Clinical trial results:
A Single-Arm, Open Label Study of Aflibercept as Maintenance Therapy Following Induction with Aflibercept in Combination with XELOX, as First-Line Treatment for Metastatic Colorectal Cancer Patient

Summary

EudraCT number	2013-000858-22
Trial protocol	IT
Global end of trial date	23 March 2015

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	AFLIBC06561

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01955629
WHO universal trial number (UTN)	U1111-1143-3015
Other trial identifiers	Study name: AMOR

Notes:

Sponsors

Sponsor organisation name	Sanofi Aventis Groupe (SAG)
Sponsor organisation address	54, rue La Boétie, Paris, France, 75008
Public contact	Trial Transparency Team, Sanofi Aventis Groupe (SAG), Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Groupe (SAG), 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	13 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Study Part 1: To determine the recommended dose for the aflibercept, oxaliplatin and capecitabine (XELOX) combination to be used in the Part 2 of the study. Study Part 2: To assess the percentage of subjects without progression of the disease at 6 months after the start of maintenance therapy with aflibercept single-agent, following the first-line induction therapy with XELOX and aflibercept combination in subjects with previously untreated metastatic colorectal cancer.

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	17 December 2013
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	Italy: 4
Worldwide total number of subjects	4
EEA total number of subjects	4

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)	0
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 2 sites in Italy. A total of 6 subjects were screened between 17 Dec 2013 and 24 Feb 2014, out of which 4 subjects were enrolled and treated.

Pre-assignment

Screening details:

Subjects enrolled in Part-1 of study to assess recommended phase 2 dose (RP2D) of combination of aflibercept with oxaliplatin and capecitabine. 3 subjects discontinued due to adverse events (AE) and 1 subject due to disease progression (DP) at dose level 1 of treatment. Part-2 of study (efficacy and safety evaluation) was not performed.

Period 1

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

Arms

Arm title	Aflibercept + XELOX (Oxaliplatin and Capecitabine)

Arm description:

Aflibercept in combination with Oxaliplatin and Capecitabine, up to 6 cycles as induction therapy, followed by aflibercept as maintenance therapy up to DP or unacceptable toxicity or subject's refusal of further treatment.

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

Dosage and administration details:

Aflibercept 6 mg/kg IV infusion (up to 2 hours) on Day 1 every 3 weeks (q3w).

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	SR96669
Other name	Eloxatin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin 100 mg/m^2 IV infusion for 2 hours on Day 1 q3w.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 850 mg/m^2 twice daily from Day 1 to Day 14 of each cycle of 3 weeks.

Number of subjects in period 1	Aflibercept + XELOX (Oxaliplatin and Capecitabine)
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Aflibercept + XELOX (Oxaliplatin and Capecitabine)
Reporting group description:	
Aflibercept in combination with Oxaliplatin and Capecitabine, up to 6 cycles as induction therapy, followed by aflibercept as maintenance therapy up to DP or unacceptable toxicity or subject's refusal of further treatment.	

Reporting group values	Aflibercept + XELOX (Oxaliplatin and Capecitabine)	Total	
Number of subjects	4	4	
Age categorical Units: Subjects			
From 65-84 years	4	4	
Gender categorical Units: Subjects			
Female	0	0	
Male	4	4	

End points

End points reporting groups

Reporting group title	Aflibercept + XELOX (Oxaliplatin and Capecitabine)

Reporting group description:

Aflibercept in combination with Oxaliplatin and Capecitabine, up to 6 cycles as induction therapy, followed by aflibercept as maintenance therapy up to DP or unacceptable toxicity or subject's refusal of further treatment.

Primary: Part 1:Number of Subjects With Dose Limiting Toxicities (DLTs)

End point title	Part 1:Number of Subjects With Dose Limiting Toxicities

End point description:

DLTs were assessed by National Cancer Institute Common Terminology Criteria for AEs version4.03 and were any of the AEs:G4 neutropenia lasting>7 days;febrile neutropenia or neutropenic infection;G4 thrombocytopenia;G3 thrombocytopenia with bleeding requiring transfusion;G4 non-hematological treatment related event;G3 nausea/vomiting/diarrhea lasting>/=4 days despite corrective measures;G3 non-hematological toxicities:anorexia,fatigue,hypertension only if G4 or not medically controlled and G3 peripheral sensory neuropathy not improved to G<2 at retreatment;urinary protein excretion of>3.5 gram per 24hours not recovered to<2.0 gram per 24hours within 2 weeks;symptomatic arterial thromboembolic events including cerebrovascular accidents,myocardial infarction,transient ischemic attacks, new onset/worsening of pre-existing angina.Evaluable DLT population was subset of whole part-1 subjects exposed to at least 1dose of treatment (even incomplete) and with evaluable DLT assessment at cycle1.

End point type	Primary

End point timeframe:

Cycle 1 (Up to 3 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 + XELOX (Oxaliplatin and Capecitabine)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Subjects	1			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Number of Subjects With Progression Free Survival (PFS) at 6 Months After the Start of Maintenance Therapy

End point title	Part 2: Number of Subjects With Progression Free Survival (PFS) at 6 Months After the Start of Maintenance Therapy[2]

End point description:

It describes the number of subjects alive without progression at 6 months after the start of Aflibercept maintenance therapy. Due to premature recruitment discontinuation, none of the planned efficacy

analysis was performed.

End point type	Primary

End point timeframe:

6 months after the start of maintenance therapy.

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: Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

End point values	Aflibercept + XELOX (Oxaliplatin and Capecitabine)			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: Subjects				

Notes:

[3] - Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Number of Subjects With Tumor Responses (Complete Response [CR], Partial Response [PR], Stable Disease [SD] or Progressive Disease [PD])

End point title	Part 1: Number of Subjects With Tumor Responses (Complete Response [CR], Partial Response [PR], Stable Disease [SD] or Progressive Disease [PD])

End point description:

Tumor assessment was performed by Abdomino-Pelvic Computed Tomography Scan or Magnetic Resonance Imaging(MRI) and chest X-ray or chest CT-scan to assess disease status at baseline and every 9 weeks during study treatment up to DP. Target lesions evaluated using Response Evaluation Criteria In Solid Tumors(RECIST) version1.1, wherein CR=disappearance of all target lesions; PR=30% decrease in sum of longest diameter(LD) of target lesions taking as reference baseline sum LD; PD=20% increase in sum of LD of target lesions taking as reference smallest sum in study and SD=small changes not met above criteria. Evaluable Population(EP) for tumor response was subset of ITT population (all subjects who gave informed consent and successfully registered into study) with measurable disease at study entry,received at least 1 cycle of study treatment, with at least 1 post baseline tumor evaluation, except for early DP or death.

End point type	Secondary

End point timeframe:

Baseline and every 9 weeks up to DP (up to 15 months).

End point values	Aflibercept + XELOX (Oxaliplatin and Capecitabine)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Subjects				
CR	0			
PR	1			

PD	0			
SD	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: PFS

End point title	Part 2: PFS

End point description:

PFS was defined as the time interval from the date of registration into the study to the date of first observation of disease progression or death (due to any cause), whichever was first. Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

End point type	Secondary

End point timeframe:

From the date of enrollment up to the date of DP or death, whichever occurred first (up to 15 months).

End point values	Aflibercept + XELOX (Oxaliplatin and Capecitabine)			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: Months				
number (not applicable)				

Notes:

[4] - Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Overall Survival (OS)

End point title	Part 2: Overall Survival (OS)

End point description:

OS was defined as the time interval from the date of registration into the study to the date of death due to any cause. In the absence of confirmation of death, survival time was to be censored at the earliest between the last date the subject was known to be alive and the end of study date. Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

End point type	Secondary

End point timeframe:

From the date of enrollment up to the date of death (up to 15 months).

