Clinical trial results:
A Multicenter, Single arm, Open Label Clinical Trial Evaluating Safety and Health-Related Quality of Life of Aflibercept in Combination with Irinotecan/5FU chemotherapy (FOLFIRI) in Patients with Metastatic Colorectal Cancer (mCRC) Previously Treated with an Oxaliplatin-Containing Regimen

Summary

EudraCT number	2012-000048-89
Trial protocol	FR
Global end of trial date	09 June 2015

Results information

Result version number	v1 (current)
This version publication date	24 June 2016
First version publication date	24 June 2016

Trial information

Trial identification

Sponsor protocol code	AFLIBL06266

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01670721
WHO universal trial number (UTN)	U1111-1128-9325
Other trial identifiers	Study Name: AFEQT

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	82 avenue Raspail, Gentilly Cedex, France, 94255
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

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	07 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of aflibercept in subjects with mCRC treated with irinotecan/5FU (FOLFIRI) after failure of an oxaliplatin-based regimen (subjects similar to those evaluated in the VELOUR trial [EFC10262, NCT00561470]) according to side effects prevention and management guidelines.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 August 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	France: 175
Worldwide total number of subjects	175
EEA total number of subjects	175

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)	80
From 65 to 84 years	95
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 38 sites in France. A total of 182 subjects were screened between 08 August 2012 and 30 June 2014, out of which 175 subjects were enrolled and treated.

Pre-assignment

Screening details:

Subjects enrolled in the study to assess the safety of Aflibercept in subjects treated with a combination of Aflibercept with FOLFIRI regimen (Irinotecan, Leucovorin and 5-Fluorouracil [5-FU]). 81 subjects with disease progression (DP) and 41 with adverse events (AEs) were considered as completed.

Period 1

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

Arms

Arm title	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)

Arm description:

Aflibercept 4 mg/kg followed by Irinotecan 180 mg/m^2 and Leucovorin 400 mg/m^2 at the same time followed by 5-FU 400 mg/m^2 followed by 5-FU 2400 mg/m^2 on Day 1 of each cycle (1 Cycle = 2 weeks), until DP, unacceptable toxicity, death, Investigator's decision or subject's refusal of further treatment.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	AVE0005
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aflibercept 4 mg/kg intravenous (IV) infusion over 60 minutes.

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

Dosage and administration details:

Irinotecan 180 mg/m^2 IV infusion over 90 minutes.

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

Dosage and administration details:

Leucovorin 400 mg/m^2 IV infusion over 120 minutes.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details: 5-FU 400 mg/m^2 bolus IV infusion over 2-4 minutes.	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU 2400 mg/m^2 continuous IV infusion over 46 hours.

Number of subjects in period 1	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)
Started	175
Completed	122
Not completed	53
Subject's decision	15
Other than specified	38

Baseline characteristics

Reporting groups	
Reporting group title	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)
Reporting group description:	
Aflibercept 4 mg/kg followed by Irinotecan 180 mg/m^2 and Leucovorin 400 mg/m^2 at the same time followed by 5-FU 400 mg/m^2 followed by 5-FU 2400 mg/m^2 on Day 1 of each cycle (1 Cycle = 2 weeks), until DP, unacceptable toxicity, death, Investigator's decision or subject's refusal of further treatment.	

Reporting group values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)	Total	
Number of subjects	175	175	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 64.5 ± 11	 -	
Gender categorical Units: Subjects			
Female	77	77	
Male	98	98	

End points

End points reporting groups

Reporting group title	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)

Reporting group description:

Aflibercept 4 mg/kg followed by Irinotecan 180 mg/m^2 and Leucovorin 400 mg/m^2 at the same time followed by 5-FU 400 mg/m^2 followed by 5-FU 2400 mg/m^2 on Day 1 of each cycle (1 Cycle = 2 weeks), until DP, unacceptable toxicity, death, Investigator's decision or subject's refusal of further treatment.

Primary: Percentage of Subjects With Adverse Events (AEs)

End point title	Percentage of Subjects With Adverse Events (AEs)[1]

End point description:

Any untoward medical occurrence in a subject who received investigational medicinal product (IMP) was considered an AE without regard to possibility of causal relationship with this treatment. Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period. On-treatment period was defined as the time from the first dose of treatment to 30 days after the last dose of treatment (either Aflibercept or FOLFIRI). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subject with both serious and non-serious AEs.

End point type	Primary

End point timeframe:

Baseline upto 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 723 days)

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)			
Subject group type	Reporting group			
Number of subjects analysed	175			
Units: Percentage of subjects				
number (not applicable)				
Any TEAE	100			
Any serious TEAE	40.6			
Any serious related TEAE	21.1			
Any TEAE leading to death	9.1			
Any TEAE (permanent treatment discontinuation)	23.4			
Any TEAE (premature treatment discontinuation)	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Health Related Quality of Life (HRQL) European Organization for Research And Treatment For Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

End point title	Change from Baseline in Health Related Quality of Life (HRQL) European Organization for Research And Treatment For Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

End point description:

EORTC QLQ-C30 (version 3.0) was self-administered questionnaire containing 30 questions. First 28 questions were evaluated on 4-category scale (1=not at all, 2=a little, 3=quite a bit, 4=very much) for 5 functional scales (physical, emotional, cognitive, role & social), 3 symptoms scales (fatigue, nausea/vomiting & pain) and other single items. Last 2 questions were evaluated on overall health and quality of life (QOL) on 7-point category scale (1=very poor & 7=excellent). Baseline corresponded to last evaluable assessment before treatment administration; deterioration: change from baseline≤ -10 and improvement: change from baseline≥ 10.QLQ-C30 analysis population: subjects who signed informed consent form; had an evaluable QLQ-C30 questionnaire at baseline and at least one evaluable assessment post baseline and received at least part of a dose of study treatment. Here, n=number of subjects with available data at specified time-points & 99999=data not available for standard deviation.

End point type	Secondary

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle; and at end of treatment (30 days after last study treatment) (maximum exposure: 99 weeks)

End point values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)			
Subject group type	Reporting group			
Number of subjects analysed	152			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=148)	69.54 (± 18.97)			
At Cycle 3 (n=130)	-7.56 (± 19.78)			
At Cycle 5 (n=99)	-10.86 (± 19.76)			
At Cycle 7 (n=72)	-8.22 (± 20)			
At Cycle 9 (n=51)	-9.31 (± 19.34)			
At Cycle 11 (n=45)	-14.81 (± 21.24)			
At Cycle 13 (n=25)	-12.67 (± 24.31)			
At Cycle 15 (n=24)	-12.5 (± 18.22)			
At Cycle 17 (n=14)	-14.29 (± 15.82)			
At Cycle 19 (n=12)	-15.28 (± 11.7)			
At Cycle 21 (n=10)	-15.83 (± 19.82)			
At Cycle 23 (n=6)	-9.72 (± 20.01)			
At Cycle 25 (n=4)	-8.33 (± 6.8)			

At Cycle 27 (n=4)	-12.5 (± 15.96)			
At Cycle 29 (n=2)	-8.33 (± 11.79)			
At Cycle 31 (n=2)	-16.67 (± 0)			
At Cycle 33 (n=1)	0 (± 99999)			
At Cycle 35 (n=1)	0 (± 99999)			
At Cycle 37 (n=2)	-8.33 (± 11.79)			
At Cycle 39 (n=2)	-8.33 (± 11.79)			
At Cycle 41 (n=2)	-8.33 (± 11.79)			
At Cycle 43 (n=2)	-12.5 (± 5.89)			
At Cycle 45 (n=2)	-4.17 (± 17.68)			
At Cycle 47 (n=1)	0 (± 99999)			
At end of study treatment (n=73)	-11.19 (± 24.38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HRQL European-Quality of Life-5 Dimension Instrument-3 Levels (EQ-5D-3L) Index Score

End point title	Change From Baseline in HRQL European-Quality of Life-5 Dimension Instrument-3 Levels (EQ-5D-3L) Index Score

End point description:

EQ-5D was a standardized HRQL questionnaire consisting of EQ-5D descriptive system and Visual Analogue Scale (VAS). EQ-5D descriptive system comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression measured on 3 levels (no problem, some problems & severe problems) within a particular EQ-5D dimension. 5 dimensional 3-level system was converted into single index utility score. Possible values for single index utility score ranged from -0.594 (severe problems in all dimensions) to 1.0 (no problem in all dimensions) on scale where 1 represented best possible health state. EQ-5D analysis population: subjects who signed informed consent form, had an evaluable EQ-5D questionnaire at baseline and at least one evaluable assessment post baseline and received at least part of one dose of study treatment. Here, n = number of subjects with available data at specified time-points & 99999=data not available for standard deviation.

End point type	Secondary

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle; and at end of treatment (30 days after last study treatment) (maximum exposure: 99 weeks)

End point values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)			
Subject group type	Reporting group			
Number of subjects analysed	148			
Units: Units on a scale				
arithmetic mean (standard deviation)				

Baseline (n=148)	0.78 (± 0.21)			
At Cycle 3 (n=127)	-0.04 (± 0.23)			
At Cycle 5 (n=96)	-0.08 (± 0.25)			
At Cycle 7 (n=72)	-0.05 (± 0.2)			
At Cycle 9 (n=49)	-0.09 (± 0.23)			
At Cycle 11 (n=43)	-0.06 (± 0.2)			
At Cycle 13 (n=24)	-0.09 (± 0.14)			
At Cycle 15 (n=25)	-0.1 (± 0.16)			
At Cycle 17 (n=14)	-0.03 (± 0.1)			
At Cycle 19 (n=12)	-0.1 (± 0.12)			
At Cycle 21 (n=10)	-0.03 (± 0.18)			
At Cycle 23 (n=6)	-0.08 (± 0.15)			
At Cycle 25 (n=3)	0.04 (± 0.22)			
At Cycle 27 (n=3)	-0.09 (± 0.2)			
At Cycle 29 (n=2)	-0.18 (± 0.04)			
At Cycle 31 (n=1)	0 (± 99999)			
At Cycle 37 (n=1)	-0.15 (± 99999)			
At Cycle 39 (n=1)	0 (± 99999)			
At Cycle 41 (n=1)	0 (± 99999)			
At Cycle 43 (n=1)	0 (± 99999)			
At Cycle 45 (n=1)	0 (± 99999)			
At end of study treatment (n=71)	-0.2 (± 0.31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HRQL EQ-5D-3L VAS Score

End point title	Change From Baseline in HRQL EQ-5D-3L VAS Score

End point description:

EQ-5D VAS was used to record subject's rating for his/her current health-related quality of life state and captured on a vertical VAS (0-100), where 0 = worst imaginable health state and 100 = best imaginable health state. Baseline corresponded to last evaluable assessment before treatment administration. EQ-5D analysis population: subjects who signed informed consent form, had an evaluable EQ-5D questionnaire at baseline and at least one evaluable assessment post baseline and received at least part of one dose of study treatment. Here, n = number of subjects with available data at specified time-points & 99999=data not available for standard deviation.

End point type	Secondary

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle; and at end of treatment (30 days after last study treatment) (maximum exposure: 99 weeks)

End point values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)			
Subject group type	Reporting group			
Number of subjects analysed	148			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=125)	69.48 (± 19.1)			
At cycle 3 (n=94)	-6.23 (± 17.82)			
At cycle 5 (n=76)	-7.62 (± 17.23)			
At cycle 7 (n=57)	-7.79 (± 14.14)			
At cycle 9 (n=38)	-7.55 (± 16.12)			
At cycle 11 (n=36)	-8.67 (± 16.09)			
At cycle 13 (n=22)	-8.95 (± 17.56)			
At cycle 15 (n=22)	-12.41 (± 19.57)			
At cycle 17 (n=13)	-10.31 (± 17.44)			
At cycle 19 (n=10)	-15.7 (± 18.19)			
At cycle 21 (n=8)	-15.13 (± 19.87)			
At cycle 23 (n=5)	-8.8 (± 10.71)			
At cycle 25 (n=2)	-13 (± 4.24)			
At cycle 27 (n=3)	-15.67 (± 9.81)			
At cycle 29 (n=2)	-17.5 (± 3.54)			
At cycle 31 (n=1)	-15 (± 99999)			
At cycle 37 (n=1)	-15 (± 99999)			
At cycle 39 (n=1)	-15 (± 99999)			
At cycle 41 (n=1)	-15 (± 99999)			
At cycle 43 (n=1)	-15 (± 99999)			
At cycle 45 (n=1)	-15 (± 99999)			
At end of study treatment (n=55)	-13.05 (± 20.82)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 723) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during 'on-treatment period' (From the first dose of treatment to 30 days after the last dose of treatment [either aflibercept or FOLFIRI]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)

Reporting group description:

Aflibercept 4 mg/kg followed by Irinotecan 180 mg/m^2 and Leucovorin 400 mg/m^2 at the same time followed by 5-FU 400 mg/m^2 followed by 5-FU 2400 mg/m^2 on Day 1 of each cycle (1 Cycle = 2 weeks), until disease progression (DP), unacceptable toxicity, death, Investigator's decision or subject's refusal of further treatment (maximum exposure: Week 99).

Serious adverse events	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)		
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 175 (40.57%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected Neoplasm			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases To Central Nervous System			
subjects affected / exposed	2 / 175 (1.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Metastatic Pain			

subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Varicose Ulceration			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hepatectomy			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intraperitoneal Hyperthermic Chemotherapy			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Disease Progression			

subjects affected / exposed	9 / 175 (5.14%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 6			
Fatigue				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General Physical Health Deterioration				
subjects affected / exposed	8 / 175 (4.57%)			
occurrences causally related to treatment / all	6 / 9			
deaths causally related to treatment / all	1 / 2			
Influenza Like Illness				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	3 / 175 (1.71%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Priapism				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Pleural Effusion				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	2 / 175 (1.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	4 / 175 (2.29%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Pulmonary Oedema				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional State				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood Alkaline Phosphatase Increased				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Laparoscopy				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Injury, poisoning and procedural complications			
Head Injury			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebellar Ischaemia			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cerebrovascular Accident			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathy Peripheral			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile Neutropenia			

subjects affected / exposed	2 / 175 (1.14%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Vitreous Haemorrhage			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	3 / 175 (1.71%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Anal Fistula			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	8 / 175 (4.57%)		
occurrences causally related to treatment / all	9 / 9		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Fistula			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	2 / 175 (1.14%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal Obstruction				
subjects affected / exposed	3 / 175 (1.71%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Pancreatitis				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal Haemorrhage				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectourethral Fistula				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Small Intestinal Perforation				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Stomatitis				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	2 / 175 (1.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Tooth Loss				

subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic Failure			
subjects affected / exposed	2 / 175 (1.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Failure			
subjects affected / exposed	2 / 175 (1.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary Retention			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone Pain			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device Related Infection			

subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Wall Abscess				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device Related Sepsis				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia Infection				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 175 (1.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lung Infection				
subjects affected / exposed	2 / 175 (1.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pelvic Abscess				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Septic Shock				

subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Tooth Infection			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	2 / 175 (1.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 175 (98.29%)		
Investigations			
Weight Decreased			

subjects affected / exposed	68 / 175 (38.86%)		
occurrences (all)	77		
Vascular disorders			
Hypertension			
subjects affected / exposed	74 / 175 (42.29%)		
occurrences (all)	106		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	13 / 175 (7.43%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	32 / 175 (18.29%)		
occurrences (all)	44		
Neuropathy Peripheral			
subjects affected / exposed	19 / 175 (10.86%)		
occurrences (all)	19		
Paraesthesia			
subjects affected / exposed	9 / 175 (5.14%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	39 / 175 (22.29%)		
occurrences (all)	48		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	98 / 175 (56.00%)		
occurrences (all)	149		
Fatigue			
subjects affected / exposed	33 / 175 (18.86%)		
occurrences (all)	43		
Pyrexia			
subjects affected / exposed	14 / 175 (8.00%)		
occurrences (all)	15		
Gastrointestinal disorders			
Abdominal Pain Upper			

subjects affected / exposed	14 / 175 (8.00%)		
occurrences (all)	14		
Abdominal Pain			
subjects affected / exposed	36 / 175 (20.57%)		
occurrences (all)	45		
Diarrhoea			
subjects affected / exposed	121 / 175 (69.14%)		
occurrences (all)	246		
Constipation			
subjects affected / exposed	39 / 175 (22.29%)		
occurrences (all)	44		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	10 / 175 (5.71%)		
occurrences (all)	11		
Rectal Haemorrhage			
subjects affected / exposed	11 / 175 (6.29%)		
occurrences (all)	11		
Proctalgia			
subjects affected / exposed	10 / 175 (5.71%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	86 / 175 (49.14%)		
occurrences (all)	139		
Stomatitis			
subjects affected / exposed	83 / 175 (47.43%)		
occurrences (all)	122		
Vomiting			
subjects affected / exposed	47 / 175 (26.86%)		
occurrences (all)	61		
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	22 / 175 (12.57%)		
occurrences (all)	22		
Dyspnoea			

subjects affected / exposed	17 / 175 (9.71%)		
occurrences (all)	21		
Epistaxis			
subjects affected / exposed	43 / 175 (24.57%)		
occurrences (all)	49		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	36 / 175 (20.57%)		
occurrences (all)	39		
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	23 / 175 (13.14%)		
occurrences (all)	23		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	25 / 175 (14.29%)		
occurrences (all)	32		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 175 (5.71%)		
occurrences (all)	10		
Back Pain			
subjects affected / exposed	18 / 175 (10.29%)		
occurrences (all)	20		
Myalgia			
subjects affected / exposed	11 / 175 (6.29%)		
occurrences (all)	13		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	59 / 175 (33.71%)		
occurrences (all)	71		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported