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Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Treatment of Patients With Metastatic Colorectal Cancer After Failure of an Oxaliplatin Based Regimen (VELOUR)

This study has been completed.

Sponsor:	Sanofi
Collaborators:	Regeneron Pharmaceuticals NSABP Foundation Inc
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00561470

Purpose

The main objective of the study was to evaluate the effectiveness of aflibercept (versus placebo) in increasing the overall survival in participants with metastatic colorectal cancer treated with FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) and that have previously failed an oxaliplatin based treatment for metastatic disease.

The secondary objectives were to compare progression-free survival, to evaluate overall response rate, to evaluate the safety profile, to assess immunogenicity of intravenous (IV) aflibercept, and to assess pharmacokinetics of IV aflibercept in both treatment arms.

Condition	Intervention	Phase
Colorectal Neoplasms Neoplasm Metastasis	Drug: Placebo Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) Drug: FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin)	Phase 3

Study Type: Interventional

Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator), Randomized, Efficacy Study
Official Title: A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks Versus Placebo in Patients With Metastatic Colorectal Cancer (MCRC) Treated With Irinotecan / 5-FU Combination (FOLFIRI) After Failure of an Oxaliplatin Based Regimen

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Overall Survival (OS) [Time Frame: From the date of the first randomization until the study data cut-off date, 07 February 2011 (approximately three years)] [Designated as safety issue: No]

  Overall Survival was the time interval from the date of randomization to the date of death due to any cause. Once disease progression was documented, participants were followed every 2 months for survival status, until death or until the study cutoff date, whichever came first. The final data cutoff date for the analysis of OS was the date when 863 deaths had occurred (07 February 2011). OS was estimated using the Kaplan-Meier method, and the Hazard Ratio was estimated using the Cox Proportional Hazard Model.

Secondary Outcome Measures:

- Progression-free Survival (PFS) Assessed by Independent Review Committee (IRC) [Time Frame: From the date of the first randomization until the occurrence of 561 OS events, 06 May 2010 (approximately 30 months)] [Designated as safety issue: No]

  PFS was the time interval from the date of randomization to the date of progression, or death from any cause if it occurs before tumor progression is documented. To evaluate disease progression, copies of all tumor imaging sets were systematically collected and assessed by the IRC. PFS was analyzed using the Kaplan-Meier method, and the Hazard Ratio was estimated using the Cox Proportional Hazard Model. The analysis for PFS was performed as planned when 561 deaths (OS events) had occurred.
- Overall Objective Response Rate (ORR) Based on the Tumor Assessment by the Independent Review Committee (IRC) as Per Response Evaluation Criteria in Solid Tumours (RECIST) Criteria [Time Frame: From the date of the first randomization until the study data cut-off date, 06 May 2010 (approximately 30 months)] [Designated as safety issue: No]

  The overall ORR was the percentage of evaluable participants who achieved complete response [CR] or partial response [PR] according to RECIST criteria version 1.0. -- CR reflected the disappearance of all tumor lesions (with no new tumors) -- PR reflected a pre-defined reduction in tumor burden Tumors were assessed by the IRC using Computerized Tomography (CT) scans or Magnetic Resonance Imaging (MRI) scans; and an observed response was confirmed by repeated imaging after 4 - 6 weeks.
- Number of Participants With Adverse Events (AE) [Time Frame: From the date of the first randomization up to 30 days after the treatment discontinuation or until TEAE was resolved or stabilized] [Designated as safety issue: Yes]

  All AEs regardless of seriousness or relationship to study treatment, spanning from the first administration of study treatment until 30 days after the last administration of study treatment, were recorded, and followed until resolution or stabilization. The number of participants with all treatment emergent adverse events (TEAE), serious adverse events (SAE), TEAE leading to death, and TEAE leading to permanent treatment discontinuation are reported.
- Immunogenicity Assessment: Number of Participants With Positive Sample(s) in the Anti-drug Antibodies (ADA) Assay and in the Neutralizing Anti-drug Antibodies (NAb) Assay [Time Frame: Baseline, every other treatment cycle, 30 days and 90 days after the last infusion of aflibercept/placebo] [Designated as safety issue: No]

  Serum samples for immunogenicity assessment were analyzed using a bridging immunoassay to detect ADA. Positive samples in the ADA assay were further analyzed in the NAb assay using a validated, non-quantitative ligand binding assay.

Enrollment: 1226
Study Start Date: November 2007
Primary Completion Date: February 2011
Study Completion Date: June 2012

Arms	Assigned Interventions
Placebo Comparator: Placebo/FOLFIRI Participants with Metastatic Colorectal Cancer administered Placebo followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) starting on Day 1 of a 2-week cycle until a treatment discontinuation criterion was met	Drug: Placebo 4 mg/kg of sterile aqueous buffered vehicle (pH 6.0) was administered intra venously (IV) over 1 hour on Day 1, every 2 weeks Drug: FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) The FOLFIRI regimen was initiated immediately after Placebo administration on Day 1 The FOLFIRI regimen included: • 180 mg/m² Irinotecan (Campto®, Camptosar®) IV infusion over 90 minutes and dl leucovorin 400 mg/m² (200 mg/m² for the l-isomer form) IV infusion over 2 hours, followed by: • 5-FU 400 mg/m² IV bolus given over 2-4 minutes, followed by: • 5-FU 2400 mg/m² continuous IV infusion over 46-hours
Experimental: Aflibercept/FOLFIRI Participants with Metastatic Colorectal Cancer administered Aflibercept followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) starting on Day 1 of a 2-week cycle until a treatment discontinuation criterion was met	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) 4 mg/kg of Aflibercept was administered IV over 1 hour on Day 1, every 2 weeks. Drug: FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) The FOLFIRI regimen was initiated immediately after Aflibercept administration on Day 1 The FOLFIRI regimen included: • 180 mg/m² Irinotecan (Campto®, Camptosar®) IV infusion over 90 minutes and dl leucovorin 400 mg/m² (200 mg/m² for the l-isomer form) IV infusion over 2 hours, followed by: • 5-FU 400 mg/m² IV bolus given over 2-4 minutes, followed by: • 5-FU 2400 mg/m² continuous IV infusion over 46-hours

Detailed Description:

Participants were

- randomized at baseline (treatment was initiated with 3 days of randomization)
- administered treatment in cycles of 14-days till a study withdrawal criterion was met
- followed up 30 days after discontinuation of treatment, and every 8 weeks until death or end of study.

The criteria for discontinuation of study treatment for a participant are:

- participant (or legal representative) chose to withdraw from treatment
- the investigator thought that continuation of the study would be detrimental to the participants well-being due to
    - disease progression
    - unacceptable AEs
    - intercurrent illnesses
    - non-compliance to the study protocol
- participant was lost to follow-up
- participant was unblinded for the investigational treatment

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Participants who met the following main selection criteria were included in the study.

Inclusion Criteria:

- Histologically or cytologically proven adenocarcinoma of the colon or rectum
- Metastatic disease that is not amenable to potentially curative treatment
- One and only one prior line of treatment for metastatic disease. This prior line should be an oxaliplatin based chemotherapy (participants who relapse within 6 months of completion of oxaliplatin based adjuvant chemotherapy are eligible)
- Prior treatment with bevacizumab is permitted.

Exclusion Criteria:

- Prior therapy with irinotecan
- Eastern Cooperative Oncology Group performance status >2

The above information is not intended to contain all considerations relevant to participation in a clinical trial.

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sanofi-aventis investigational site number 804005
Dnipropetrovsk, Ukraine
sanofi-aventis investigational site number 804004
Donetsk, Ukraine, 83092
sanofi-aventis investigational site number 804006
Kharkiv, Ukraine, 61037
sanofi-aventis investigational site number 804002
Kharkov, Ukraine, 61070
United Kingdom
sanofi-aventis investigational site number 826001
Aberdeen, United Kingdom, AB25 2ZD
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London, United Kingdom, EC1A 7BE
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sanofi-aventis investigational site number 826005
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Investigators

Study Director:	Clinical Sciences & Operations	sanofi-aventis

More Information

Responsible Party:	Sanofi
Study ID Numbers:	EFC10262 EudraCT 2007-000820-42
Health Authority:	United States: Food and Drug Administration Spain: Spanish Agency of Medicines Australia: Department of Health and Ageing Therapeutic Goods Administration

Study Results

Participant Flow

Recruitment Details	Between 19 November 2007 and 16 March 2010, 614 participants were randomized to the placebo arm and 612 participants were randomized to the aflibercept arm.

Reporting Groups

	Description
Placebo/FOLFIRI	Participants with Metastatic Colorectal Cancer administered Placebo followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks
Aflibercept/FOLFIRI	Participants with Metastatic Colorectal Cancer administered 4 mg/kg of Aflibercept, followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks

Overall Study

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
Started	614	612
TREATED	609	607
SAFETY POPULATION	605 [1]	611 [2]
ONGOING TREATMENT	11 [3]	14 [3]
Completed	0 [4]	0 [4]
Not Completed	614	612
Adverse Event	74	163

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
Disease progression	437	305
poor compliance to protocol	4	4
Lost to Follow-up	2	0
Physician Decision	21	20
Consent Withdrawn	2	6
Subject request	43	77
Metastatic surgery	10	12
Unauthorized procedure	3	1
Randomized but not treated	5	5
Missed visit window	1	4
Planning surgery	1	1
Ongoing Treatment	11	14

[1] Treated participants excluding 4 who received at least 1 dose of Aflibercept
[2] Treated participants including 4 from Placebo/FOLFIRI who received at least 1 dose of Aflibercept
[3] Participants continuing treatment on the cutoff date of the final analysis
[4] Participants met treatment discontinuation criteria or were ongoing treatment on the cutoff date

Baseline Characteristics

Reporting Groups

	Description
Placebo/Folfiri	Participants with Metastatic Colorectal Cancer administered Placebo and FOLFIRI (Irinotecan, 5- Fluorouracil, and Leucovorin)
Aflibercept/Folfiri	Participants with Metastatic Colorectal Cancer administered 4 mg/kg of Aflibercept and FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin)

Baseline Measures

	Placebo/Folfiri	Aflibercept/Folfiri	Total
Number of Participants	614	612	1226
Age, Continuous [units: years]	60.2 (10.8)	59.5 (10.5)	59.8 (10.7)

	Placebo/Folfiri	Aflibercept/Folfiri	Total
Mean (Standard Deviation)			
Age, Customized [units: participants]			
<65 years	376	407	783
>=65 but <75 years	199	172	371
>=75 years	39	33	72
Gender, Customized [units: participants]			
Male	353	365	718
Female	261	247	508
Race/Ethnicity, Customized [units: participants]			
Caucasian/White	523	548	1071
Black	27	16	43
Asian/Oriental	51	35	86
Other	13	13	26
Region of Enrollment [units: participants]			
ARGENTINA	4	2	6
AUSTRALIA	42	54	96
AUSTRIA	3	4	7
BELGIUM	37	45	82
BRAZIL	21	27	48
CHILE	31	33	64
CZECH REPUBLIC	30	47	77
DENMARK	9	6	15
ESTONIA	7	3	10
FRANCE	1	1	2
GERMANY	23	12	35

	Placebo/Folfiri	Aflibercept/Folfiri	Total
GREECE	9	10	19
ITALY	26	23	49
KOREA, REPUBLIC OF	39	26	65
NETHERLANDS	20	14	34
NEW ZEALAND	13	7	20
NORWAY	14	19	33
POLAND	24	32	56
PUERTO RICO	4	2	6
ROMANIA	16	16	32
RUSSIAN FEDERATION	35	40	75
SOUTH AFRICA	36	31	67
SPAIN	27	28	55
SWEDEN	10	4	14
TURKEY	4	2	6
UKRAINE	11	11	22
UNITED KINGDOM	47	52	99
UNITED STATES	71	61	132
Eastern Cooperative Oncology Group (ECOG) performance status score [1] [units: participants]			
Participants with ECOG Score = 0	350	349	699
Participants with ECOG Score = 1	250	250	500
Participants with ECOG Score = 2	14	13	27
Prior Bevacizumab [2] [units: participants]			
Yes	187	186	373

	Placebo/Folfiri	Aflibercept/Folfiri	Total
No	427	426	853

[1] The ECOG score assesses how the disease affects a participant's daily living abilities. It ranges from 0-5, with 0 being the best and 5 being the worst outcome. "0" reflects a fully active participant, able to carry on all pre-disease performance without restriction. "1" reflects a participant restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. "2" reflects an ambulatory participant, who is up and about more than 50% of waking hours, and capable of all self-care but unable to carry out any work activities.

[2] Number of participants randomized in the prior bevacizumab stratum as per the interactive voice response system (IVRS).

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Overall Survival (OS)
Measure Description	Overall Survival was the time interval from the date of randomization to the date of death due to any cause. Once disease progression was documented, participants were followed every 2 months for survival status, until death or until the study cutoff date, whichever came first. The final data cutoff date for the analysis of OS was the date when 863 deaths had occurred (07 February 2011). OS was estimated using the Kaplan-Meier method, and the Hazard Ratio was estimated using the Cox Proportional Hazard Model.
Time Frame	From the date of the first randomization until the study data cut-off date, 07 February 2011 (approximately three years)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population (ITT) – all participants who gave informed consent and were randomized.

Reporting Groups

	Description
Placebo/FOLFIRI	Participants with Metastatic Colorectal Cancer administered Placebo followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks
Aflibercept/FOLFIRI	Participants with Metastatic Colorectal Cancer administered 4 mg/kg of Aflibercept, followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks

Measured Values

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
Number of Participants Analyzed	614	612

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
Number of Events (Death) Analyzed	460	403
Overall Survival (OS) [units: months] Median (Inter-Quartile Range)	12.06 (6.83 to 21.03)	13.50 (7.62 to 25.59)

Statistical Analysis 1 for Overall Survival (OS)

Statistical Analysis Overview	Comparison Groups	Placebo/FOLFIRI, Aflibercept/FOLFIRI
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0032
	Comments	Stratified Log-Rank test p-value. Stratified on ECOG Performance Status and prior Bevacizumab according to IVRS using the Cox Proportional Hazard Model. Significance threshold was set to 0.0466 using the O'Brien-Fleming alpha spending function.
	Method	Other [Stratified Log-Rank test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Stratified Hazard Ratio]
	Estimated Value	0.817
	Confidence Interval	(2-Sided) 95.34% 0.713 to 0.937
	Estimation Comments	Stratified on ECOG Performance Status (0 vs 1 vs 2) and prior Bevacizumab (yes vs no) according to IVRS using the Cox Proportional Hazard Model. Significance threshold was set to 0.0466 using the O'Brien-Fleming alpha spending function.

2. Secondary Outcome Measure:

Measure Title	Progression-free Survival (PFS) Assessed by Independent Review Committee (IRC)

Measure Description	PFS was the time interval from the date of randomization to the date of progression, or death from any cause if it occurs before tumor progression is documented. To evaluate disease progression, copies of all tumor imaging sets were systematically collected and assessed by the IRC. PFS was analyzed using the Kaplan-Meier method, and the Hazard Ratio was estimated using the Cox Proportional Hazard Model. The analysis for PFS was performed as planned when 561 deaths (OS events) had occurred.
Time Frame	From the date of the first randomization until the occurrence of 561 OS events, 06 May 2010 (approximately 30 months)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) population included all participants who gave informed consent and were randomized.

Reporting Groups

	Description
Placebo/FOLFIRI	Participants with Metastatic Colorectal Cancer administered Placebo followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks
Aflibercept/FOLFIRI	Participants with Metastatic Colorectal Cancer administered 4 mg/kg of Aflibercept, followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks

Measured Values

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
Number of Participants Analyzed	614	612
Number of First PFS Events Analyzed	454	393
Progression-free Survival (PFS) Assessed by Independent Review Committee (IRC) [units: months] Median (Inter-Quartile Range)	4.67 (2.60 to 9.10)	6.90 (3.84 to 10.05)

Statistical Analysis 1 for Progression-free Survival (PFS) Assessed by Independent Review Committee (IRC)

Statistical Analysis Overview	Comparison Groups	Placebo/FOLFIRI, Aflibercept/FOLFIRI
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.00007
	Comments	Stratified on ECOG Performance Status (0 vs 1 vs 2) and prior Bevacizumab (yes vs no) according to IVRS
	Method	Other [Stratified Log-Rank test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Stratified Hazard ratio]
	Estimated Value	0.758
	Confidence Interval	(2-Sided) 99.99% 0.578 to 0.995
	Estimation Comments	Stratified on ECOG Performance Status (0 vs 1 vs 2) and prior Bevacizumab (yes vs no) according to IVRS using the Cox Proportional Hazard Model.

3. Secondary Outcome Measure:

Measure Title	Overall Objective Response Rate (ORR) Based on the Tumor Assessment by the Independent Review Committee (IRC) as Per Response Evaluation Criteria in Solid Tumours (RECIST) Criteria
Measure Description	The overall ORR was the percentage of evaluable participants who achieved complete response [CR] or partial response [PR] according to RECIST criteria version 1.0. • CR reflected the disappearance of all tumor lesions (with no new tumors) • PR reflected a pre-defined reduction in tumor burden Tumors were assessed by the IRC using Computerized Tomography (CT) scans or Magnetic Resonance Imaging (MRI) scans; and an observed response was confirmed by repeated imaging after 4 – 6 weeks.
Time Frame	From the date of the first randomization until the study data cut-off date, 06 May 2010 (approximately 30 months)
Safety Issue?	No

Analysis Population Description

The evaluable patient population (EPP) for tumor response included all randomized participants with measurable disease at study entry, as per IRC evaluation, and with at least one valid post-baseline tumor evaluation.

Reporting Groups

	Description
Placebo/FOLFIRI	Participants with Metastatic Colorectal Cancer administered Placebo followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks
Aflibercept/FOLFIRI	Participants with Metastatic Colorectal Cancer administered 4 mg/kg of Aflibercept, followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks

Measured Values

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
Number of Participants Analyzed	530	531
Overall Objective Response Rate (ORR) Based on the Tumor Assessment by the Independent Review Committee (IRC) as Per Response Evaluation Criteria in Solid Tumours (RECIST) Criteria [units: percentage of participants] Number (95% Confidence Interval)	11.1 (8.5 to 13.8)	19.8 (16.4 to 23.2)

Statistical Analysis 1 for Overall Objective Response Rate (ORR) Based on the Tumor Assessment by the Independent Review Committee (IRC) as Per Response Evaluation Criteria in Solid Tumours (RECIST) Criteria

Statistical Analysis Overview	Comparison Groups	Placebo/FOLFIRI, Aflibercept/FOLFIRI
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0001
	Comments	[Not specified]
	Method	Other [Stratified Cochran-Mantel-Haenszel]
	Comments	Stratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no) according to IVRS.

4. Secondary Outcome Measure:

Measure Title	Number of Participants With Adverse Events (AE)
Measure Description	All AEs regardless of seriousness or relationship to study treatment, spanning from the first administration of study treatment until 30 days after the last administration of study treatment, were recorded, and followed until resolution or stabilization. The number of participants with all treatment emergent adverse events (TEAE), serious adverse events (SAE), TEAE leading to death, and TEAE leading to permanent treatment discontinuation are reported.
Time Frame	From the date of the first randomization up to 30 days after the treatment discontinuation or until TEAE was resolved or stabilized

Safety Issue?	Yes

Analysis Population Description

The safety population was the subset of the ITT population that took at least one dose of study treatment. Analyses was based on the treatment actually received (any participant who received at least one dose of aflibercept, even when receiving the rest of study treatment with placebo, was counted in the aflibercept treatment arm).

Reporting Groups

	Description
Placebo/FOLFIRI	Participants with Metastatic Colorectal Cancer administered Placebo followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks
Aflibercept/FOLFIRI	Participants with Metastatic Colorectal Cancer administered 4 mg/kg of Aflibercept, followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks

Measured Values

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
Number of Participants Analyzed	605	611
Number of Participants With Adverse Events (AE) [units: participants]		
Treatment-Emergent Adverse Event (TEAE)	592	606
Serious TEAE	198	294
TEAE leading to Death	29	37
TEAE causing permanent treatment discontinuation	73	164

5. Secondary Outcome Measure:

Measure Title	Immunogenicity Assessment: Number of Participants With Positive Sample(s) in the Anti-drug Antibodies (ADA) Assay and in the Neutralizing Anti-drug Antibodies (NAb) Assay
Measure Description	Serum samples for immunogenicity assessment were analyzed using a bridging immunoassay to detect ADA. Positive samples in the ADA assay were further analyzed in the NAb assay using a validated, non-quantitative ligand binding assay.
Time Frame	Baseline, every other treatment cycle, 30 days and 90 days after the last infusion of aflibercept/placebo
Safety Issue?	No

Analysis Population Description

Immunogenicity population included all participants who were treated and tested for immunogenicity at least once post-baseline.

Reporting Groups

	Description
Placebo/FOLFIRI	Participants with Metastatic Colorectal Cancer administered Placebo and FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin)
Aflibercept/FOLFIRI	Participants with Metastatic Colorectal Cancer administered Aflibercept and FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin)

Measured Values

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
Number of Participants Analyzed	526	521
Immunogenicity Assessment: Number of Participants With Positive Sample(s) in the Anti-drug Antibodies (ADA) Assay and in the Neutralizing Anti-drug Antibodies (NAb) Assay [units: participants]		
At least one positive sample in the ADA assay	18	8
At least one positive sample in the NAb assay	2	1

Reported Adverse Events

Time Frame	From treatment initiation to 7 February, 2011
Additional Description	[Not specified]

Reporting Groups

	Description
Placebo/FOLFIRI	Participants with Metastatic Colorectal Cancer administered Placebo followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks
Aflibercept/FOLFIRI	Participants with Metastatic Colorectal Cancer administered 4 mg/kg of Aflibercept, followed by FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) every two weeks

Serious Adverse Events

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Total	198/605 (32.73%)	294/611 (48.12%)
Blood and lymphatic system disorders		
Anaemia [A] *	3/605 (0.5%)	7/611 (1.15%)
Coagulopathy [A] *	0/605 (0%)	2/611 (0.33%)
Febrile neutropenia [A] *	6/605 (0.99%)	19/611 (3.11%)
Neutropenia [A] *	4/605 (0.66%)	11/611 (1.8%)
Pancytopenia [A] *	0/605 (0%)	2/611 (0.33%)
Thrombocytopenia [A] *	3/605 (0.5%)	2/611 (0.33%)
Thrombotic microangiopathy [A] *	0/605 (0%)	1/611 (0.16%)
Cardiac disorders		
Acute myocardial infarction [A] *	0/605 (0%)	2/611 (0.33%)
Angina pectoris [A] *	0/605 (0%)	1/611 (0.16%)
Atrial fibrillation [A] *	2/605 (0.33%)	3/611 (0.49%)
Cardiac failure congestive [A] *	0/605 (0%)	1/611 (0.16%)
Intracardiac thrombus [A] *	0/605 (0%)	1/611 (0.16%)
Myocardial infarction [A] *	0/605 (0%)	1/611 (0.16%)
Myocardial ischaemia [A] *	1/605 (0.17%)	0/611 (0%)
Pericarditis [A] *	1/605 (0.17%)	0/611 (0%)
Sinus bradycardia [A] *	0/605 (0%)	1/611 (0.16%)
Endocrine disorders		
Hypercalcaemia of malignancy [A] *	1/605 (0.17%)	0/611 (0%)
Eye disorders		

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Periorbital oedema [A] *	0/605 (0%)	1/611 (0.16%)
Gastrointestinal disorders		
Abdominal pain [A] *	7/605 (1.16%)	12/611 (1.96%)
Abdominal pain lower [A] *	1/605 (0.17%)	1/611 (0.16%)
Abdominal pain upper [A] *	3/605 (0.5%)	4/611 (0.65%)
Anal haemorrhage [A] *	1/605 (0.17%)	0/611 (0%)
Aphthous stomatitis [A] *	0/605 (0%)	1/611 (0.16%)
Ascites [A] *	4/605 (0.66%)	3/611 (0.49%)
Colitis [A] *	1/605 (0.17%)	4/611 (0.65%)
Colitis ischaemic [A] *	0/605 (0%)	1/611 (0.16%)
Colonic fistula [A] *	1/605 (0.17%)	0/611 (0%)
Colonic obstruction [A] *	0/605 (0%)	2/611 (0.33%)
Constipation [A] *	4/605 (0.66%)	6/611 (0.98%)
Diarrhoea [A] *	14/605 (2.31%)	44/611 (7.2%)
Duodenal obstruction [A] *	1/605 (0.17%)	0/611 (0%)
Duodenal ulcer haemorrhage [A] *	0/605 (0%)	1/611 (0.16%)
Duodenal ulcer perforation [A] *	1/605 (0.17%)	1/611 (0.16%)
Enteritis [A] *	1/605 (0.17%)	2/611 (0.33%)
Enterocolitis [A] *	0/605 (0%)	1/611 (0.16%)
Enterocutaneous fistula [A] *	0/605 (0%)	1/611 (0.16%)
Faecal incontinence [A] *	1/605 (0.17%)	0/611 (0%)
Gastritis [A] *	0/605 (0%)	1/611 (0.16%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Gastrointestinal haemorrhage [A] *	0/605 (0%)	3/611 (0.49%)
Gastrointestinal hypomotility [A] *	1/605 (0.17%)	0/611 (0%)
Gastrointestinal inflammation [A] *	0/605 (0%)	3/611 (0.49%)
Gastrointestinal obstruction [A] *	2/605 (0.33%)	1/611 (0.16%)
Gastrointestinal perforation [A] *	1/605 (0.17%)	0/611 (0%)
Gastrooesophageal reflux disease [A] *	0/605 (0%)	1/611 (0.16%)
Gingivitis [A] *	0/605 (0%)	1/611 (0.16%)
Haematemesis [A] *	2/605 (0.33%)	0/611 (0%)
Haemorrhoids [A] *	0/605 (0%)	2/611 (0.33%)
Ileal perforation [A] *	0/605 (0%)	1/611 (0.16%)
Ileitis [A] *	0/605 (0%)	1/611 (0.16%)
Ileus [A] *	5/605 (0.83%)	4/611 (0.65%)
Intestinal obstruction [A] *	11/605 (1.82%)	10/611 (1.64%)
Large intestinal haemorrhage [A] *	0/605 (0%)	1/611 (0.16%)
Large intestinal obstruction [A] *	0/605 (0%)	1/611 (0.16%)
Lower gastrointestinal haemorrhage [A] *	0/605 (0%)	1/611 (0.16%)
Mallory-weiss syndrome [A] *	0/605 (0%)	1/611 (0.16%)
Mechanical ileus [A] *	2/605 (0.33%)	1/611 (0.16%)
Mesenteric vein thrombosis [A] *	0/605 (0%)	1/611 (0.16%)
Nausea [A] *	3/605 (0.5%)	4/611 (0.65%)
Neutropenic colitis [A] *	0/605 (0%)	1/611 (0.16%)
Pancreatitis [A] *	1/605 (0.17%)	0/611 (0%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Periodontitis [A] *	0/605 (0%)	1/611 (0.16%)
Peritonitis [A] *	1/605 (0.17%)	1/611 (0.16%)
Proctalgia [A] *	0/605 (0%)	3/611 (0.49%)
Rectal haemorrhage [A] *	4/605 (0.66%)	6/611 (0.98%)
Rectal obstruction [A] *	0/605 (0%)	1/611 (0.16%)
Rectal stenosis [A] *	1/605 (0.17%)	0/611 (0%)
Small intestinal obstruction [A] *	2/605 (0.33%)	5/611 (0.82%)
Small intestinal perforation [A] *	1/605 (0.17%)	1/611 (0.16%)
Stomatitis [A] *	0/605 (0%)	8/611 (1.31%)
Subileus [A] *	0/605 (0%)	2/611 (0.33%)
Vomiting [A] *	7/605 (1.16%)	10/611 (1.64%)
General disorders		
Asthenia [A] *	4/605 (0.66%)	5/611 (0.82%)
Death [A] *	1/605 (0.17%)	2/611 (0.33%)
Disease progression [A] *	14/605 (2.31%)	16/611 (2.62%)
Fatigue [A] *	3/605 (0.5%)	2/611 (0.33%)
General physical health deterioration [A] *	1/605 (0.17%)	1/611 (0.16%)
Malaise [A] *	0/605 (0%)	1/611 (0.16%)
Medical device complication [A] *	0/605 (0%)	1/611 (0.16%)
Mucosal inflammation [A] *	0/605 (0%)	1/611 (0.16%)
Non-cardiac chest pain [A] *	1/605 (0.17%)	2/611 (0.33%)
Oedema peripheral [A] *	3/605 (0.5%)	0/611 (0%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Pain [A] *	1/605 (0.17%)	2/611 (0.33%)
Pyrexia [A] *	15/605 (2.48%)	10/611 (1.64%)
Sudden death [A] *	1/605 (0.17%)	0/611 (0%)
Suprapubic pain [A] *	1/605 (0.17%)	0/611 (0%)
Thrombosis in device [A] *	0/605 (0%)	2/611 (0.33%)
Hepatobiliary disorders		
Bile duct obstruction [A] *	0/605 (0%)	1/611 (0.16%)
Biliary colic [A] *	1/605 (0.17%)	0/611 (0%)
Cholangitis [A] *	1/605 (0.17%)	1/611 (0.16%)
Cholecystitis [A] *	1/605 (0.17%)	4/611 (0.65%)
Hepatic function abnormal [A] *	1/605 (0.17%)	0/611 (0%)
Hepatic haemorrhage [A] *	0/605 (0%)	1/611 (0.16%)
Hepatitis [A] *	1/605 (0.17%)	0/611 (0%)
Hepatotoxicity [A] *	1/605 (0.17%)	0/611 (0%)
Hyperbilirubinaemia [A] *	4/605 (0.66%)	2/611 (0.33%)
Jaundice cholestatic [A] *	1/605 (0.17%)	0/611 (0%)
Immune system disorders		
Hypersensitivity [A] *	2/605 (0.33%)	0/611 (0%)
Infections and infestations		
Abscess jaw [A] *	0/605 (0%)	1/611 (0.16%)
Anal abscess [A] *	1/605 (0.17%)	1/611 (0.16%)
Appendicitis [A] *	0/605 (0%)	1/611 (0.16%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Bacterial sepsis [A] *	0/605 (0%)	1/611 (0.16%)
Beta haemolytic streptococcal infection [A] *	0/605 (0%)	1/611 (0.16%)
Bronchitis [A] *	0/605 (0%)	1/611 (0.16%)
Bronchopneumonia [A] *	1/605 (0.17%)	0/611 (0%)
Catheter site infection [A] *	0/605 (0%)	3/611 (0.49%)
Clostridial infection [A] *	0/605 (0%)	1/611 (0.16%)
Cystitis [A] *	1/605 (0.17%)	0/611 (0%)
Device related infection [A] *	6/605 (0.99%)	5/611 (0.82%)
Device related sepsis [A] *	0/605 (0%)	1/611 (0.16%)
Diverticulitis [A] *	0/605 (0%)	1/611 (0.16%)
Emphysematous cystitis [A] *	0/605 (0%)	1/611 (0.16%)
Enterocolitis infectious [A] *	0/605 (0%)	1/611 (0.16%)
Escherichia infection [A] *	1/605 (0.17%)	0/611 (0%)
Gastroenteritis [A] *	2/605 (0.33%)	1/611 (0.16%)
Infection [A] *	1/605 (0.17%)	1/611 (0.16%)
Lobar pneumonia [A] *	5/605 (0.83%)	0/611 (0%)
Lower respiratory tract infection [A] *	2/605 (0.33%)	1/611 (0.16%)
Lung infection [A] *	1/605 (0.17%)	1/611 (0.16%)
Neutropenic infection [A] *	5/605 (0.83%)	4/611 (0.65%)
Neutropenic sepsis [A] *	0/605 (0%)	3/611 (0.49%)
Oesophageal candidiasis [A] *	0/605 (0%)	1/611 (0.16%)
Oral candidiasis [A] *	0/605 (0%)	1/611 (0.16%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Pelvic abscess [A] *	0/605 (0%)	1/611 (0.16%)
Perinephric abscess [A] *	0/605 (0%)	1/611 (0.16%)
Perirectal abscess [A] *	0/605 (0%)	3/611 (0.49%)
Peritonitis bacterial [A] *	0/605 (0%)	1/611 (0.16%)
Pharyngitis [A] *	0/605 (0%)	1/611 (0.16%)
Pneumonia [A] *	5/605 (0.83%)	11/611 (1.8%)
Pneumonia streptococcal [A] *	0/605 (0%)	1/611 (0.16%)
Rectal abscess [A] *	0/605 (0%)	1/611 (0.16%)
Respiratory tract infection [A] *	0/605 (0%)	1/611 (0.16%)
Sepsis [A] *	5/605 (0.83%)	8/611 (1.31%)
Septic shock [A] *	0/605 (0%)	2/611 (0.33%)
Sinusitis [A] *	0/605 (0%)	1/611 (0.16%)
Staphylococcal sepsis [A] *	0/605 (0%)	1/611 (0.16%)
Subcutaneous abscess [A] *	0/605 (0%)	1/611 (0.16%)
Upper respiratory tract infection [A] *	0/605 (0%)	1/611 (0.16%)
Urinary tract infection [A] *	3/605 (0.5%)	8/611 (1.31%)
Viral diarrhoea [A] *	1/605 (0.17%)	0/611 (0%)
Viral infection [A] *	1/605 (0.17%)	0/611 (0%)
Injury, poisoning and procedural complications		
Ankle fracture [A] *	0/605 (0%)	1/611 (0.16%)
Fall [A] *	1/605 (0.17%)	0/611 (0%)
Femoral neck fracture [A] *	1/605 (0.17%)	0/611 (0%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Femur fracture [A] *	1/605 (0.17%)	0/611 (0%)
Gastrointestinal stoma complication [A] *	0/605 (0%)	3/611 (0.49%)
Head injury [A] *	1/605 (0.17%)	0/611 (0%)
Incisional hernia [A] *	0/605 (0%)	1/611 (0.16%)
Limb traumatic amputation [A] *	0/605 (0%)	1/611 (0.16%)
Pneumothorax traumatic [A] *	1/605 (0.17%)	0/611 (0%)
Post procedural haemorrhage [A] *	1/605 (0.17%)	2/611 (0.33%)
Skin laceration [A] *	1/605 (0.17%)	0/611 (0%)
Subdural haematoma [A] *	0/605 (0%)	1/611 (0.16%)
Wound dehiscence [A] *	1/605 (0.17%)	0/611 (0%)
Investigations		
Blood bilirubin increased [A] *	1/605 (0.17%)	0/611 (0%)
Blood creatine increased [A] *	0/605 (0%)	1/611 (0.16%)
Blood creatinine increased [A] *	2/605 (0.33%)	2/611 (0.33%)
C-reactive protein increased [A] *	1/605 (0.17%)	0/611 (0%)
Haemoglobin decreased [A] *	0/605 (0%)	1/611 (0.16%)
Hepatic enzyme increased [A] *	0/605 (0%)	1/611 (0.16%)
International normalised ratio increased [A] *	0/605 (0%)	1/611 (0.16%)
Neutrophil count decreased [A] *	0/605 (0%)	1/611 (0.16%)
Metabolism and nutrition disorders		
Decreased appetite [A] *	2/605 (0.33%)	3/611 (0.49%)
Dehydration [A] *	7/605 (1.16%)	24/611 (3.93%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Diabetes mellitus [A] *	0/605 (0%)	1/611 (0.16%)
Failure to thrive [A] *	1/605 (0.17%)	0/611 (0%)
Hypoglycaemia [A] *	0/605 (0%)	2/611 (0.33%)
Hyponatraemia [A] *	0/605 (0%)	2/611 (0.33%)
Hypoproteinaemia [A] *	1/605 (0.17%)	0/611 (0%)
Musculoskeletal and connective tissue disorders		
Back pain [A] *	4/605 (0.66%)	3/611 (0.49%)
Bone pain [A] *	1/605 (0.17%)	1/611 (0.16%)
Bursitis [A] *	1/605 (0.17%)	0/611 (0%)
Fistula [A] *	0/605 (0%)	1/611 (0.16%)
Musculoskeletal chest pain [A] *	2/605 (0.33%)	0/611 (0%)
Osteonecrosis of jaw [A] *	0/605 (0%)	1/611 (0.16%)
Pathological fracture [A] *	1/605 (0.17%)	0/611 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Benign neoplasm of cervix uteri [A] *	0/605 (0%)	1/611 (0.16%)
Bladder cancer [A] *	0/605 (0%)	1/611 (0.16%)
Cancer pain [A] *	1/605 (0.17%)	1/611 (0.16%)
Metastases to central nervous system [A] *	1/605 (0.17%)	1/611 (0.16%)
Metastatic pain [A] *	3/605 (0.5%)	2/611 (0.33%)
Tumour associated fever [A] *	0/605 (0%)	1/611 (0.16%)
Tumour pain [A] *	1/605 (0.17%)	1/611 (0.16%)
Nervous system disorders		

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Aphasia [A] *	1/605 (0.17%)	0/611 (0%)
Brachial plexopathy [A] *	1/605 (0.17%)	0/611 (0%)
Cerebrovascular accident [A] *	0/605 (0%)	1/611 (0.16%)
Coma [A] *	0/605 (0%)	1/611 (0.16%)
Convulsion [A] *	0/605 (0%)	1/611 (0.16%)
Disturbance in attention [A] *	1/605 (0.17%)	0/611 (0%)
Haemorrhage intracranial [A] *	1/605 (0.17%)	0/611 (0%)
Headache [A] *	1/605 (0.17%)	3/611 (0.49%)
Metabolic encephalopathy [A] *	0/605 (0%)	1/611 (0.16%)
Migraine [A] *	0/605 (0%)	1/611 (0.16%)
Peripheral sensory neuropathy [A] *	0/605 (0%)	1/611 (0.16%)
Presyncope [A] *	0/605 (0%)	1/611 (0.16%)
Spinal cord compression [A] *	1/605 (0.17%)	0/611 (0%)
Syncope [A] *	3/605 (0.5%)	1/611 (0.16%)
Transient ischaemic attack [A] *	0/605 (0%)	2/611 (0.33%)
Psychiatric disorders		
Anxiety [A] *	0/605 (0%)	1/611 (0.16%)
Confusional state [A] *	2/605 (0.33%)	2/611 (0.33%)
Depression [A] *	0/605 (0%)	1/611 (0.16%)
Hallucination [A] *	0/605 (0%)	1/611 (0.16%)
Mental status changes [A] *	0/605 (0%)	1/611 (0.16%)
Renal and urinary disorders		

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Bladder neck obstruction [A] *	0/605 (0%)	1/611 (0.16%)
Cystitis haemorrhagic [A] *	0/605 (0%)	1/611 (0.16%)
Haematuria [A] *	2/605 (0.33%)	1/611 (0.16%)
Hydronephrosis [A] *	3/605 (0.5%)	1/611 (0.16%)
Nephrolithiasis [A] *	1/605 (0.17%)	0/611 (0%)
Nephrotic syndrome [A] *	0/605 (0%)	1/611 (0.16%)
Obstructive uropathy [A] *	1/605 (0.17%)	0/611 (0%)
Proteinuria [A] *	0/605 (0%)	1/611 (0.16%)
Renal failure [A] *	1/605 (0.17%)	1/611 (0.16%)
Renal failure acute [A] *	0/605 (0%)	2/611 (0.33%)
Renal impairment [A] *	0/605 (0%)	2/611 (0.33%)
Renal vein thrombosis [A] *	0/605 (0%)	1/611 (0.16%)
Urinary incontinence [A] *	1/605 (0.17%)	0/611 (0%)
Urinary retention [A] *	1/605 (0.17%)	4/611 (0.65%)
Urinary tract obstruction [A] *	1/605 (0.17%)	0/611 (0%)
Reproductive system and breast disorders		
Balanitis [A] *	0/605 (0%)	1/611 (0.16%)
Pelvic pain [A] *	1/605 (0.17%)	0/611 (0%)
Respiratory, thoracic and mediastinal disorders		
Acute pulmonary oedema [A] *	0/605 (0%)	1/611 (0.16%)
Acute respiratory distress syndrome [A] *	0/605 (0%)	1/611 (0.16%)
Acute respiratory failure [A] *	0/605 (0%)	1/611 (0.16%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Atelectasis [A] *	0/605 (0%)	1/611 (0.16%)
Cough [A] *	0/605 (0%)	1/611 (0.16%)
Dyspnoea [A] *	3/605 (0.5%)	3/611 (0.49%)
Epistaxis [A] *	0/605 (0%)	2/611 (0.33%)
Interstitial lung disease [A] *	2/605 (0.33%)	0/611 (0%)
Oropharyngeal pain [A] *	0/605 (0%)	1/611 (0.16%)
Pleural effusion [A] *	0/605 (0%)	1/611 (0.16%)
Pleuritic pain [A] *	0/605 (0%)	1/611 (0.16%)
Pneumomediastinum [A] *	0/605 (0%)	1/611 (0.16%)
Pneumonia aspiration [A] *	0/605 (0%)	1/611 (0.16%)
Pneumonitis [A] *	1/605 (0.17%)	1/611 (0.16%)
Pneumothorax [A] *	0/605 (0%)	2/611 (0.33%)
Pulmonary artery thrombosis [A] *	0/605 (0%)	1/611 (0.16%)
Pulmonary embolism [A] *	12/605 (1.98%)	19/611 (3.11%)
Pulmonary hypertension [A] *	0/605 (0%)	1/611 (0.16%)
Skin and subcutaneous tissue disorders		
Rash maculo-papular [A] *	0/605 (0%)	1/611 (0.16%)
Vascular disorders		
Arterial thrombosis limb [A] *	1/605 (0.17%)	0/611 (0%)
Circulatory collapse [A] *	1/605 (0.17%)	1/611 (0.16%)
Deep vein thrombosis [A] *	7/605 (1.16%)	7/611 (1.15%)
Embolism arterial [A] *	0/605 (0%)	1/611 (0.16%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Hypertension [A] *	0/605 (0%)	10/611 (1.64%)
Hypotension [A] *	0/605 (0%)	1/611 (0.16%)
Hypovolaemic shock [A] *	0/605 (0%)	1/611 (0.16%)
Jugular vein thrombosis [A] *	2/605 (0.33%)	0/611 (0%)
Orthostatic hypotension [A] *	0/605 (0%)	1/611 (0.16%)
Pelvic venous thrombosis [A] *	2/605 (0.33%)	0/611 (0%)
Subclavian vein thrombosis [A] *	2/605 (0.33%)	1/611 (0.16%)
Superior vena caval occlusion [A] *	0/605 (0%)	1/611 (0.16%)
Thrombophlebitis [A] *	1/605 (0.17%)	0/611 (0%)
Vena cava thrombosis [A] *	2/605 (0.33%)	2/611 (0.33%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.1

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Total	575/605 (95.04%)	599/611 (98.04%)
Blood and lymphatic system disorders		
Neutropenia [A] *	202/605 (33.39%)	229/611 (37.48%)
Gastrointestinal disorders		
Abdominal pain [A] *	141/605 (23.31%)	158/611 (25.86%)
Abdominal pain upper [A] *	46/605 (7.6%)	63/611 (10.31%)
Constipation [A] *	146/605 (24.13%)	135/611 (22.09%)
Diarrhoea [A] *	335/605 (55.37%)	411/611 (67.27%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Dyspepsia [A] *	56/605 (9.26%)	50/611 (8.18%)
Haemorrhoids [A] *	13/605 (2.15%)	34/611 (5.56%)
Nausea [A] *	327/605 (54.05%)	322/611 (52.7%)
Proctalgia [A] *	11/605 (1.82%)	32/611 (5.24%)
Stomatitis [A] *	199/605 (32.89%)	304/611 (49.75%)
Vomiting [A] *	199/605 (32.89%)	194/611 (31.75%)
General disorders		
Asthenia [A] *	77/605 (12.73%)	109/611 (17.84%)
Fatigue [A] *	234/605 (38.68%)	292/611 (47.79%)
Oedema peripheral [A] *	42/605 (6.94%)	52/611 (8.51%)
Pyrexia [A] *	73/605 (12.07%)	77/611 (12.6%)
Infections and infestations		
Urinary tract infection [A] *	35/605 (5.79%)	51/611 (8.35%)
Investigations		
Weight decreased [A] *	87/605 (14.38%)	195/611 (31.91%)
Metabolism and nutrition disorders		
Decreased appetite [A] *	143/605 (23.64%)	195/611 (31.91%)
Dehydration [A] *	12/605 (1.98%)	33/611 (5.4%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	40/605 (6.61%)	31/611 (5.07%)
Back pain [A] *	69/605 (11.4%)	72/611 (11.78%)
Pain in extremity [A] *	33/605 (5.45%)	34/611 (5.56%)
Nervous system disorders		

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Dizziness [A] *	53/605 (8.76%)	36/611 (5.89%)
Dysgeusia [A] *	32/605 (5.29%)	42/611 (6.87%)
Headache [A] *	53/605 (8.76%)	136/611 (22.26%)
Lethargy [A] *	28/605 (4.63%)	33/611 (5.4%)
Neuropathy peripheral [A] *	30/605 (4.96%)	34/611 (5.56%)
Psychiatric disorders		
Insomnia [A] *	45/605 (7.44%)	47/611 (7.69%)
Renal and urinary disorders		
Proteinuria [A] *	9/605 (1.49%)	63/611 (10.31%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	58/605 (9.59%)	67/611 (10.97%)
Dysphonia [A] *	20/605 (3.31%)	155/611 (25.37%)
Dyspnoea [A] *	51/605 (8.43%)	69/611 (11.29%)
Epistaxis [A] *	45/605 (7.44%)	168/611 (27.5%)
Oropharyngeal pain [A] *	19/605 (3.14%)	45/611 (7.36%)
Rhinorrhoea [A] *	11/605 (1.82%)	38/611 (6.22%)
Skin and subcutaneous tissue disorders		
Alopecia [A] *	182/605 (30.08%)	164/611 (26.84%)
Hyperhidrosis [A] *	33/605 (5.45%)	17/611 (2.78%)
Palmar-plantar erythrodysaesthesia syndrome [A] *	26/605 (4.3%)	67/611 (10.97%)
Rash [A] *	35/605 (5.79%)	41/611 (6.71%)
Skin hyperpigmentation [A] *	17/605 (2.81%)	50/611 (8.18%)

	Placebo/FOLFIRI	Aflibercept/FOLFIRI
	Affected/At Risk (%)	Affected/At Risk (%)
Vascular disorders		
Hypertension [A] *	65/605 (10.74%)	250/611 (40.92%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The investigator shall have the right to independently publish study results from his site after a multicenter publication, or 12 months after the completion of the study by all sites. He must provide the sponsor a copy of any such publication derived from the study for review and comment at least 45 days (20 days for abstracts) in advance of any submission, and delay publication till the approval of the publication is given in writing by the Sponsor (not to exceed ninety days).

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