End point values	Aflibercept + XELOX (Oxaliplatin and Capecitabine)			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: Months				
number (not applicable)				

Notes:

[5] - Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Overall Rate of Resectability of Metastatic Lesions

End point title	Part 2: Overall Rate of Resectability of Metastatic Lesions

End point description:

Overall metastases resection rate was defined as the percentage of subjects reaching an R0 metastases resection, defined as the complete absence of invasive carcinoma on histological examination at the time of definitive surgery (if performed). Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

End point type	Secondary

End point timeframe:

12 months after the last subject enrolled.

End point values	Aflibercept + XELOX (Oxaliplatin and Capecitabine)			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: Percentage of Subjects				
number (not applicable)				

Notes:

[6] - Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Subjecs With CR or PR

End point title	Part 2: Number of Subjecs With CR or PR

End point description:

Tumor assessment was performed by Abdomino-Pelvic Computed Tomography Scan or MRI and chest X-ray or chest CT-scan to assess the disease status at baseline and then every 9 weeks during study treatment up to DP. Target lesions were evaluated using RECIST version 1.1, wherein CR = disappearance of all target lesions; PR = 30% decrease in the sum of the LD of target lesions taking as reference the baseline sum LD. Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

End point type	Secondary

End point timeframe:

Baseline and every 9 weeks up to end of study completion (15 months).

End point values	Aflibercept + XELOX (Oxaliplatin and Capecitabine)			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: Subjects				

Notes:

[7] - Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Pharmacodynamic Parameters: Modulation of Circulating Analytes

End point title	Part 2: Pharmacodynamic Parameters: Modulation of Circulating Analytes

End point description:

Blood and tumor samples were to be collected to evaluate the pharmacodynamic parameters including the assessment of the modulation of circulating analytes such as cytokines and angiogenic factors. Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

End point type	Secondary

End point timeframe:

Baseline (within 21 days before registration); Day 1/pre-dose of Cycle 1, 2 and 3 of induction phase and maintenance phase; 30 ± 3 days after the last aflibercept administration.

End point values	Aflibercept + XELOX (Oxaliplatin and Capecitabine)			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: Not applicable				

Notes:

[8] - Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Aflibercept Biomarkers Evaluation

End point title	Part 2: Aflibercept Biomarkers Evaluation

End point description:

Blood and tumor samples were to be collected to evaluate proteomic biomarkers such as factors and receptors related to angiogenesis process, inflammation, and tumor progression. Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

End point type	Secondary

End point timeframe:

Baseline (within 21 days before registration); Day 1/pre-dose of Cycle 1, 2 and 3 of induction phase and maintenance phase; 30 ± 3 days after the last aflibercept administration.

End point values	Aflibercept + XELOX (Oxaliplatin and Capecitabine)			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: Not applicable				

Notes:

[9] - Due to premature recruitment discontinuation, none of the planned efficacy analysis was performed.

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 30 days after the last administration of treatment regardless of seriousness or relationship to study treatment.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (from the first study treatment administration to 30 days after the last study treatment administration).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Aflibercept + XELOX (Oxaliplatin and Capecitabine)

Reporting group description:

Aflibercept in combination with Oxaliplatin and Capecitabine, up to 6 cycles as induction therapy, followed by aflibercept as maintenance therapy up to DP or unacceptable toxicity or subject's refusal of further treatment.

Serious adverse events	Aflibercept + XELOX (Oxaliplatin and Capecitabine)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Aflibercept + XELOX (Oxaliplatin and Capecitabine)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Dysphonia subjects affected / exposed occurrences (all) Hiccups subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1 2 / 4 (50.00%) 2		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Investigations Weight decreased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Injury, poisoning and procedural complications Incisional hernia subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia	 1 / 4 (25.00%) 1 2 / 4 (50.00%) 2		

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hydronephrosis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all) Flank pain subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Infections and infestations Device related infection subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all)	 2 / 4 (50.00%) 2 1 / 4 (25.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study enrollment was prematurely halted due to safety reasons.

Notes: