EU Clinical Trials Register

Clinical trial results:
A Multicenter, Single arm, Open Label Clinical Trial to Evaluate the Safety and Health-Related Quality of Life of Aflibercept in Patients with Metastatic Colorectal Cancer (mCRC) Previously Treated with an Oxaliplatin-Containing Regimen

Summary

EudraCT number	2011-005724-17
Trial protocol	BE SE DK FI DE NL IT ES IE CZ SI HU
Global end of trial date	31 January 2017

Results information

Result version number	v1
This version publication date	15 February 2018
First version publication date	15 February 2018

Trial information

Trial identification

Sponsor protocol code	AFLIBC06097

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01571284
WHO universal trial number (UTN)	U1111-1125-8949

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette , Chilly-Mazarin, France, 91380
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	14 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide mCRC subjects (similar to the subjects evaluated in the VELOUR [EFC10262] phase III trial) and investigators with access to aflibercept, prior to its marketing authorization and/or commercial availability and to document the aflibercept overall safety in this subject population.

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	30 May 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	Brazil: 41
Country: Number of subjects enrolled	Canada: 49
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Thailand: 111
Country: Number of subjects enrolled	Turkey: 40
Country: Number of subjects enrolled	United Kingdom: 54
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Spain: 77
Country: Number of subjects enrolled	Sweden: 5

Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 42
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Italy: 200
Worldwide total number of subjects	779
EEA total number of subjects	471

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)	475
From 65 to 84 years	303
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 151 sites in 23 countries. A total of 798 subjects were screened between 30 May 2012 and 03 January 2015, out of which 781 subjects were enrolled and 779 subjects were 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]). 403 subjects with disease progression (DP) and 209 with adverse events were considered as completed.

Period 1

Period 1 title	Overall (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 IV infusion over 60 minutes followed by Irinotecan 180 mg/m^2 IV infusion over 90 minutes and Leucovorin 400 mg/m^2 IV infusion over 120 minutes at the same time followed by 5-FU 400 mg/m^2 IV bolus over 2-4 minutes followed by 5-FU 2400 mg/m^2 continuous IV infusion over 46 hours 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	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aflibercept (referred to also as VEGF-Trap or AVE0005) was to be provided as a 25 mg/mL concentrate solution for infusion. Aflibercept for intravenous (IV) administration, in 5 mM sodium phosphate, 5 mM sodium citrate, 100 mM sodium chloride, 20% (w/v) sucrose, and 0.1% (w/v) polysorbate 20, pH 6.0, is formulated as a sterile, non-pyrogenic, colorless to pale yellow colored, 25 mg/mL solution, packaged in a type 1, clear borosilicate glass vial closed with a flanged cap with tear-off lid and inserted sealing disc, Flurotec® coated. 100 mg/4 mL in a 5 mL vial and 200 mg/8 mL in a 10 mL vial Sealed, sterile, single-use vials at a concentration of 25 mg/mL were to be supplied.

Number of subjects in period 1	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)
Started	779
Safety population	779
Completed	612
Not completed	167
Other than specified above	80
Subject's decision	84
Lost to follow-up	3

Baseline characteristics

Reporting groups

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

Reporting group description:

Aflibercept 4 mg/kg IV infusion over 60 minutes followed by Irinotecan 180 mg/m^2 IV infusion over 90 minutes and Leucovorin 400 mg/m^2 IV infusion over 120 minutes at the same time followed by 5-FU 400 mg/m^2 IV bolus over 2-4 minutes followed by 5-FU 2400 mg/m^2 continuous IV infusion over 46 hours 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	779	779	
Age categorical			
Units: Subjects			
Age continuous			
Here Number analyzed = subjects analyzed for specified categories			
Units: years			
arithmetic mean	60.3		
standard deviation	± 11.0	-	
Gender categorical			
Units: Subjects			
Female	314	314	
Male	465	465	
Race/Ethnicity, Customized			
Units: Subjects			
White	631	631	
Black or African	8	8	
American Asian	121	121	
Other	19	19	
Location of Primary Tumor			
Units: Subjects			
Colon	406	406	
Recto sigmoid	171	171	
Rectum	200	200	
Other	2	2	
Histology			
Units: Subjects			
Adenocarcinoma	778	778	
Other	1	1	
Any Relevant Medical/Surgical History			
Units: Subjects			
Any Relevant Medical/Surgical History	640	640	
Unknown	139	139	
History of Thrombovascular Event and/or Presence of Cardiovascular Risk Factor			

Units: Subjects			
History of Thrombovascular Event and/or Presence o	424	424	
Unknown	355	355	
Location of Primary Tumor			
Units: Subjects			
Colon	406	406	
Recto sigmoid	171	171	
Rectum	200	200	
Other	2	2	
Histology			
Units: Subjects			
Adenocarcinoma	778	778	
Other	1	1	
Organs with Metastases at Baseline			
Units: Subjects			
= 1	358	358	
>1	421	421	
Eastern Cooperative Oncology Group Performance Status (ECOG PS)			
Measure Description: ECOG PS is used to assess how the disease affects the daily living abilities of the subject. It ranges on the scale from 0-5 (0= normal activity; 1= symptoms but ambulatory; 2= in bed for less than (<) 50 percent (%) of the time; 3= in bed for greater than (>) 50% of the time; 4= 100% bedridden; 5= dead.			
Units: Subjects			
ECOG PS = 0	484	484	
ECOG PS = 1	292	292	
Missing	3	3	
Body Surface Area (BSA)			
Units: m^2			
arithmetic mean	1.80		
standard deviation	± 0.23	-	
Systolic Blood Pressure			
Data for Systolic Blood Pressure is reported for a total of 776 subjects.			
Units: mmHg			
arithmetic mean	126.4		
standard deviation	± 13.4	-	
Diastolic Blood Pressure			
Data for Diastolic Blood Pressure is reported for a total of 776 subjects.			
Units: mmHg			
arithmetic mean	76.4		
standard deviation	± 9.0	-	
Time From Initial Histological Diagnosis till Baseline Visit			
Units: Months			
arithmetic mean	19.1		
standard deviation	± 17.2	-	

End points

End points reporting groups

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

Aflibercept 4 mg/kg IV infusion over 60 minutes followed by Irinotecan 180 mg/m^2 IV infusion over 90 minutes and Leucovorin 400 mg/m^2 IV infusion over 120 minutes at the same time followed by 5-FU 400 mg/m^2 IV bolus over 2-4 minutes followed by 5-FU 2400 mg/m^2 continuous IV infusion over 46 hours 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: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)[1]
End point description:	

Any untoward medical occurrence in a subject who received investigational medicinal product (IMP) was considered an adverse event (AE) without regard to possibility of causal relationship with this treatment.A serious adverse event: 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 subjects with both serious and non-serious AEs. National Cancer Institute Common Terminology Criteria (NCI-CTCAE) Version 4.03 was used to assess severity (Grade 1=mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling) of AEs. Safety population defined as the subjects who signed the informed consent form and received at least one dose of study treatment.

End point type	Primary
End point timeframe:	

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

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	779			
Units: Subjects				
Any TEAE (All Grades)	769			
Any TEAEs (Grades 3-4)	609			
Any serious TEAE	272			
Any serious related TEAE	159			
Any TEAE leading to death	47			
Any TEAE (permanent treatment discontinuation)	208			
Any TEAE (premature treatment discontinuation)	104			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Hematological Parameters During Treatment

End point title	Number of Subjects With Abnormal Hematological Parameters During Treatment[2]

End point description:

Abnormal hematological parameters included: anaemia, thrombocytopenia, leukopenia and neutropenia. Number of subjects with each of these parameters were analyzed by grades (All Grades and Grades 3-4 as per NCI CTCAE (Version 4.03), where Grade 1=mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. All Grades included Grades 1-4. Safety population. Here, 'n' signifies number of subjects with available data for specified categories.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[2] - 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	779			
Units: Subjects				
Anaemia: All Grades (n= 744)	535			
Anaemia: Grades 3-4 (n= 744)	14			
Thrombocytopenia: All Grades (n= 745)	293			
Thrombocytopenia: Grades 3-4 (n= 745)	13			
Leukopenia: All Grades (n =745)	532			
Leukopenia: Grades 3-4 (n =745)	72			
Neutropenia: All Grades (n= 744)	450			
Neutropenia: Grades 3-4 (n= 744)	227			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With International Normalized Ratio (INR)

End point title	Number of Subjects With International Normalized Ratio

End point description:

The INR is a derived measure of the prothrombin time. The INR is the ratio of a subject's prothrombin time to a normal control sample. Normal range (without anti coagulation therapy): 0.8-1.2; Targeted range (with anti coagulation therapy) 2.0-3.0. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[3] - 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	779			
Units: subjects				
INR<1.5 (n= 110)	106			
INR>=1.5 to <3 (n =110)	0			
INR>=3 to <5 (n =110)	2			
INR>=5 (n =110)	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Electrolytes Parameters

End point title	Number of Subjects With Abnormal Electrolytes Parameters[4]

End point description:

Abnormal electrolytes parameters included: hyponatremia, hypernatremia, hypocalcemia, hypercalcemia, hypokalemia, and hyperkalemia. Number of subjects with each of these parameters were analyzed by grades (All Grades and Grades 3-4 as per NCI CTCAE Version 4.03, where Grade 1=mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. All Grades included Grades 1-4. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[4] - 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	779			
Units: subjects				
Hyponatremia: All Grades (n= 736)	181			
Hyponatremia: Grades 3-4 (n= 736)	32			
Hypernatremia: All Grades (n= 736)	75			

Hypernatremia: Grades 3-4 (n=736)	1			
Hypocalcemia: All Grades (682)	213			
Hypocalcemia: Grades 3-4 (682)	5			
Hypercalcemia: All Grades (682)	52			
Hypercalcemia: Grades 3-4 (682)	2			
Hypokalemia: All Grades (734)	121			
Hypokalemia: Grades 3-4 (734)	16			
Hyperkalemia: All Grades (734)	166			
Hyperkalemia: Grades 3-4 (734)	10			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Renal and Liver Function Parameters

End point title	Number of Subjects With Abnormal Renal and Liver Function Parameters[5]

End point description:

Renal and liver function parameters included: creatinine, hyperbilirubinemia, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase. Number of subjects with each of these parameters were analyzed by grades (All Grades and Grades 3-4) as per NCI CTCAE version 4.03, where Grade 1=mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. All Grades included Grades 1-4. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[5] - 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	779			
Units: subjects				
Creatinine: All Grades (n= 737)	161			
Creatinine: Grades 3-4 (n= 737)	2			
Hyperbilirubinemia: All Grades (n= 734)	130			
Hyperbilirubinemia: Grades 3-4 (n= 734)	9			
AST: All Grades (n= 727)	342			
AST: Grades 3-4 (n= 727)	12			
ALT: All Grades (n= 736)	270			
ALT: Grades 3-4 (n= 736)	10			
Alkaline phosphatase: All Grades (n= 733)	465			
Alkaline phosphatase: Grades 3-4 (n= 733)	23			

Statistical analyses

No statistical analyses for this end point

Primary: Creatinine Clearance of Aflibercept Plus FOLFIRI

End point title	Creatinine Clearance of Aflibercept Plus FOLFIRI[6]

End point description:

Creatinine clearance is a measure of kidney function. Creatinine clearance rate is the volume of blood plasma that is cleared of creatinine by the kidneys per unit time. Creatinine clearance can be measured directly or estimated using established formulas. For this study, the creatinine clearance was calculated using the Cockroft-Gault or Modification of Diet in Renal Disease (MDRD). Safety population. Here, subjects analysed = subjects evaluable for this end point.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[6] - 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	312			
Units: mL/min				
arithmetic mean (standard deviation)	71.4 (± 29.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Other Abnormal Biochemistry Parameters

End point title	Number of Subjects With Other Abnormal Biochemistry Parameters[7]

End point description:

Other abnormal biochemistry parameters included: hypoglycemia, hyperglycemia and hypoalbuminemia. Number of subjects with each of these parameters were analyzed by grades (All Grades and Grades 3-4) as per NCI CTCAE Version 4.03, where Grade 1= mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. All Grades included Grades 1-4. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever

comes last) (maximum exposure: 214 weeks)

Notes:

[7] - 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	779			
Units: subjects				
Hypoglycemia: All Grades (n= 725)	90			
Hypoglycemia: Grades 3-4 (n= 725)	6			
Hyperglycemia: All Grades (n= 725)	403			
Hyperglycemia: Grades 3-4 (n= 725)	30			
Hypoalbuminemia: All Grades (n= 689)	241			
Hypoalbuminemia: Grades 3-4 (n= 689)	6			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Non-Gradable Biochemistry Parameters

End point title	Number of Subjects With Abnormal Non-Gradable Biochemistry Parameters[8]

End point description:

Non-gradeable biochemistry parameters included; chloride, urea, total protein, blood urea nitrogen (BUN) and lactate dehydrogenase (LDH). Number of subjects with <lower limit of normal ranges (LLN) and >upper limit of normal ranges (ULN) for each of these parameters were reported. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[8] - 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	779			
Units: subjects				
Chloride<LLN (n= 711)	135			
Chloride>ULN (n= 711)	217			
BUN<LLN (n= 258)	41			
BUN>ULN (n= 258)	83			

UREA<LLN (n= 591)	60
UREA>ULN (n= 591)	250
LDH<LLN (n= 723)	79
LDH>ULN (n= 723)	423
Total proteins<LLN (n= 711)	162
Total proteins>ULN (n= 711)	77

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Proteinuria Events

End point title	Number of Subjects With Proteinuria Events[9]

End point description:

Proteinuria is defined as the ratio of protein to creatinine. Number of subjects with proteinuria were analyzed by grades (Grades 1, 2, 3 ,4) as per NCI CTCAE Version 4.03 where Grade 1= mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening/disabling. Safety population.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[9] - 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	779			
Units: subjects				
Grade 1	286			
Grade 2	123			
Grade 3	54			
Grade 4	5			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Proteinuria Grade >=2

End point title	Number of Subjects With Proteinuria Grade >=2[10]

End point description:

Proteinuria is defined as the ratio of protein to creatinine. Number of subjects with proteinuria grade >=2 (graded as per NCI CTCAE Version 4.03), where Grade>=2 represents moderate to life-threatening/disabling event. Safety population.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[10] - 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	779			
Units: subjects	182			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Urinary Protein-Creatinine Ratio (UPCR)

End point title	Number of Subjects With Urinary Protein-Creatinine Ratio (UPCR)[11]

End point description:

Urinary protein creatinine ratio (UPCR) corresponds to the ratio of the urinary protein and urinary creatinine concentration (expressed in mg/dL). This ratio provides an accurate quantification of 24-hours urinary protein excretion. There is a high correlation between morning UPCR and 24-hour proteinuria in subjects with normal or reduced renal functions. Normal ratio is < or = 1. Safety population. Here 'n' signifies number of subjects with available data for specified categories.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[11] - 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	779			
Units: subjects				
UPCR<=1 (n= 367)	265			
UPCR>=1 to <=2 (n= 367)	51			
UPCR>=2 to <=3 (n= 367)	24			
UPCR>3 (n= 367)	27			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Proteinuria (Grade>=2) Concomitant With Hematuria and /or Hypertension

End point title	Number of Subjects With Proteinuria (Grade>=2) Concomitant With Hematuria and /or Hypertension[12]

End point description:

Proteinuria is defined as the presence of excess proteins in the urine (assessed either by spot sample, dipstick/ urine protein or 24 hour urine collection). Hematuria is defined as the presence of blood in urine (positive dipstick for RBC or reported AE). Number of subjects with proteinuria grade >=2 (graded as per NCI CTCAE Version 4.03), where Grade>=2 represents moderate to life-threatening/disabling event.Hypertension (high blood pressure) is defined as having a blood pressure reading of more than 140/90 mmHg over a number of weeks. Safety population.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[12] - 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	779			
Units: subjects				
Proteinuria with hematuria	72			
Proteinuria with hypertension	4			
Proteinuria with hematuria and hypertension	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Cycle Delay and/or Dose Modification

End point title	Number of Subjects With Cycle Delay and/or Dose

End point description:

A theoretical cycle is a 2 week period i.e. 14 days. A cycle is delayed if duration of previous cycle is greater than 14+2 days ; dose modification includes dose reduction and dose omission. Safety population defined as the subjects who signed the informed consent form and received at least one dose of study treatment.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last treatment administration (either Aflibercept or FOLFIRI whichever comes last) (maximum exposure: 214 weeks)

Notes:

[13] - 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	779			
Units: Subjects				
No delay and no dose modification	119			
Any delay and/or dose modification	660			
Delay only	163			
Delay and Aflibercept modified	39			
Delay and FOLFIRI modified	308			
Delay and Aflibercept and Folfiri modified	97			
Only Aflibercept modified	5			
Only FOLFIRI modified	43			
Both Aflibercept and FOLFIRI modified	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean 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 Score): Global Health Status

End point title	Mean 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 Score): Global Health Status

End point description:

EORTC-QLQ-C30: cancer-specific instrument with 30 questions(Q). First 28 Q used 4-point scale(S)(1=not at all,2=a little,3=quite a bit,4=very much)for evaluating 5 functional S(physical,role,emotional,cognitive,social),3 symptom S (fatigue,nausea/vomiting,pain) & other single items. For each item,high score=high level symptomatology.Last 2Q=subject's assessment of overall health & quality of life (qol) on 7-point S(1=very poor to 7=excellent).EORTC QLQ-C30 observed values & change from baseline(B) for global health status (scoring of Q 29 & 30) & 5 functional S,3 symptom S & other single items (scoring of Q1 to 28). Answers converted into grading S, with values between 0 & 100. High score=favourable outcome with best qol for subject. EORTC QLQ-C30 analysis population:subjects who signed informed consent form; had evaluable QLQ-C30 questionnaire at B & >=1 evaluable assessment post B & received at least part of 1 dose of study treatment.'n'= subjects analysed at specified time-points.

End point type	Secondary

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at the end of treatment (EOT) (within 30 days of last treatment) (maximum exposure: 214 weeks)

End point values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)			
Subject group type	Reporting group			
Number of subjects analysed	636			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 630)	68.61 (± 20.48)			
Change at Cycle 3 (n= 549)	-3.34 (± 18.83)			
Change at Cycle 5 (n= 429)	-4.70 (± 18.89)			
Change at Cycle 7 (n= 344)	-3.63 (± 22.02)			
Change at Cycle 9 (n= 273)	-3.97 (± 21.31)			
Change at Cycle 11 (n= 232)	-5.85 (± 22.26)			
Change at Cycle 13 (n= 151)	-2.26 (± 21.69)			
Change at Cycle 15 (n= 123)	-3.05 (± 22.46)			
Change at Cycle 17 (n= 85)	-1.18 (± 22.50)			
Change at Cycle 19 (n= 60)	-2.36 (± 22.92)			
Change at Cycle 21 (n= 45)	-5.56 (± 23.77)			
Change at Cycle 23 (n= 34)	-6.86 (± 19.94)			
Change at Cycle 25 (n= 29)	-8.05 (± 16.89)			
Change at Cycle 27 (n= 23)	-10.14 (± 17.58)			
Change at Cycle 29 (n= 20)	-8.33 (± 14.05)			
Change at Cycle 31 (n= 15)	-9.44 (± 16.92)			
Change at Cycle 33 (n= 11)	-11.36 (± 21.82)			
Change at Cycle 35 (n =10)	-5.83 (± 20.81)			
Change at EOT (n= 340)	-8.82 (± 23.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in HRQL EORTC QLQ-C30 Score: Functional Scales

End point title	Mean Change From Baseline in HRQL EORTC QLQ-C30 Score: Functional Scales

End point description:

EORTC-QLQ-C30: cancer-specific instrument with 30 questions (Q) for evaluation of new chemotherapy & provides an assessment of subject reported outcome dimensions. First 28 Q used 4-point scale(1=not at all,2=a little,3=quite a bit,4=very much)for evaluating 5 functional scales (physical,role,emotional,cognitive,social), 3 symptom scales (fatigue,nausea/vomiting,pain) & other single items. For each item,high score=high level of symptomatology/problem. Last 2 Q=subject's assessment of overall health & quality of life, coded on 7-point scale (1=very poor to 7=excellent). EORTC QLQ-C30 observed values & change from baseline for global health status (scoring of Q 29 & 30) & 5 functional scales, 3 symptom scales & other single items (scoring of Q 1 to 28).Answers were converted into grading scale, with values between 0 & 100. High score=favourable outcome with a best quality of life for subject. EORTC QLQ-C30 analysis population.'n' signifies =subjects analysed at

End point type	Secondary

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at EOT (within 30 days of last treatment) (maximum exposure: 214 weeks)

End point values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)			
Subject group type	Reporting group			
Number of subjects analysed	636			
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical - Baseline (n= 634)	81.79 (± 19.41)			
Physical - Change at Cycle 3 (n= 551)	-3.73 (± 15.15)			
Physical - Change at Cycle 5 (n= 439)	-3.95 (± 15.22)			
Physical - Change at Cycle 7 (n= 342)	-4.62 (± 16.23)			
Physical - Change at Cycle 9 (n= 275)	-4.36 (± 15.79)			
Physical - Change at Cycle 11 (n= 235)	-6.99 (± 17.89)			
Physical - Change at Cycle 13 (n= 154)	-4.99 (± 16.17)			
Physical - Change at Cycle 15 (n= 122)	-3.54 (± 15.99)			
Physical - Change at Cycle 17 (n= 87)	-5.10 (± 16.20)			
Physical - Change at Cycle 19 (n= 61)	-5.68 (± 16.23)			
Physical - Change at Cycle 21 (n= 46)	-5.70 (± 13.01)			
Physical - Change at Cycle 23 (n =36)	-7.87 (± 14.38)			
Physical - Change at Cycle 25 (n= 29)	-5.75 (± 12.18)			
Physical - Change at Cycle 27 (n= 23)	-6.59 (± 11.64)			
Physical - Change at Cycle 29 (n= 20)	-7.67 (± 11.09)			
Physical - Change at Cycle 31 (n= 15)	-9.33 (± 14.65)			
Physical - Change at Cycle 33 (n= 11)	-5.45 (± 9.81)			

