ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 06/21/2013

Study of Aflibercept And Modified FOLFOX6 As First-Line Treatment In Patients With Metastatic Colorectal Cancer (AFFIRM)

This study has been completed.

Sponsor:	Sanofi
Collaborators:	
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00851084

Purpose

The primary objective of the study is to estimate the progression-free survival rate at 12 months for the two arms of the study.

Secondary objectives include the evaluation of overall objective response rate to treatment, progression-free survival, overall survival, safety and documentation of potential immunogenicity of aflibercept.

This study was a non-comparative randomized trial and was not powered for a comparison of any of the efficacy endpoints.

Rather, the aim of the trial was to get, for all endpoints, an estimation of the efficacy and safety of aflibercept combined with a modified FOLFOX6 regimen. In such type of non-comparative randomized trial, the control FOLFOLX6 arm was intended to only act as a check on the similarity of the current patients to the historical controls with respect to clinical outcome when given FOLFOX6 treatment.

Condition	Intervention	Phase
Colorectal Neoplasms Neoplasm Metastasis	Drug: aflibercept Drug: oxaliplatin Drug: 5-FU Drug: Folinic Acid	Phase 2

Study Type: Interventional

Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Efficacy Study
Official Title: Randomized, Multinational, Study Of Aflibercept And Modified FOLFOX6 As First-Line Treatment In Patients With Metastatic Colorectal Cancer

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Progression Free Survival (PFS) Rate at 12 Months [Time Frame: 12 months] [Designated as safety issue: No]

  PFS rate at 12 months was defined as the percentage of patients alive without disease progression at 12 months after randomization. The primary efficacy analysis was based on assessment by the Independent Review Committee (IRC). The study was not powered for comparison of PFS rate at 12 months between the two arms (non-comparative, open-label study). Progression was defined using Response Evaluation Criteria In Solid Tumors (RECIST v1.0), as at least a 20 percent increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non target-lesions.

Secondary Outcome Measures:

- Progression Free Survival (PFS) [Time Frame: From the date of the first randomization until the study data cut-off date, 14 April 2011 (approximately 26 months)] [Designated as safety issue: No]

  PFS was defined as the time from the date of randomization to the date of tumor progression or death from any cause, whichever occurred first. PFS was based on tumor assessment by the Independent Review Committee (IRC). PFS was estimated from Kaplan-Meier Curves. The study was not powered for comparison of PFS between the two arms (non-comparative, open-label study). Progression was defined using Response Evaluation Criteria In Solid Tumors (RECIST v1.0), as at least a 20 percent increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non target-lesions.
- Overall Objective Response Rate (ORR) [Time Frame: From the date of the first randomization until the study data cut-off date, 14 April 2011 (approximately 26 months)] [Designated as safety issue: No]

  Summary of overall objective response rate based on tumor assessment by the Independent Review Committee (IRC) as per Response Evaluation Criteria in Solid Tumours (RECIST) criteria. ORR was defined as the proportion of patients with confirmed Complete Response (CR) or confirmed Partial Response (PR) relative to the total number of patients in the analysis population. Per RECIST v 1.0 target lesions evaluation and assessed by tumor imaging: Complete Response (CR): Disappearance of all target lesions; Partial Response (PR): >=30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. The study was not powered for comparison of ORR between the two arms (non-comparative, open-label study).
- Overall Survival (OS) [Time Frame: From the date of the first randomization until the study data cut-off date, 14 April 2011 (approximately 26 months)] [Designated as safety issue: No]

  Overall survival was defined as the time from the date of randomization to the date of death due to any cause. In absence of confirmation of death, survival time was censored at the earliest between the last date the patient was known to be alive and the study cutoff date. The study was not powered for comparison of OS between the two arms (non-comparative, open-label study).
- Number of Participants With Treatment-emergent Adverse Events (TEAE) [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]

  Summary of treatment-emergent adverse events in the safety population. The National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE), version 3.0 was used in this study to grade the severity of AEs.
- Immunogenicity of Intravenous (IV) Aflibercept [Time Frame: Any time post baseline and 90 days after the last infusion of aflibercept, according to baseline status] [Designated as safety issue: No]

  The antidrug antibody (ADA) assay was evaluated for participants receiving aflibercept.

Enrollment: 268
Study Start Date: February 2009
Primary Completion Date: April 2011

Study Completion Date: January 2012

Arms	Assigned Interventions
Active Comparator: mFOLFOX6 only modified FOLFOX6 chemotherapy regimen	Drug: oxaliplatin administration: IV infusion Drug: 5-FU administration: IV infusion Drug: Folinic Acid administration: IV infusion
Experimental: mFOLFOX6 + aflibercept modified FOLFOX6 chemotherapy regimen in combination with aflibercept	Drug: aflibercept administration: IV infusion Other Names: ZALTRAP™ AVE0005 Drug: oxaliplatin administration: IV infusion Drug: 5-FU administration: IV infusion Drug: Folinic Acid administration: IV infusion

Eligibility

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

Criteria

Inclusion Criteria:

- Histologically proven adenocarcinoma of the colon or the rectum
- Metastatic disease not amenable to potentially curative treatment

Exclusion Criteria:

- Prior therapy for metastatic cancer of the colon or the rectum
- Prior treatment with angiogenesis inhibitors

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

Contacts and Locations

Locations

- Australia
  - sanofi-aventis investigational site number 036004
    - Douglas, Australia, 4814
  - sanofi-aventis investigational site number 036001
    - Hunter Region Mail Centre, Australia, 2310
  - sanofi-aventis investigational site number 036003
    - Hunter Region Mail Centre, Australia, 2310
- Germany
  - sanofi-aventis investigational site number 276003
    - Berlin, Germany, 13353
  - sanofi-aventis investigational site number 276007
    - Dresden, Germany, 01307
  - sanofi-aventis investigational site number 276001
    - Hannover, Germany, 30625
  - sanofi-aventis investigational site number 276006
    - Homberg, Germany, 66421
  - sanofi-aventis investigational site number 276004
    - Mannheim, Germany, 68167
  - sanofi-aventis investigational site number 276002
    - Münster, Germany, 48149
  - sanofi-aventis investigational site number 276005
    - Recklinghausen, Germany, 45659
- Italy
  - sanofi-aventis investigational site number 380005
    - Bari, Italy, 70126
  - sanofi-aventis investigational site number 380001
    - Firenze, Italy, 50141
  - sanofi-aventis investigational site number 380002
    - Milano, Italy, 20121
  - sanofi-aventis investigational site number 380003
    - Taormina, Italy, 98039
  - sanofi-aventis investigational site number 380004
    - Torino, Italy, 10126
- Korea, Republic of
  - sanofi-aventis investigational site number 410003
    - Busan, Korea, Republic of, 614-735
  - sanofi-aventis investigational site number 410004
    - Cheongju, Korea, Republic of, 361-711
  - sanofi-aventis investigational site number 410005
    - Daegu, Korea, Republic of, 700-721
  - sanofi-aventis investigational site number 410002

Daejeon, Korea, Republic of
sanofi-aventis investigational site number 410007
Goyang-Si, Gyeonggi-Do, Korea, Republic of, 410-769
sanofi-aventis investigational site number 410001
Seoul, Korea, Republic of, 152-703
sanofi-aventis investigational site number 410006
Seoul, Korea, Republic of, 120-752
sanofi-aventis investigational site number 410008
Ulsan, Korea, Republic of, 682-714
Russian Federation
sanofi-aventis investigational site number 643002
Pyatigorsk, Russian Federation, 357500
sanofi-aventis investigational site number 643005
Saint-Petersburg, Russian Federation, 197758
sanofi-aventis investigational site number 643001
Sochi, Russian Federation, 354057
Spain
sanofi-aventis investigational site number 724005
Barcelona, Spain, 08036
sanofi-aventis investigational site number 724001
Madrid, Spain, 28040
sanofi-aventis investigational site number 724004
Madrid, Spain, 28007
sanofi-aventis investigational site number 724002
Sabadell, Spain, 08208
sanofi-aventis investigational site number 724007
Santiago De Compostela, Spain, 15706
sanofi-aventis investigational site number 724003
Valencia, Spain, 46009
United Kingdom
sanofi-aventis investigational site number 826004
Leeds, United Kingdom, LS9 7TF
sanofi-aventis investigational site number 826001
Leicester, United Kingdom, LE1 5WW
sanofi-aventis investigational site number 826002
Manchester, United Kingdom, M20 4BX
sanofi-aventis investigational site number 826003
Slough, United Kingdom, SL2 4HL
sanofi-aventis investigational site number 826005
Southampton, United Kingdom, SO16 6YD

