 / 44 (25.00%)	
occurrences (all)	97	22	
Constipation			

subjects affected / exposed	48 / 195 (24.62%)	11 / 44 (25.00%)	
occurrences (all)	66	23	
Abdominal pain			
subjects affected / exposed	36 / 195 (18.46%)	10 / 44 (22.73%)	
occurrences (all)	67	18	
Diarrhoea			
subjects affected / exposed	132 / 195 (67.69%)	30 / 44 (68.18%)	
occurrences (all)	401	104	
Stomatitis			
subjects affected / exposed	12 / 195 (6.15%)	8 / 44 (18.18%)	
occurrences (all)	21	13	
Rectal Bleeding			
subjects affected / exposed	19 / 195 (9.74%)	6 / 44 (13.64%)	
occurrences (all)	29	7	
Odynophagia			
subjects affected / exposed	7 / 195 (3.59%)	5 / 44 (11.36%)	
occurrences (all)	7	7	
Dry mouth			
subjects affected / exposed	13 / 195 (6.67%)	4 / 44 (9.09%)	
occurrences (all)	17	5	
Dyspepsia			
subjects affected / exposed	14 / 195 (7.18%)	3 / 44 (6.82%)	
occurrences (all)	16	5	
Pain in upper abdomen			
subjects affected / exposed	12 / 195 (6.15%)	3 / 44 (6.82%)	
occurrences (all)	17	5	
Rectal tenesmus			
subjects affected / exposed	1 / 195 (0.51%)	2 / 44 (4.55%)	
occurrences (all)	1	2	
Aphthous ulcer			
subjects affected / exposed	9 / 195 (4.62%)	2 / 44 (4.55%)	
occurrences (all)	9	2	
Asthenia			
subjects affected / exposed	110 / 195 (56.41%)	32 / 44 (72.73%)	
occurrences (all)	298	101	
Respiratory, thoracic and mediastinal			

disorders			
Epistaxis			
subjects affected / exposed	37 / 195 (18.97%)	7 / 44 (15.91%)	
occurrences (all)	69	14	
Rhinorrhoea			
subjects affected / exposed	13 / 195 (6.67%)	3 / 44 (6.82%)	
occurrences (all)	28	4	
Dyspnoea			
subjects affected / exposed	10 / 195 (5.13%)	3 / 44 (6.82%)	
occurrences (all)	11	7	
Cold			
subjects affected / exposed	16 / 195 (8.21%)	3 / 44 (6.82%)	
occurrences (all)	20	4	
Dysphonia			
subjects affected / exposed	7 / 195 (3.59%)	2 / 44 (4.55%)	
occurrences (all)	7	2	
Cough			
subjects affected / exposed	5 / 195 (2.56%)	2 / 44 (4.55%)	
occurrences (all)	5	3	
Skin and subcutaneous tissue disorders			
Eruption			
subjects affected / exposed	61 / 195 (31.28%)	11 / 44 (25.00%)	
occurrences (all)	153	30	
Palmoplantar erythrodysesthesia syndrome			
subjects affected / exposed	18 / 195 (9.23%)	6 / 44 (13.64%)	
occurrences (all)	23	12	
Skin fissures			
subjects affected / exposed	24 / 195 (12.31%)	5 / 44 (11.36%)	
occurrences (all)	41	9	
Dry skin			
subjects affected / exposed	22 / 195 (11.28%)	5 / 44 (11.36%)	
occurrences (all)	26	10	
Acne			
subjects affected / exposed	20 / 195 (10.26%)	5 / 44 (11.36%)	
occurrences (all)	36	11	
Dermatitis			

subjects affected / exposed	20 / 195 (10.26%)	3 / 44 (6.82%)	
occurrences (all)	24	3	
Nail disorder			
subjects affected / exposed	4 / 195 (2.05%)	2 / 44 (4.55%)	
occurrences (all)	8	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 195 (5.64%)	6 / 44 (13.64%)	
occurrences (all)	12	8	
Bone pain			
subjects affected / exposed	2 / 195 (1.03%)	2 / 44 (4.55%)	
occurrences (all)	2	2	
Infections and infestations			
Paronychia			
subjects affected / exposed	25 / 195 (12.82%)	6 / 44 (13.64%)	
occurrences (all)	41	9	
Respiratory tract infection			
subjects affected / exposed	6 / 195 (3.08%)	2 / 44 (4.55%)	
occurrences (all)	6	2	
Gingivitis			
subjects affected / exposed	3 / 195 (1.54%)	2 / 44 (4.55%)	
occurrences (all)	3	4	
Pharyngitis			
subjects affected / exposed	1 / 195 (0.51%)	2 / 44 (4.55%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	8 / 195 (4.10%)	2 / 44 (4.55%)	
occurrences (all)	8	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	42 / 195 (21.54%)	8 / 44 (18.18%)	
occurrences (all)	69	16	
Hyperglycaemia			
subjects affected / exposed	2 / 195 (1.03%)	2 / 44 (4.55%)	
occurrences (all)	10	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2013	Relevant modification to the Protocol (version 4 is generated), expansion of 5 centers, PI´s updates.
18 March 2014	Relevant modification to the Protocol (version 5 is generated with addition of sub-study and IC for subs study), expansion of 1 center, change of PiS-IC of the project and that of the sub study.
26 July 2016	Modifications of annexes 8 and 10 (sub study) to the protocol, HIP-CI change of project screening, general and specific PiS-IC change of sub study assay, change of 2 test lab managers, addition of new central laboratory to the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32278676