Physical - Change at Cycle 35 (n= 10)	-10.00 (± 13.05)			
Physical - Change at EOT (n= 341)	-11.16 (± 21.65)			
Role - Baseline (n= 633)	79.91 (± 26.25)			
Role - Change at Cycle 3 (n= 551)	-6.26 (± 25.22)			
Role - Change at Cycle 5 (n= 442)	-5.66 (± 23.26)			
Role - Change at Cycle 7 (n= 342)	-6.68 (± 24.29)			
Role - Change at Cycle 9 (n= 275)	-6.55 (± 23.95)			
Role - Change at Cycle 11 (n= 234)	-8.76 (± 26.35)			
Role - Change at Cycle 13 (n= 154)	-7.36 (± 23.41)			
Role - Change at Cycle 15 (n= 123)	-7.18 (± 21.98)			
Role - Change at Cycle 17 (n= 87)	-9.58 (± 22.54)			
Role - Change at Cycle 19 (n= 61)	-9.84 (± 22.44)			
Role - Change at Cycle 21 (n= 46)	-9.78 (± 18.11)			
Role - Change at Cycle 23 (n= 36)	-10.65 (± 18.32)			
Role - Change at Cycle 25 (n= 29)	-10.92 (± 17.97)			
Role - Change at Cycle 27 (n= 23)	-10.14 (± 17.22)			
Role - Change at Cycle 29 (n= 20)	-10.83 (± 17.33)			
Role - Change at Cycle 31 (n= 15)	-14.44 (± 18.76)			
Role - Change at Cycle 33 (n= 11)	-15.15 (± 15.73)			
Role - Change at Cycle 35 (n= 10)	-15.00 (± 16.57)			
Role - Change at EOT (n= 340)	-12.11 (± 28.22)			
Emotional - Baseline (n= 634)	78.96 (± 20.60)			
Emotional - Change at Cycle 3 (n= 553)	1.14 (± 19.95)			
Emotional - Change at Cycle 5 (n =436)	0.74 (± 19.32)			
Emotional - Change at Cycle 7 (n= 344)	1.58 (± 20.91)			
Emotional - Change at Cycle 9 (n= 275)	1.69 (± 21.38)			
Emotional - Change at Cycle 11 (n= 235)	0.08 (± 20.40)			
Emotional - Change at Cycle 13 (n= 152)	0.93 (± 20.08)			
Emotional - Change at Cycle 15 (n= 124)	2.51 (± 20.23)			
Emotional - Change at Cycle 17 (n= 87)	2.91 (± 18.23)			
Emotional - Change at Cycle 19 (n= 60)	1.39 (± 17.60)			
Emotional - Change at Cycle 21 (n= 44)	0.06 (± 17.86)			
Emotional - Change at Cycle 23 (n= 35)	1.75 (± 19.29)			
Emotional - Change at Cycle 25 (n= 29)	4.98 (± 15.86)			
Emotional - Change at Cycle 27 (n= 23)	1.57 (± 17.64)			

Emotional - Change at Cycle 29 (n= 20)	2.64 (± 17.88)				
Emotional - Change at Cycle 31 (n= 15)	1.30 (± 17.78)				
Emotional - Change at Cycle 33 (n= 11)	0.25 (± 3.82)				
Emotional - Change at Cycle 35 (n= 10)	-0.00 (± 5.56)				
Emotional - Change at EOT (n= 345)	-2.87 (± 22.52)				
Cognitive - Baseline (n= 635)	86.90 (± 19.26)				
Cognitive - Change at Cycle 3 (n= 555)	-1.77 (± 16.92)				
Cognitive - Change at Cycle 5 (n= 437)	-1.87 (± 16.58)				
Cognitive - Change at Cycle 7 (n= 343)	-1.99 (± 19.71)				
Cognitive - Change at Cycle 9 (n= 275)	-2.18 (± 20.17)				
Cognitive - Change at Cycle 11 (n= 234)	-4.27 (± 20.29)				
Cognitive - Change at Cycle 13 (n= 153)	-2.83 (± 17.40)				
Cognitive - Change at Cycle 15 (n= 124)	-2.28 (± 19.40)				
Cognitive - Change at Cycle 17 (n= 87)	-3.45 (± 19.38)				
Cognitive - Change at Cycle 19 (n= 60)	-5.00 (± 22.19)				
Cognitive - Change at Cycle 21 (n= 45)	-5.56 (± 16.28)				
Cognitive - Change at Cycle 23 (n= 35)	-5.71 (± 14.54)				
Cognitive - Change at Cycle 25 (n= 29)	-6.90 (± 21.14)				
Cognitive - Change at Cycle 27 (n= 23)	-5.80 (± 16.37)				
Cognitive - Change at Cycle 29 (n= 20)	-6.67 (± 18.26)				
Cognitive - Change at Cycle 31 (n= 15)	-5.56 (± 15.00)				
Cognitive - Change at Cycle 33 (n= 11)	-10.61 (± 17.12)				
Cognitive - Change at Cycle 35 (n= 10)	-11.67 (± 13.72)				
Cognitive- Change at EOT (n= 345)	-4.98 (± 22.67)				
Social - Baseline (n= 634)	80.57 (± 24.68)				
Social - Change at Cycle 3 (n= 554)	-2.05 (± 22.83)				
Social - Change at Cycle 5 (n= 437)	-2.86 (± 21.60)				
Social - Change at Cycle 7 (n= 345)	-4.78 (± 23.65)				
Social - Change at Cycle 9 (n= 274)	-4.56 (± 23.84)				
Social - Change at Cycle 11 (n= 235)	-7.09 (± 24.83)				
Social - Change at Cycle 13 (n= 153)	-5.56 (± 24.03)				
Social - Change at Cycle 15 (n= 124)	-6.18 (± 23.23)				

Social - Change at Cycle 17 (n= 87)	-5.56 (± 22.69)				
Social - Change at Cycle 19 (n= 60)	-5.28 (± 22.02)				
Social - Change at Cycle 21 (n= 45)	-5.56 (± 21.61)				
Social - Change at Cycle 23 (n= 35)	-7.62 (± 17.78)				
Social - Change at Cycle 25 (n= 29)	-4.60 (± 18.31)				
Social - Change at Cycle 27 (n= 23)	-2.17 (± 17.63)				
Social - Change at Cycle 29 (n= 20)	-5.00 (± 18.81)				
Social - Change at Cycle 31 (n= 15)	-7.78 (± 25.09)				
Social - Change at Cycle 33 (n= 11)	-1.52 (± 17.41)				
Social - Change at Cycle 35 (n= 10)	-1.67 (± 14.59)				
Social - Change at EOT (n= 344)	-9.01 (± 26.23)				

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HRQL EORTC QLQ-C30 Score: Symptom Scales

End point title	Change From Baseline in HRQL EORTC QLQ-C30 Score: Symptom Scales

End point description:

EORTC-QLQ-C30:cancer-specific instrument with 30 questions (Q) for evaluation of new chemotherapy & provides an assessment of subjects reported outcome dimensions. First 28 Q used 4-point scale(1=not at all,2=a little,3=quite a bit,4=very much) for evaluating 5 functional scales (physical,role,emotional,cognitive,social), 3 symptom scales (fatigue,nausea/vomiting,pain) & other single items. For each item,high score=high level of symptomatology/problem. Last 2 Q=subject's assessment of overall health & quality of life, coded on 7-point scale (1=very poor to 7=excellent). EORTC QLQ-C30 observed values & change from baseline for global health status (scoring of Q 29 & 30) & 5 functional scales, 3 symptom scales & other single items (scoring of Q 1 to 28). Answers were converted into grading scale, with values between 0 and 100. A high score=favorable outcome with a best quality of life for subject. EORTC QLQ-C30 analysis population. Here, 'n'=subjects analysed at

End point type	Secondary

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at EOT (within 30 days of last treatment) (maximum exposure: 214 weeks)

End point values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)				
Subject group type	Reporting group				
Number of subjects analysed	636				
Units: units on a scale					

arithmetic mean (standard deviation)					
Fatigue - Baseline (n= 633)	29.16 (± 23.48)				
Fatigue - Change at Cycle 3 (n =551)	7.35 (± 21.62)				
Fatigue - Change at Cycle 5 (n= 443)	8.40 (± 21.88)				
Fatigue - Change at Cycle 7 (n= 344)	9.54 (± 22.60)				
Fatigue - Change at Cycle 9 (n= 276)	7.89 (± 21.80)				
Fatigue - Change at Cycle 11 (n= 235)	11.30 (± 23.73)				
Fatigue - Change at Cycle 13 (n= 154)	8.33 (± 21.72)				
Fatigue - Change at Cycle 15 (n= 123)	7.41 (± 22.38)				
Fatigue - Change at Cycle 17 (n= 87)	6.70 (± 21.25)				
Fatigue - Change at Cycle 19 (n= 61)	8.93 (± 19.83)				
Fatigue - Change at Cycle 21 (n= 46)	10.39 (± 17.90)				
Fatigue - Change at Cycle 23 (n= 36)	10.80 (± 18.49)				
Fatigue - Change at Cycle 25 (n= 29)	7.66 (± 19.94)				
Fatigue - Change at Cycle 27 (n= 23)	9.66 (± 18.74)				
Fatigue - Change at Cycle 29 (n= 20)	11.67 (± 18.55)				
Fatigue - Change at Cycle 31 (n= 15)	14.07 (± 21.61)				
Fatigue - Change at Cycle 33 (n= 11)	15.15 (± 21.81)				
Fatigue - Change at Cycle 35 (n= 10)	14.44 (± 18.92)				
Fatigue - Change at EOT (n= 343)	12.31 (± 25.56)				
Nausea and Vomiting - Baseline (n= 635)	5.88 (± 13.99)				
Nausea and Vomiting - Change at Cycle 3 (n= 554)	6.68 (± 19.81)				
Nausea and Vomiting - Change at Cycle 5 (n= 442)	6.98 (± 19.79)				
Nausea and Vomiting - Change at Cycle 7 (n= 343)	6.61 (± 18.07)				
Nausea and Vomiting - Change at Cycle 9 (n= 277)	6.20 (± 19.68)				
Nausea and Vomiting - Change at Cycle 11 (n= 236)	8.97 (± 19.83)				
Nausea and Vomiting - Change at Cycle 13 (n= 154)	6.82 (± 14.71)				
Nausea and Vomiting - Change at Cycle 15 (n= 124)	6.85 (± 16.33)				
Nausea and Vomiting - Change at Cycle 17 (n= 87)	3.45 (± 15.49)				
Nausea and Vomiting - Change at Cycle 19 (n= 61)	6.56 (± 14.04)				
Nausea and Vomiting - Change at Cycle 21 (n= 46)	3.99 (± 14.14)				
Nausea and Vomiting - Change at Cycle 23 (n= 36)	7.87 (± 10.90)				
Nausea and Vomiting - Change at Cycle 25 (n= 29)	4.02 (± 8.52)				
Nausea and Vomiting - Change at Cycle 27 (n= 23)	7.25 (± 11.04)				
Nausea and Vomiting - Change at Cycle 29 (n= 20)	1.67 (± 5.13)				

Nausea and Vomiting - Change at Cycle 31 (n= 15)	13.33 (± 28.31)			
Nausea and Vomiting - Change at Cycle 33 (n= 11)	3.03 (± 6.74)			
Nausea and Vomiting - Change at Cycle 35 (n= 10)	3.33 (± 7.03)			
Nausea and Vomiting - Change at EOT (n= 344)	6.64 (± 21.11)			
Pain - Baseline (n= 636)	20.47 (± 25.08)			
Pain - Change at Cycle 3 (n= 554)	2.68 (± 25.02)			
Pain - Change at Cycle 5 (n= 444)	2.52 (± 23.48)			
Pain - Change at Cycle 7 (n= 345)	3.00 (± 24.98)			
Pain - Change at Cycle 9 (n= 276)	2.72 (± 24.45)			
Pain - Change at Cycle 11 (n= 236)	6.64 (± 23.68)			
Pain - Change at Cycle 13 (n= 155)	5.16 (± 19.79)			
Pain - Change at Cycle 15 (n= 124)	7.26 (± 21.91)			
Pain - Change at Cycle 17 (n= 87)	9.39 (± 22.97)			
Pain - Change at Cycle 19 (n= 61)	8.74 (± 22.28)			
Pain - Change at Cycle 21 (n= 46)	7.25 (± 18.14)			
Pain - Change at Cycle 23 (n= 36)	8.33 (± 19.31)			
Pain - Change at Cycle 25 (n= 29)	5.75 (± 21.02)			
Pain - Change at Cycle 27 (n= 23)	5.07 (± 17.72)			
Pain - Change at Cycle 29 (n= 20)	4.17 (± 16.11)			
Pain - Change at Cycle 31 (n= 15)	10.00 (± 23.40)			
Pain - Change at Cycle 33 (n= 11)	7.58 (± 22.81)			
Pain - Change at Cycle 35 (n= 10)	6.67 (± 21.08)			
Pain - Change at EOT (n= 347)	10.85 (± 28.99)			
Dyspnoea - Baseline (n= 627)	13.45 (± 22.01)			
Dyspnoea - Change at Cycle 3 (n= 542)	3.63 (± 22.96)			
Dyspnoea - Change at Cycle 5 (n= 435)	5.75 (± 24.06)			
Dyspnoea - Change at Cycle 7 (n= 339)	6.98 (± 24.47)			
Dyspnoea - Change at Cycle 9 (n= 271)	6.89 (± 24.38)			
Dyspnoea - Change at Cycle 11 (n= 232)	8.19 (± 26.59)			
Dyspnoea - Change at Cycle 13 (n= 152)	6.36 (± 25.37)			
Dyspnoea - Change at Cycle 15 (n= 121)	3.58 (± 24.65)			
Dyspnoea - Change at Cycle 17 (n= 84)	5.16 (± 24.54)			
Dyspnoea - Change at Cycle 19 (n= 59)	6.78 (± 26.82)			
Dyspnoea - Change at Cycle 21 (n= 44)	3.79 (± 22.98)			
Dyspnoea - Change at Cycle 23 (n= 33)	4.04 (± 20.00)			
Dyspnoea - Change at Cycle 25 (n= 27)	1.23 (± 21.64)			
Dyspnoea - Change at Cycle 27 (n= 22)	3.03 (± 22.79)			
Dyspnoea - Change at Cycle 29 (n= 19)	-1.75 (± 23.50)			
Dyspnoea - Change at Cycle 31 (n= 14)	16.67 (± 28.50)			
Dyspnoea - Change at Cycle 33 (n= 10)	16.67 (± 17.57)			
Dyspnoea - Change at Cycle 35 (n= 10)	16.67 (± 23.57)			
Dyspnoea - Change at EOT (n= 337)	6.53 (± 25.79)			

Insomnia - Baseline (n= 628)	24.15 (± 28.09)			
Insomnia - Change at Cycle 3 (n= 544)	0.37 (± 27.36)			
Insomnia - Change at Cycle 5 (n= 438)	-0.08 (± 28.48)			
Insomnia - Change at Cycle 7 (n= 338)	-2.37 (± 29.63)			
Insomnia - Change at Cycle 9 (n= 274)	-0.24 (± 29.37)			
Insomnia - Change at Cycle 11 (n= 234)	2.56 (± 28.86)			
Insomnia - Change at Cycle 13 (n= 153)	0.65 (± 26.89)			
Insomnia - Change at Cycle 15 (n= 122)	-2.19 (± 27.01)			
Insomnia - Change at Cycle 17 (n= 87)	-1.92 (± 25.60)			
Insomnia - Change at Cycle 19 (n= 61)	1.64 (± 23.12)			
Insomnia - Change at Cycle 21 (n= 45)	0.74 (± 25.11)			
Insomnia - Change at Cycle 23 (n= 36)	-0.93 (± 33.32)			
Insomnia - Change at Cycle 25 (n= 29)	-0.00 (± 28.17)			
Insomnia - Change at Cycle 27 (n= 22)	-1.52 (± 24.07)			
Insomnia - Change at Cycle 29 (n= 20)	-3.33 (± 30.40)			
Insomnia - Change at Cycle 31 (n= 15)	-4.44 (± 41.53)			
Insomnia - Change at Cycle 33 (n= 11)	-6.06 (± 32.72)			
Insomnia - Change at Cycle 35 (n= 10)	-3.33 (± 33.15)			
Insomnia - Change at EOT (n= 339)	5.31 (± 32.50)			
Appetite loss - Baseline (n= 631)	17.38 (± 26.01)			
Appetite loss - Change at Cycle 3 (n= 546)	9.10 (± 28.64)			
Appetite loss - Change at Cycle 5 (n= 436)	9.02 (± 28.14)			
Appetite loss - Change at Cycle 7 (n= 342)	9.84 (± 27.80)			
Appetite loss - Change at Cycle 9 (n= 274)	9.98 (± 27.18)			
Appetite loss - Change at Cycle 11 (n= 234)	14.53 (± 28.27)			
Appetite loss - Change at Cycle 13 (n= 150)	10.67 (± 27.12)			
Appetite loss - Change at Cycle 15 (n= 121)	10.74 (± 25.90)			
Appetite loss - Change at Cycle 17 (n= 86)	8.91 (± 24.75)			
Appetite loss - Change at Cycle 19 (n= 61)	9.84 (± 24.60)			
Appetite loss - Change at Cycle 21 (n= 46)	13.04 (± 25.80)			
Appetite loss - Change at Cycle 23 (n= 35)	12.38 (± 25.67)			
Appetite loss - Change at Cycle 25 (n= 29)	11.49 (± 20.46)			

Appetite loss - Change at Cycle 27 (n= 23)	15.94 (± 22.18)			
Appetite loss - Change at Cycle 29 (n= 20)	15.00 (± 20.16)			
Appetite loss - Change at Cycle 31 (n= 15)	15.56 (± 24.77)			
Appetite loss - Change at Cycle 33 (n= 11)	15.15 (± 22.92)			
Appetite loss - Change at Cycle 35 (n= 10)	16.67 (± 17.57)			
Appetite loss - Change at EOT (n= 338)	12.03 (± 33.48)			
Constipation - Baseline (n= 632)	12.71 (± 21.61)			
Constipation - Change at Cycle 3 (n= 550)	2.42 (± 25.25)			
Constipation - Change at Cycle 5 (n= 433)	3.77 (± 26.52)			
Constipation - Change at Cycle 7 (n= 342)	2.63 (± 26.09)			
Constipation - Change at Cycle 9 (n= 274)	5.35 (± 26.68)			
Constipation - Change at Cycle 11 (n= 234)	4.42 (± 26.47)			
Constipation - Change at Cycle 13 (n= 153)	4.58 (± 25.95)			
Constipation - Change at Cycle 15 (n= 122)	4.92 (± 26.30)			
Constipation - Change at Cycle 17 (n= 86)	5.43 (± 23.35)			
Constipation - Change at Cycle 19 (n= 60)	8.33 (± 21.81)			
Constipation - Change at Cycle 21 (n= 44)	6.06 (± 18.00)			
Constipation - Change at Cycle 23 (n= 36)	9.26 (± 21.98)			
Constipation - Change at Cycle 25 (n= 29)	5.75 (± 17.97)			
Constipation - Change at Cycle 27 (n= 23)	1.45 (± 12.22)			
Constipation - Change at Cycle 29 (n= 20)	6.67 (± 20.52)			
Constipation - Change at Cycle 31 (n= 15)	22.22 (± 32.53)			
Constipation - Change at Cycle 33 (n= 11)	12.12 (± 16.82)			
Constipation - Change at Cycle 35 (n= 10)	10.00 (± 16.10)			
Constipation - Change at EOT (n= 344)	3.78 (± 27.33)			
Diarrhoea - Baseline (n= 633)	10.37 (± 19.47)			
Diarrhoea - Change at Cycle 3 (n= 549)	11.72 (± 28.16)			
Diarrhoea - Change at Cycle 5 (n= 433)	10.85 (± 28.29)			
Diarrhoea - Change at Cycle 7 (n= 344)	14.63 (± 29.94)			
Diarrhoea - Change at Cycle 9 (n= 274)	11.44 (± 26.44)			
Diarrhoea - Change at Cycle 11 (n= 235)	15.46 (± 27.26)			

Diarrhoea - Change at Cycle 13 (n= 151)	11.26 (± 24.00)			
Diarrhoea - Change at Cycle 15 (n= 121)	11.02 (± 28.02)			
Diarrhoea - Change at Cycle 17 (n= 87)	10.34 (± 21.75)			
Diarrhoea - Change at Cycle 19 (n= 59)	15.25 (± 25.76)			
Diarrhoea - Change at Cycle 21 (n= 45)	14.07 (± 24.09)			
Diarrhoea - Change at Cycle 23 (n= 36)	18.52 (± 21.74)			
Diarrhoea - Change at Cycle 25 (n= 29)	10.34 (± 22.01)			
Diarrhoea - Change at Cycle 27 (n= 22)	13.64 (± 19.68)			
Diarrhoea - Change at Cycle 29 (n= 20)	16.67 (± 25.36)			
Diarrhoea - Change at Cycle 31 (n= 15)	20.00 (± 24.56)			
Diarrhoea - Change at Cycle 33 (n= 11)	18.18 (± 22.92)			
Diarrhoea - Change at Cycle 35 (n= 10)	30.00 (± 18.92)			
Diarrhoea - Change at EOT (n= 342)	7.31 (± 24.26)			
Financial difficulties - Baseline (n= 628)	20.12 (± 30.25)			
Financial difficulties - Change at Cycle 3 (n= 547	-1.83 (± 23.80)			
Financial difficulties - Change at Cycle 5 (n=430)	-1.32 (± 24.00)			
Financial difficulties - Change at Cycle 7 (n=337)	-0.99 (± 27.68)			
Financial difficulties - Change at Cycle 9 (n=270)	-0.49 (± 26.80)			
Financial difficulties - Change at Cycle 11(n=232)	3.30 (± 25.64)			
Financial difficulties - Change at Cycle 13(n=150)	1.11 (± 27.96)			
Financial difficulties - Change at Cycle 15(n=122)	-0.27 (± 27.94)			
Financial difficulties - Change at Cycle 17 (n=87)	0.77 (± 27.36)			
Financial difficulties - Change at Cycle 19 (n=60)	1.67 (± 29.70)			
Financial difficulties - Change at Cycle 21 (n=45)	4.44 (± 25.23)			
Financial difficulties - Change at Cycle 23 (n=34)	2.94 (± 23.74)			
Financial difficulties - Change at Cycle 25 (n=29)	-4.60 (± 19.36)			
Financial difficulties - Change at Cycle 27 (n=23)	-2.90 (± 24.44)			
Financial difficulties - Change at Cycle 29 (n=20)	0.00 (± 21.63)			
Financial difficulties - Change at Cycle 31 (n=15)	-2.22 (± 19.79)			
Financial difficulties - Change at Cycle 33 (n=11)	-3.03 (± 17.98)			
Financial difficulties - Change at Cycle 35 (n=10)	0.00 (± 15.71)			

Financial difficulties - Change at EOT (n=337)	2.97 (± 27.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HRQL EQ-5D-3L Quality of Life: Single Index Utility Score

End point title	Change From Baseline in HRQL EQ-5D-3L Quality of Life: Single Index Utility 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 (either Aflibercept or FOLFIRI). Here, 'n'=subjects analyzed at specified timepoints.