Investigators

Principal Investigator:	John Zalcberg, MD	Peter Mc Callum Cancer Centre, Melbourne, Australia

More Information

Responsible Party:	Sanofi
Study ID Numbers:	EFC10668 EudraCT 2008-004178-41
Health Authority:	United Kingdom: Medicines and Healthcare Products Regulatory Agency

Study Results

Participant Flow

Pre-Assignment Details	There were 268 patients screened (informed consent signed) for this study. Of these screened patients, 236 patients were subsequently randomly assigned to treatments. 32 patients were screen failures.

Reporting Groups

	Description
mFOLFOX6 Only	modified FOLFOX6
mFOLFOX6 + Aflibercept	modified FOLFOX6 in combination with aflibercept

Overall Study

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
Started	117	119
Completed	0 [1]	0 [1]
Not Completed	117	119
Randomized but not treated	1	0
Adverse Event	26	36
Disease progression	52	47
Poor compliance to protocol	1	1
Physician Decision	13	14
Consent withdrawn	0	2
Withdrawal by Subject	11	12

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
Metastatic surgery	6	6
Not specified	7	1

[1] Participants continued treatment until they met treatment discontinuation criteria.

Baseline Characteristics

Reporting Groups

	Description
mFOLFOX6 Only	modified FOLFOX6
mFOLFOX6 + Aflibercept	modified FOLFOX6 in combination with aflibercept

Baseline Measures

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept	Total
Number of Participants	117	119	236
Age, Continuous [units: Years] Mean (Standard Deviation)	62.4 (9.7)	61.8 (9.0)	62.1 (9.4)
Age, Customized [units: Participants]			
<65	65	70	135
>=65 but <75	43	45	88
>=75	9	4	13
Gender, Male/Female [units: Participants]			
Female	49	43	92
Male	68	76	144
Race/Ethnicity, Customized [units: Participants]			
Caucasian/White	90	97	187
Black	0	1	1
Asian/Oriental	27	20	47

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept	Total
Other	0	1	1
Region of Enrollment [units: participants]			
United Kingdom	22	28	50
Korea, Republic of	26	20	46
Germany	18	24	42
Spain	24	18	42
Russian Federation	15	15	30
Italy	10	5	15
Australia	2	9	11
Body Surface Are (BSA) [units: m^2] Mean (Standard Deviation)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression Free Survival (PFS) Rate at 12 Months
Measure Description	PFS rate at 12 months was defined as the percentage of patients alive without disease progression at 12 months after randomization. The primary efficacy analysis was based on assessment by the Independent Review Committee (IRC). The study was not powered for comparison of PFS rate at 12 months between the two arms (non-comparative, open-label study). Progression was defined using Response Evaluation Criteria In Solid Tumors (RECIST v1.0), as at least a 20 percent increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non target-lesions.
Time Frame	12 months
Safety Issue?	No

Analysis Population Description

Analyses of PFS rate was performed in the evaluable patient (EP) population as the primary analysis population. Overall, 9 patients from the randomized population were excluded from the EP population.

Reporting Groups

	Description
mFOLFOX6 Only	modified FOLFOX6
mFOLFOX6 + Aflibercept	modified FOLFOX6 in combination with aflibercept

Measured Values

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
Number of Participants Analyzed	111	116
Progression Free Survival (PFS) Rate at 12 Months [units: percentage of participants] Number (95% Confidence Interval)	21.2 (12.2 to 30.3)	25.8 (17.2 to 34.4)

2. Secondary Outcome Measure:

Measure Title	Progression Free Survival (PFS)
Measure Description	PFS was defined as the time from the date of randomization to the date of tumor progression or death from any cause, whichever occurred first. PFS was based on tumor assessment by the Independent Review Committee (IRC). PFS was estimated from Kaplan-Meier Curves. The study was not powered for comparison of PFS between the two arms (non-comparative, open-label study). Progression was defined using Response Evaluation Criteria In Solid Tumors (RECIST v1.0), as at least a 20 percent increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non target-lesions.
Time Frame	From the date of the first randomization until the study data cut-off date, 14 April 2011 (approximately 26 months)
Safety Issue?	No

Analysis Population Description

Evaluable patient (EP) population. A total of 55 patients (32 in the mFOLFOX6 group and 23 in the mFOLFOX6 + aflibercept group) were without an event at the cutoff date for the PFS analysis by IRC.

Reporting Groups

	Description
mFOLFOX6 Only	modified FOLFOX6
mFOLFOX6 + Aflibercept	modified FOLFOX6 in combination with aflibercept

Measured Values

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
Number of Participants Analyzed	111	116
Number of Events Analyzed	79	93
Progression Free Survival (PFS) [units: Months] Median (95% Confidence Interval)	8.77 (7.622 to 9.265)	8.48 (7.885 to 9.922)

3. Secondary Outcome Measure:

Measure Title	Overall Objective Response Rate (ORR)
Measure Description	Summary of overall objective response rate based on tumor assessment by the Independent Review Committee (IRC) as per Response Evaluation Criteria in Solid Tumours (RECIST) criteria. ORR was defined as the proportion of patients with confirmed Complete Response (CR) or confirmed Partial Response (PR) relative to the total number of patients in the analysis population. Per RECIST v 1.0 target lesions evaluation and assessed by tumor imaging: Complete Response (CR): Disappearance of all target lesions; Partial Response (PR): >=30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. The study was not powered for comparison of ORR between the two arms (non-comparative, open-label study).
Time Frame	From the date of the first randomization until the study data cut-off date, 14 April 2011 (approximately 26 months)
Safety Issue?	No

Analysis Population Description
Evaluable Patient population.

Reporting Groups

	Description
mFOLFOX6 Only	modified FOLFOX6
mFOLFOX6 + Aflibercept	modified FOLFOX6 in combination with aflibercept

Measured Values

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
Number of Participants Analyzed	111	116
Overall Objective Response Rate (ORR) [units: percentage of participants]	45.9 (36.4 to 55.7)	49.1 (39.7 to 58.6)

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
Number (95% Confidence Interval)		

4. Secondary Outcome Measure:

Measure Title	Overall Survival (OS)
Measure Description	Overall survival was defined as the time from the date of randomization to the date of death due to any cause. In absence of confirmation of death, survival time was censored at the earliest between the last date the patient was known to be alive and the study cutoff date. The study was not powered for comparison of OS between the two arms (non-comparative, open-label study).
Time Frame	From the date of the first randomization until the study data cut-off date, 14 April 2011 (approximately 26 months)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population (ITT) – all participants who gave informed consent and were randomized. Of the 268 screened participants, 236 were randomly assigned to treatments, whereas 32 participants were screen failures.

Reporting Groups

	Description
mFOLFOX6 Only	modified FOLFOX6
mFOLFOX6 + Aflibercept	modified FOLFOX6 in combination with aflibercept

Measured Values

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
Number of Participants Analyzed	117	119
Number of Events (Death) Analyzed	50	51
Overall Survival (OS) [units: months] Median (95% Confidence Interval)	22.31 (15.57 to NA) [1]	19.45 (15.64 to NA) [1]

[1] Insufficient number of participants with events. Data have limited maturity and the Kaplan-Meier estimates of median OS are inherently imprecise.

5. Secondary Outcome Measure:

Measure Title	Number of Participants With Treatment-emergent Adverse Events (TEAE)
Measure Description	Summary of treatment-emergent adverse events in the safety population. The National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE), version 3.0 was used in this study to grade the severity of AEs.
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

Of the total 235 patients included in the safety population, 116 patients received mFOLFOX6 and 119 patients received mFOLFOX6 + aflibercept. One patient, randomly assigned to the mFOLFOX6 arm did not receive any study treatment and was therefore excluded from the safety analyses.

Reporting Groups

	Description
mFOLFOX6 Only	modified FOLFOX6
mFOLFOX6 + Aflibercept	modified FOLFOX6 in combination with aflibercept

Measured Values

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
Number of Participants Analyzed	116	119
Number of Participants With Treatment-emergent Adverse Events (TEAE) [units: participants]		
Treatment Emergent Adverse Event (TEAE)	115	119
Grade 3-4 TEAE	87	108
Treatment emergent Serious Adverse Event (SAE)	32	55
TEAE leading to death	2	8
Premature treatment discontinuation	NA [1]	34
Permanent treatment discontinuation	26	37

[1] Analysis was limited to mFOLFOX6 + aflibercept arm.

6. Secondary Outcome Measure:

Measure Title	Immunogenicity of Intravenous (IV) Aflibercept
Measure Description	The antidrug antibody (ADA) assay was evaluated for participants receiving aflibercept.
Time Frame	Any time post baseline and 90 days after the last infusion of aflibercept, according to baseline status
Safety Issue?	No

Analysis Population Description

Participants treated with aflibercept and evaluable for antibody assessment.

Reporting Groups

	Description
Negative or Missing	Negative or missing antidrug antibody (ADA) assay status at Baseline for those participants treated with aflibercept.
Positive	Positive antidrug antibody (ADA) assay status at Baseline for those participants treated with aflibercept.

Measured Values

	Negative or Missing	Positive
Number of Participants Analyzed	112	3
Immunogenicity of Intravenous (IV) Aflibercept [units: participants]		
ADA Negative post-baseline	105	1
ADA Positive (drug specific) post-baseline	7	2
ADA Negative 90 days after last dose	45	1
ADA Positive 90 days after last dose	0	1

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	Of the total 235 patients included in the safety population, 116 patients received mFOLFOX6 and 119 patients received aflibercept+mFOLFOX6. One patient, randomly assigned to the mFOLFOX6 arm did not receive any study treatment and was therefore excluded from the safety analyses.

Reporting Groups

	Description
mFOLFOX6 Only	modified FOLFOX6
mFOLFOX6 + Aflibercept	modified FOLFOX6 in combination with aflibercept

Serious Adverse Events

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Total	32/116 (27.59%)	55/119 (46.22%)
Blood and lymphatic system disorders		
Febrile neutropenia [A] *	2/116 (1.72%)	2/119 (1.68%)
Neutropenia [A] *	1/116 (0.86%)	3/119 (2.52%)
Cardiac disorders		
Sinoatrial block [A] *	0/116 (0%)	1/119 (0.84%)
Ventricular arrhythmia [A] *	0/116 (0%)	1/119 (0.84%)
Endocrine disorders		
Adrenal insufficiency [A] *	0/116 (0%)	1/119 (0.84%)
Eye disorders		
Retinal detachment [A] *	1/116 (0.86%)	0/119 (0%)
Vision blurred [A] *	1/116 (0.86%)	0/119 (0%)
Gastrointestinal disorders		
Abdominal pain [A] *	2/116 (1.72%)	2/119 (1.68%)
Anal fistula [A] *	0/116 (0%)	1/119 (0.84%)
Ascites [A] *	1/116 (0.86%)	0/119 (0%)
Colonic obstruction [A] *	3/116 (2.59%)	0/119 (0%)
Constipation [A] *	0/116 (0%)	2/119 (1.68%)
Diarrhoea [A] *	3/116 (2.59%)	3/119 (2.52%)

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Dysphagia [A] *	1/116 (0.86%)	0/119 (0%)
Haematochezia [A] *	0/116 (0%)	1/119 (0.84%)
Ileal perforation [A] *	0/116 (0%)	1/119 (0.84%)
Intestinal obstruction [A] *	4/116 (3.45%)	2/119 (1.68%)
Large intestine perforation [A] *	0/116 (0%)	1/119 (0.84%)
Mechanical ileus [A] *	1/116 (0.86%)	0/119 (0%)
Melaena [A] *	1/116 (0.86%)	1/119 (0.84%)
Nausea [A] *	1/116 (0.86%)	0/119 (0%)
Rectal haemorrhage [A] *	0/116 (0%)	1/119 (0.84%)
Small intestinal obstruction [A] *	0/116 (0%)	1/119 (0.84%)
Stomatitis [A] *	1/116 (0.86%)	0/119 (0%)
Subileus [A] *	0/116 (0%)	1/119 (0.84%)
Vomiting [A] *	2/116 (1.72%)	3/119 (2.52%)
General disorders		
Disease progression [A] *	1/116 (0.86%)	4/119 (3.36%)
Fatigue [A] *	1/116 (0.86%)	2/119 (1.68%)
General physical health deterioration [A] *	1/116 (0.86%)	0/119 (0%)
Medical device complication [A] *	0/116 (0%)	1/119 (0.84%)
Pyrexia [A] *	3/116 (2.59%)	6/119 (5.04%)
Hepatobiliary disorders		
Bile duct obstruction [A] *	1/116 (0.86%)	0/119 (0%)
Hyperbilirubinaemia [A] *	1/116 (0.86%)	0/119 (0%)

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Immune system disorders		
Drug hypersensitivity [A] *	0/116 (0%)	3/119 (2.52%)
Infections and infestations		
Abdominal infection [A] *	1/116 (0.86%)	0/119 (0%)
Bacterial infection [A] *	0/116 (0%)	1/119 (0.84%)
Bronchopneumonia [A] *	0/116 (0%)	1/119 (0.84%)
Catheter site infection [A] *	3/116 (2.59%)	3/119 (2.52%)
Cystitis [A] *	1/116 (0.86%)	0/119 (0%)
Device related infection [A] *	0/116 (0%)	1/119 (0.84%)
Folliculitis [A] *	0/116 (0%)	1/119 (0.84%)
Fungaemia [A] *	1/116 (0.86%)	0/119 (0%)
Gastroenteritis [A] *	1/116 (0.86%)	0/119 (0%)
Gastroenteritis norovirus [A] *	0/116 (0%)	2/119 (1.68%)
Infection [A] *	1/116 (0.86%)	0/119 (0%)
Infectious peritonitis [A] *	0/116 (0%)	2/119 (1.68%)
Lower respiratory tract infection [A] *	0/116 (0%)	1/119 (0.84%)
Neutropenic infection [A] *	1/116 (0.86%)	0/119 (0%)
Neutropenic sepsis [A] *	1/116 (0.86%)	1/119 (0.84%)
Pneumonia [A] *	1/116 (0.86%)	4/119 (3.36%)
Pneumonia viral [A] *	0/116 (0%)	1/119 (0.84%)
Pyelonephritis [A] *	1/116 (0.86%)	0/119 (0%)
Sepsis [A] *	0/116 (0%)	1/119 (0.84%)

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Septic shock [A] *	0/116 (0%)	1/119 (0.84%)
Staphylococcal sepsis [A] *	0/116 (0%)	1/119 (0.84%)
Subcutaneous abscess [A] *	0/116 (0%)	1/119 (0.84%)
Urinary tract infection [A] *	0/116 (0%)	2/119 (1.68%)
Urosepsis [A] *	0/116 (0%)	1/119 (0.84%)
Injury, poisoning and procedural complications		
Anastomotic leak [A] *	0/116 (0%)	1/119 (0.84%)
Head injury [A] *	0/116 (0%)	1/119 (0.84%)
Postoperative wound complication [A] *	0/116 (0%)	1/119 (0.84%)
Investigations		
Neutrophil count decreased [A] *	0/116 (0%)	1/119 (0.84%)
Metabolism and nutrition disorders		
Dehydration [A] *	1/116 (0.86%)	1/119 (0.84%)
Malnutrition [A] *	0/116 (0%)	1/119 (0.84%)
Musculoskeletal and connective tissue disorders		
Pathological fracture [A] *	1/116 (0.86%)	0/119 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Neoplasm progression [A] *	0/116 (0%)	1/119 (0.84%)
Nervous system disorders		
Convulsion [A] *	0/116 (0%)	1/119 (0.84%)
Haemorrhage intracranial [A] *	0/116 (0%)	1/119 (0.84%)
Ischaemic stroke [A] *	1/116 (0.86%)	0/119 (0%)
Lethargy [A] *	1/116 (0.86%)	0/119 (0%)

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Peripheral sensory neuropathy [A] *	1/116 (0.86%)	0/119 (0%)
Posterior reversible encephalopathy syndrome [A] *	0/116 (0%)	1/119 (0.84%)
Presyncope [A] *	1/116 (0.86%)	1/119 (0.84%)
Renal and urinary disorders		
Haematuria [A] *	1/116 (0.86%)	0/119 (0%)
Proteinuria [A] *	0/116 (0%)	1/119 (0.84%)
Renal failure [A] *	0/116 (0%)	2/119 (1.68%)
Urinary retention [A] *	0/116 (0%)	1/119 (0.84%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome [A] *	0/116 (0%)	2/119 (1.68%)
Dyspnoea [A] *	0/116 (0%)	2/119 (1.68%)
Epistaxis [A] *	0/116 (0%)	1/119 (0.84%)
Pulmonary embolism [A] *	3/116 (2.59%)	4/119 (3.36%)
Skin and subcutaneous tissue disorders		
Pyoderma gangrenosum [A] *	0/116 (0%)	1/119 (0.84%)
Social circumstances		
Social stay hospitalisation [A] *	0/116 (0%)	1/119 (0.84%)
Surgical and medical procedures		
Malignant tumour excision [A] *	0/116 (0%)	1/119 (0.84%)
Tumour excision [A] *	1/116 (0.86%)	0/119 (0%)
Vascular disorders		
Circulatory collapse [A] *	1/116 (0.86%)	0/119 (0%)

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Hypertensive crisis [A] *	0/116 (0%)	1/119 (0.84%)
Lymphatic fistula [A] *	0/116 (0%)	1/119 (0.84%)
Subclavian vein thrombosis [A] *	0/116 (0%)	1/119 (0.84%)

* 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%

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Total	114/116 (98.28%)	117/119 (98.32%)
Blood and lymphatic system disorders		
Anaemia [A] *	11/116 (9.48%)	11/119 (9.24%)
Febrile neutropenia [A] *	2/116 (1.72%)	6/119 (5.04%)
Leukopenia [A] *	10/116 (8.62%)	11/119 (9.24%)
Neutropenia [A] *	64/116 (55.17%)	53/119 (44.54%)
Thrombocytopenia [A] *	25/116 (21.55%)	14/119 (11.76%)
Eye disorders		
Lacrimation increased [A] *	3/116 (2.59%)	6/119 (5.04%)
Gastrointestinal disorders		
Abdominal pain [A] *	25/116 (21.55%)	21/119 (17.65%)
Abdominal pain upper [A] *	14/116 (12.07%)	8/119 (6.72%)
Constipation [A] *	31/116 (26.72%)	37/119 (31.09%)
Diarrhoea [A] *	51/116 (43.97%)	69/119 (57.98%)
Dyspepsia [A] *	12/116 (10.34%)	21/119 (17.65%)

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Mouth ulceration [A] *	1/116 (0.86%)	6/119 (5.04%)
Nausea [A] *	62/116 (53.45%)	62/119 (52.1%)
Proctalgia [A] *	3/116 (2.59%)	6/119 (5.04%)
Stomatitis [A] *	44/116 (37.93%)	60/119 (50.42%)
Vomiting [A] *	28/116 (24.14%)	34/119 (28.57%)
General disorders		
Asthenia [A] *	30/116 (25.86%)	24/119 (20.17%)
Fatigue [A] *	30/116 (25.86%)	41/119 (34.45%)
Oedema peripheral [A] *	8/116 (6.9%)	13/119 (10.92%)
Pyrexia [A] *	18/116 (15.52%)	15/119 (12.61%)
Immune system disorders		
Drug hypersensitivity [A] *	6/116 (5.17%)	4/119 (3.36%)
Infections and infestations		
Nasopharyngitis [A] *	8/116 (6.9%)	16/119 (13.45%)
Upper respiratory tract infection [A] *	5/116 (4.31%)	6/119 (5.04%)
Urinary tract infection [A] *	12/116 (10.34%)	12/119 (10.08%)
Investigations		
Alanine aminotransferase increased [A] *	6/116 (5.17%)	2/119 (1.68%)
Aspartate aminotransferase increased [A] *	6/116 (5.17%)	3/119 (2.52%)
Weight decreased [A] *	6/116 (5.17%)	15/119 (12.61%)
Metabolism and nutrition disorders		
Decreased appetite [A] *	37/116 (31.9%)	41/119 (34.45%)
Musculoskeletal and connective tissue disorders		

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Arthralgia [A] *	6/116 (5.17%)	2/119 (1.68%)
Back pain [A] *	11/116 (9.48%)	9/119 (7.56%)
Musculoskeletal pain [A] *	2/116 (1.72%)	8/119 (6.72%)
Nervous system disorders		
Dizziness [A] *	11/116 (9.48%)	12/119 (10.08%)
Dysaesthesia [A] *	7/116 (6.03%)	7/119 (5.88%)
Dysgeusia [A] *	16/116 (13.79%)	11/119 (9.24%)
Headache [A] *	9/116 (7.76%)	39/119 (32.77%)
Lethargy [A] *	13/116 (11.21%)	14/119 (11.76%)
Neuropathy peripheral [A] *	24/116 (20.69%)	23/119 (19.33%)
Neurotoxicity [A] *	6/116 (5.17%)	0/119 (0%)
Paraesthesia [A] *	25/116 (21.55%)	18/119 (15.13%)
Peripheral sensory neuropathy [A] *	35/116 (30.17%)	23/119 (19.33%)
Polyneuropathy [A] *	16/116 (13.79%)	16/119 (13.45%)
Psychiatric disorders		
Depression [A] *	3/116 (2.59%)	7/119 (5.88%)
Insomnia [A] *	3/116 (2.59%)	10/119 (8.4%)
Renal and urinary disorders		
Proteinuria [A] *	1/116 (0.86%)	28/119 (23.53%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	14/116 (12.07%)	12/119 (10.08%)
Dysphonia [A] *	3/116 (2.59%)	22/119 (18.49%)
Dyspnoea [A] *	8/116 (6.9%)	22/119 (18.49%)

	mFOLFOX6 Only	mFOLFOX6 + Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Epistaxis [A] *	15/116 (12.93%)	34/119 (28.57%)
Oropharyngeal pain [A] *	3/116 (2.59%)	8/119 (6.72%)
Rhinorrhoea [A] *	2/116 (1.72%)	6/119 (5.04%)
Skin and subcutaneous tissue disorders		
Alopecia [A] *	15/116 (12.93%)	13/119 (10.92%)
Dry skin [A] *	6/116 (5.17%)	5/119 (4.2%)
Palmar-plantar erythrodysaesthesia syndrome [A] *	6/116 (5.17%)	20/119 (16.81%)
Pruritus [A] *	6/116 (5.17%)	5/119 (4.2%)
Rash [A] *	7/116 (6.03%)	6/119 (5.04%)
Skin hyperpigmentation [A] *	6/116 (5.17%)	5/119 (4.2%)
Vascular disorders		
Deep vein thrombosis [A] *	2/116 (1.72%)	7/119 (5.88%)
Hypertension [A] *	8/116 (6.9%)	64/119 (53.78%)
Phlebitis [A] *	0/116 (0%)	6/119 (5.04%)

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

Limitations and Caveats

The overall survival (OS) data are severely limited due to the low number of events (<50%) in both arms, therefore median OS cannot be accurately estimated due to limitations of available data.

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 to a journal, and delay publication till the approval of the publication is given in writing by the Sponsor (not to exceed ninety days).

Results Point of Contact:

Name/Official Title: Trial Transparency Team
Organization: Sanofi
Phone:
Email: Contact-Us@sanofi.com