End point type	Secondary

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at EOT (within 30 days of last treatment) (maximum exposure: 214 weeks)

End point values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)			
Subject group type	Reporting group			
Number of subjects analysed	623			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 623)	0.77 (± 0.24)			
Change at Cycle 3 (n= 536)	-0.02 (± 0.23)			
Change at Cycle 5 (n= 428)	-0.03 (± 0.22)			
Change at Cycle 7 (n= 335)	-0.04 (± 0.23)			
Change at Cycle 9 (n= 269)	-0.05 (± 0.24)			
Change at Cycle 11 (n= 226)	-0.07 (± 0.25)			
Change at Cycle 13 (n= 149)	-0.05 (± 0.20)			
Change at Cycle 15 (n= 119)	-0.06 (± 0.23)			
Change at Cycle 17 (n= 81)	-0.05 (± 0.24)			
Change at Cycle 19 (n= 58)	-0.05 (± 0.18)			
Change at Cycle 21 (n= 44)	-0.09 (± 0.20)			
Change at Cycle 23 (n= 34)	-0.14 (± 0.26)			
Change at Cycle 25 (n= 28)	-0.08 (± 0.21)			
Change at Cycle 27 (n= 23)	-0.08 (± 0.21)			

Change at Cycle 29 (n= 20)	-0.08 (± 0.20)			
Change at Cycle 31 (n= 15)	-0.12 (± 0.30)			
Change at Cycle 33 (n= 11)	0.02 (± 0.14)			
Change at Cycle 35 (n= 10)	-0.05 (± 0.14)			
Change at EOT (n= 343)	-0.11 (± 0.30)			

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 was a standardized HRQL questionnaire consisting of EQ-5D descriptive system & VAS. EQ-5D descriptive system comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort & 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. The VAS recorded respondent's self-rated health on a vertical visual analogue scale. The VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at top & 0 (Worst imaginable health state) at bottom. This information can be used as a quantitative measure of health outcome as judged by individual respondents. EQ-5D analysis population. Here, 'n'=subjects analysed at specified time points.

End point type	Secondary

End point timeframe:

Pre-dose at Baseline, Day 1 of every odd cycle (from Cycle 3 to 35); at EOT (within 30 days of last treatment) (maximum exposure: 214 weeks)

End point values	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)			
Subject group type	Reporting group			
Number of subjects analysed	623			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 577)	72.81 (± 18.28)			
Change at Cycle 3 (n= 482)	-1.85 (± 15.35)			
Change at Cycle 5 (n= 381)	-2.15 (± 14.31)			
Change at Cycle 7 (n= 303)	-2.20 (± 16.33)			
Change at Cycle 9 (n= 236)	-2.74 (± 14.28)			
Change at Cycle 11 (n= 203)	-3.10 (± 14.40)			
Change at Cycle 13 (n= 134)	-2.36 (± 15.29)			
Change at Cycle 15 (n= 103)	-1.05 (± 15.51)			

Change at Cycle 17 (n= 74)	-1.91 (± 13.54)			
Change at Cycle 19 (n= 52)	-3.06 (± 13.85)			
Change at Cycle 21 (n= 38)	-2.13 (± 14.98)			
Change at Cycle 23 (n= 30)	-5.77 (± 13.50)			
Change at Cycle 25 (n= 25)	-7.28 (± 10.53)			
Change at Cycle 27 (n= 17)	-4.94 (± 8.68)			
Change at Cycle 29 (n= 15)	-8.80 (± 10.12)			
Change at Cycle 31 (n= 13)	-6.69 (± 12.61)			
Change at Cycle 33 (n= 10)	-7.90 (± 13.08)			
Change at Cycle 35 (n= 8)	-8.88 (± 11.53)			
Change at EOT (n= 310)	-6.67 (± 17.38)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to the final visit (214 weeks) 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]). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

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

Reporting group description:

Aflibercept 4 mg/kg IV infusion over 60 minutes followed by Irinotecan 180 mg/m^2 IV infusion over 90 minutes and Leucovorin 400 mg/m^2 IV infusion over 120 minutes at the same time followed by 5-FU 400 mg/m^2 IV bolus over 2-4 minutes followed by 5-FU 2400 mg/m^2 continuous IV infusion over 46 hours 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.

Serious adverse events	Aflibercept + FOLFIRI (Irinotecan, 5-FU & Leucovorin)		
Total subjects affected by serious adverse events			
subjects affected / exposed	272 / 779 (34.92%)		
number of deaths (all causes)	48		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases To Central Nervous System			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour Associated Fever			

subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	4 / 779 (0.51%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	11 / 779 (1.41%)		
occurrences causally related to treatment / all	10 / 13		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	2 / 779 (0.26%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Orthostatic Hypotension			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral Ischaemia			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vena Cava Thrombosis			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cancer Surgery			
subjects affected / exposed	2 / 779 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions				
Asthenia				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Chest Pain				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disease Progression				
subjects affected / exposed	23 / 779 (2.95%)			
occurrences causally related to treatment / all	0 / 23			
deaths causally related to treatment / all	0 / 19			
Fatigue				
subjects affected / exposed	4 / 779 (0.51%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
General Physical Health Deterioration				
subjects affected / exposed	5 / 779 (0.64%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	2 / 2			
Malaise				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple Organ Dysfunction Syndrome				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pain				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pyrexia				
subjects affected / exposed	12 / 779 (1.54%)			
occurrences causally related to treatment / all	6 / 18			
deaths causally related to treatment / all	0 / 0			
Sudden Death				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Immune system disorders				
Anaphylactic Shock				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute Pulmonary Oedema				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Atelectasis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	4 / 779 (0.51%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			

Hiccups				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonia Aspiration				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonitis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	9 / 779 (1.16%)			
occurrences causally related to treatment / all	9 / 9			
deaths causally related to treatment / all	0 / 0			
Pulmonary Haemorrhage				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Respiratory Failure				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Thoracic Haemorrhage				

subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional State			
subjects affected / exposed	4 / 779 (0.51%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental Exposure To Product			
subjects affected / exposed	2 / 779 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Accidental Overdose			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anastomotic Leak			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contrast Media Reaction			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Stoma Complication			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hip Fracture				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meniscus Injury				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stoma Site Haemorrhage				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Myocardial Infarction				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Angina Pectoris				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Flutter				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial Thrombosis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure				

subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure Congestive				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-Respiratory Arrest				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Coronary Artery Thrombosis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular Tachycardia				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ventricular Tachycardia				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised Tonic-Clonic Seizure				

subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paraparesis			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Posterior Reversible Encephalopathy Syndrome			
subjects affected / exposed	3 / 779 (0.39%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Subarachnoid Haemorrhage			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
White Matter Lesion			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 779 (0.90%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 0		
Febrile Neutropenia			
subjects affected / exposed	12 / 779 (1.54%)		
occurrences causally related to treatment / all	12 / 12		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	14 / 779 (1.80%)			
occurrences causally related to treatment / all	17 / 18			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombotic Microangiopathy				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Retinal Detachment				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal Pain				
subjects affected / exposed	8 / 779 (1.03%)			
occurrences causally related to treatment / all	2 / 9			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain Upper				
subjects affected / exposed	4 / 779 (0.51%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Anal Fissure				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Anal Fistula				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anorectal Ulcer				

subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	39 / 779 (5.01%)			
occurrences causally related to treatment / all	42 / 43			
deaths causally related to treatment / all	0 / 0			
Duodenal Ulcer Haemorrhage				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enterocutaneous Fistula				
subjects affected / exposed	4 / 779 (0.51%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Enterovesical Fistula				

subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Faecaloma	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Fistula Of Small Intestine	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Gastrointestinal Fistula	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Gastrointestinal Haemorrhage	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Gastrointestinal Hypomotility	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	0 / 2
deaths causally related to treatment / all	0 / 0
Gastrointestinal Perforation	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Gingival Bleeding	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Haematemesis	

subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Haemorrhoids	
subjects affected / exposed	2 / 779 (0.26%)
occurrences causally related to treatment / all	1 / 2
deaths causally related to treatment / all	0 / 0
Haemorrhoids Thrombosed	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Ileus	
subjects affected / exposed	2 / 779 (0.26%)
occurrences causally related to treatment / all	0 / 2
deaths causally related to treatment / all	0 / 0
Ileus Paralytic	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Inguinal Hernia	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Intestinal Obstruction	
subjects affected / exposed	12 / 779 (1.54%)
occurrences causally related to treatment / all	0 / 13
deaths causally related to treatment / all	0 / 2
Intestinal Perforation	
subjects affected / exposed	4 / 779 (0.51%)
occurrences causally related to treatment / all	3 / 4
deaths causally related to treatment / all	1 / 1
Large Intestine Perforation	

subjects affected / exposed	4 / 779 (0.51%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 2			
Lower Gastrointestinal Haemorrhage				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Odynophagia				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proctalgia				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal Haemorrhage				

subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal Perforation				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal Tenesmus				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small Intestinal Obstruction				
subjects affected / exposed	4 / 779 (0.51%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Stomatitis				
subjects affected / exposed	9 / 779 (1.16%)			
occurrences causally related to treatment / all	9 / 9			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	10 / 779 (1.28%)			
occurrences causally related to treatment / all	8 / 10			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Cholecystitis				

subjects affected / exposed	2 / 779 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholecystitis Acute			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic Failure			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Jaundice Cholestatic			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Portal Hypertension			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	3 / 779 (0.39%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Hydronephrosis			

subjects affected / exposed	3 / 779 (0.39%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Nephrotic Syndrome				
subjects affected / exposed	5 / 779 (0.64%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Prerenal Failure				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proteinuria				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary Retention				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back Pain				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal Chest Pain				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal Pain				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neck Pain				

subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations

Abdominal Abscess

subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			

Abdominal Infection

subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Abdominal Wall Abscess

subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Bronchitis

subjects affected / exposed	3 / 779 (0.39%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			

Catheter Site Abscess

subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Device Related Infection

subjects affected / exposed	7 / 779 (0.90%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 1			

Diabetic Foot Infection

subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Escherichia Urinary Tract Infection

subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile Infection				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis Escherichia Coli				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster Meningoencephalitis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	5 / 779 (0.64%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Infective Myositis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella Infection				

subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Localised Infection				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower Respiratory Tract Infection				
subjects affected / exposed	3 / 779 (0.39%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Lung Infection				
subjects affected / exposed	3 / 779 (0.39%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenic Infection				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic Sepsis				
subjects affected / exposed	3 / 779 (0.39%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	2 / 2			
Parainfluenzae Virus Infection				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic Abscess				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Periodontitis				

subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Pharyngitis	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Phlebitis Infective	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Pneumonia	
subjects affected / exposed	8 / 779 (1.03%)
occurrences causally related to treatment / all	3 / 8
deaths causally related to treatment / all	0 / 0
Pyelonephritis	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Rectal Abscess	
subjects affected / exposed	1 / 779 (0.13%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Respiratory Tract Infection	
subjects affected / exposed	3 / 779 (0.39%)
occurrences causally related to treatment / all	2 / 3
deaths causally related to treatment / all	0 / 0
Sepsis	
subjects affected / exposed	7 / 779 (0.90%)
occurrences causally related to treatment / all	6 / 8
deaths causally related to treatment / all	2 / 2
Septic Shock	

subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Sinusitis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal Bacteraemia				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheobronchitis				
subjects affected / exposed	2 / 779 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper Respiratory Tract Infection				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				
subjects affected / exposed	5 / 779 (0.64%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 779 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased Appetite				

subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	5 / 779 (0.64%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 779 (0.13%)		
occurrences causally related to treatment / all	1 / 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	744 / 779 (95.51%)		
Investigations			
Weight Decreased			
subjects affected / exposed	171 / 779 (21.95%)		
occurrences (all)	185		
Vascular disorders			
Hypertension			
subjects affected / exposed	369 / 779 (47.37%)		
occurrences (all)	557		
Nervous system disorders			
Headache			
subjects affected / exposed	105 / 779 (13.48%)		
occurrences (all)	133		
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	277 / 779 (35.56%)		
occurrences (all)	611		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	192 / 779 (24.65%)		
occurrences (all)	318		
Fatigue			
subjects affected / exposed	283 / 779 (36.33%)		
occurrences (all)	415		
Pyrexia			
subjects affected / exposed	87 / 779 (11.17%)		
occurrences (all)	112		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	150 / 779 (19.26%)		
occurrences (all)	194		
Abdominal Pain Upper			
subjects affected / exposed	67 / 779 (8.60%)		
occurrences (all)	77		
Constipation			
subjects affected / exposed	148 / 779 (19.00%)		
occurrences (all)	180		
Diarrhoea			
subjects affected / exposed	464 / 779 (59.56%)		
occurrences (all)	1000		
Nausea			
subjects affected / exposed	337 / 779 (43.26%)		
occurrences (all)	640		
Proctalgia			
subjects affected / exposed	39 / 779 (5.01%)		
occurrences (all)	44		
Stomatitis			
subjects affected / exposed	329 / 779 (42.23%)		
occurrences (all)	570		
Vomiting			

subjects affected / exposed	190 / 779 (24.39%)		
occurrences (all)	311		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	57 / 779 (7.32%)		
occurrences (all)	65		
Dysphonia			
subjects affected / exposed	131 / 779 (16.82%)		
occurrences (all)	153		
Dyspnoea			
subjects affected / exposed	62 / 779 (7.96%)		
occurrences (all)	69		
Epistaxis			
subjects affected / exposed	153 / 779 (19.64%)		
occurrences (all)	193		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	143 / 779 (18.36%)		
occurrences (all)	144		
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	79 / 779 (10.14%)		
occurrences (all)	89		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	102 / 779 (13.09%)		
occurrences (all)	133		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	54 / 779 (6.93%)		
occurrences (all)	61		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	47 / 779 (6.03%)		
occurrences (all)	50		
Metabolism and nutrition disorders			

Decreased Appetite			
subjects affected / exposed	206 / 779 (26.44%)		
occurrences (all)	263		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported