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Aflibercept Compared to Placebo in Term of Efficacy in Patients Treated With Gemcitabine for Metastatic Pancreatic Cancer (VANILLA)

This study has been terminated.
(Data Monitoring Committee concluded after a planned interim analysis that aflibercept added to gemcitabine would be unable to demonstrate improved survival)

Sponsor:	Sanofi
Collaborators:	Regeneron Pharmaceuticals
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00574275

Purpose

The main objective of the study was to evaluate the effectiveness of aflibercept treatment by comparison to placebo in increasing the overall survival (OS) in participants with metastatic pancreatic cancer, treated with gemcitabine.

The secondary objectives were to evaluate progression free survival, clinical benefit, overall response, safety and immunogenicity of aflibercept, in the two treatment arms (Arm 1: Aflibercept and Gemcitabine; Arm 2: Placebo and Gemcitabine).

The study included an interim analysis of OS. In accordance with the study protocol, an interim analysis was performed for the purpose of futility and overwhelming efficacy. On the basis of the interim analysis, the Data Monitoring Committee (DMC) recommended that this study be terminated for futility based on predefined boundary rules.

Condition	Intervention	Phase
Pancreatic Neoplasm	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) Drug: Placebo Drug: Gemcitabine	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 Treated With Gemcitabine for Metastatic Pancreatic Cancer

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Overall Survival (OS) [Time Frame: From the first randomization until the end of study data cutoff date (approximately 2 years)] [Designated as safety issue: No]
  OS is the time interval from the date of randomization to the date of death due to any cause. If death was not observed during the study, data on OS were censored at the earlier of the last date participant was known to be alive, or the study data cutoff date (11 September 2009). OS time was estimated from Kaplan-Meier Plots.

Secondary Outcome Measures:

- Progression Free Survival (PFS) Based on Response Evaluation Criteria in Solid Tumors [RECIST] Criteria [Time Frame: From the first randomization until the end of study data cutoff date (approximately 2 years)] [Designated as safety issue: No]
  PFS was the time interval from the date of registration to the date of progression, or death from any cause if it occurs before tumor progression is documented. Tumor progression was assessed using RECIST criteria, by which progression was a pre-defined increase in the size of existing tumors or appearance of one or more new tumors. If a participant did not progress or die, the progression was censored to the date of the last valid tumor assessment or data cut-off, whichever was earlier. Median PFS time was estimated from Kaplan-Meier Plots.
- Objective Response Rate (ORR) Assessed by the Investigators According to RECIST Criteria [Time Frame: From the first randomization until the end of the study data cutoff date (approximately 2 years)] [Designated as safety issue: No]
  Objective response (OR) included complete response [CR] and partial response [PR]. OR was to be assessed by the Investigators according to RECIST criteria, and confirmed by repeating tumor imaging at least 4 weeks after the first radiological documentation of response. CR would reflect the disappearance of all tumor lesions and PR would reflect a defined reduction of tumor burden. However, OR analysis was not performed, as the study was terminated due to futility.
- Clinical Benefit [Time Frame: From the first randomization until the end of the study data cutoff date (approximately 2 years)] [Designated as safety issue: No]
  Clinical benefit was to be assessed in all participants by time to symptom worsening (TTSW), evaluated from the time of randomization to symptom worsening, as well as by improvement in tumor related symptoms. However, this analysis was not performed, as the study was terminated due to futility.
- Safety-Number of Participants With Adverse Events (AE) [Time Frame: up to 30 days after treatment discontinuation. SAEs and related AEs were followed till resolved or stabilized.] [Designated as safety issue: Yes]
  All AEs regardless of seriousness or relationship to study treatment, spanning from the signature of informed consent until 30 days after the last administration of study treatment, were recorded. 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.
- Number of Participants With Anti-drug Antibodies [Time Frame: Up to 90 days post last dose of study drug] [Designated as safety issue: No]
  Anti-drug antibodies in the participants blood sample were detected using a validated immunoassay. The validated lower limit of detection (LLOD) for the assay was about 5.4 ng/mL in the absence of aflibercept and about 25.2 ng/mL in the presence of 20 µg/mL of aflibercept.

Enrollment: 546
Study Start Date: December 2007
Primary Completion Date: October 2009
Study Completion Date: November 2010

Arms	Assigned Interventions
Placebo Comparator: Placebo and Gemcitabine Participants with metastatic pancreatic cancer administered Placebo and 1000 mg/m^2 Gemcitabine.	Drug: Placebo 4 mg/kg was administered intravenously (IV) over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle Drug: Gemcitabine 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles. Other Names: Gemzar
Experimental: Aflibercept and Gemcitabine Participants with metastatic pancreatic cancer administered 4 mg/kg Aflibercept and 1000 mg/m^2 Gemcitabine.	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) 4 mg/kg was administered intravenously (IV) over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. Drug: Gemcitabine 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles. Other Names: Gemzar

Detailed Description:

The study included:

- A screening visit of up to 21 days prior to randomization
- Randomization at baseline
- A Treatment period (initiated within 3 days of randomization), which included 28-day treatment cycles in both arms until predefined treatment discontinuation criteria were met
- A follow-up visit 30 days after discontinuation of treatment,
- A post study treatment follow-up period until death or the study cutoff date.

The criteria for treatment discontinuation were:

- 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, such as:
  - Disease progression
  - Unacceptable AEs not manageable by symptomatic therapy, dose delay, or dose modification
  - Intercurrent illness that prevented further administration of study treatment

- Noncompliance with the study protocol
- Participant was lost to follow-up
- Unblinding of the participant's investigational treatment

Eligibility

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

Criteria

Inclusion Criteria:

- Cytologically or histologically confirmed evidence of epithelial cancer (adenocarcinoma) of the exocrine pancreas
- Metastatic disease
- No prior chemotherapy for pancreatic disease
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1 or 2
- Adequate renal, liver and bone marrow functions

Exclusion Criteria:

- Less than 42 days elapsed from prior major surgery (28 days from other prior surgery) to the time of randomization
- Prior treatment with anti-VEGF or VEGF-Receptor-inhibitors
- Uncontrolled hypertension
- Pregnancy or breastfeeding
- Participant with reproductive potential (M/F) without effective method of contraception

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

Contacts and Locations

Locations

United States, New Jersey
sanofi-aventis administrative office
Bridgewater, New Jersey, United States, 08807
Argentina
sanofi-aventis administrative office
Buenos Aires, Argentina
Austria
sanofi-aventis administrative office
Wien, Austria
Belgium
sanofi-aventis administrative office
Diegem, Belgium
Bulgaria

sanofi-aventis administrative office
Sofia, Bulgaria
Canada
sanofi-aventis administrative office
Laval, Canada
Chile
sanofi-aventis administrative office
Santiago, Chile
Colombia
sanofi-aventis administrative office
Santafe de Bogota, Colombia
Cyprus
sanofi-aventis administrative office
Nikosia, Cyprus
Czech Republic
sanofi-aventis administrative office
Praha, Czech Republic
France
sanofi-aventis administrative office
Paris, France
Germany
sanofi-aventis administrative office
Berlin, Germany
Greece
sanofi-aventis administrative office
Athens, Greece
Hungary
sanofi-aventis administrative office
Budapest, Hungary
India
sanofi-aventis administrative office
Mumbai, India
Italy
sanofi-aventis administrative office
Milano, Italy
Mexico
sanofi-aventis administrative office
Mexico, Mexico
Poland
sanofi-aventis administrative office
Warszawa, Poland
Puerto Rico
sanofi-aventis administrative office
Puerto Rico, Puerto Rico
Romania

sanofi-aventis administrative office
Bucuresti, Romania
Russian Federation
sanofi-aventis administrative office
Moscow, Russian Federation
Slovakia
sanofi-aventis administrative office
Brastislava, Slovakia
Spain
sanofi-aventis administrative office
Barcelona, Spain
Switzerland
sanofi-aventis administrative office
Geneva, Switzerland

Investigators

Study Director:	Clinical Sciences & Operations	sanofi-aventis

More Information

Responsible Party:	Sanofi
Study ID Numbers:	EFC10547 EudraCT 2007-003476-19
Health Authority:	United States: Food and Drug Administration Italy: Ministry of Health Poland: Ministry of Health

Study Results

Participant Flow

Recruitment Details	Between December 2007 and September 2009, a total of 546 participants were randomized in the study: 275 to the placebo group and 271 to the aflibercept group. On the basis of the interim analysis, the Data Monitoring Committee (DMC) recommended that this study be terminated for futility based on predefined boundary rules.

Reporting Groups

	Description
Placebo and Gemcitabine	• Placebo: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.
Aflibercept and Gemcitabine	• Aflibercept: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

Overall Study

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
Started	275	271
TREATED	273	268
SAFETY POPULATION	271 [1]	270 [2]
Completed	0 [3]	0 [3]
Not Completed	275	271
Randomized but not treated	2	3
Adverse Event	32	76
Disease progression	160	146
Lost to Follow-up	2	1
Study stopped based on DMC decision	62	23
Withdrawal by Subject	15	17
Error calculating tumor measurement	1	0
Physician Decision	1	1
Protocol Violation	0	1
Patient and Investigator decision	0	1
Insurance change	0	1
Operation for curative intent	0	1

[1] Excludes 2 participants who received 1 dose of Aflibercept

[2] Includes 2 participants from the Placebo and Gemcitabine arm who received 1 dose of Aflibercept

[3] All participants stopped when they met treatment discontinuation criteria or by DMC recommendation

Baseline Characteristics

Reporting Groups

	Description
Placebo/Gemcitabine	• Placebo: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.
Aflibercept/Gemcitabine	• Aflibercept: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

Baseline Measures

	Placebo/Gemcitabine	Aflibercept/Gemcitabine	Total
Number of Participants	275	271	546
Age, Continuous [units: Years] Mean (Standard Deviation)	60.4 (10.0)	62.0 (9.4)	61.2 (9.7)
Age, Customized [units: participants]			
<65 years	179	161	340
>=65 but <75 years	77	90	167
>=75 years	19	20	39
Gender, Customized [units: participants]			
Male	157	160	317
Female	118	111	229
Race/Ethnicity, Customized [units: participants]			
Caucasian/White	267	256	523
Black	2	3	5

	Placebo/Gemcitabine	Aflibercept/Gemcitabine	Total
Asian/Oriental	3	7	10
Other	3	5	8
Region of Enrollment [units: participants]			
ARGENTINA	3	0	3
AUSTRIA	6	2	8
BELGIUM	18	16	34
BULGARIA	12	11	23
CANADA	15	16	31
CHILE	8	8	16
CYPRUS	3	3	6
CZECH REPUBLIC	10	14	24
FRANCE	11	13	24
GERMANY	15	10	25
GREECE	5	7	12
HUNGARY	7	10	17
INDIA	3	3	6
ITALY	17	24	41
MEXICO	1	2	3
POLAND	12	11	23
PUERTO RICO	1	0	1
ROMANIA	13	8	21
RUSSIAN FEDERATION	19	19	38
SLOVAKIA	5	3	8
SPAIN	13	14	27
SWITZERLAND	8	9	17
UNITED STATES	70	68	138

	Placebo/Gemcitabine	Aflibercept/Gemcitabine	Total
Eastern Cooperative Oncology Group (ECOG) Performance Status Score [1] [units: participants]			
Participants with ECOG Score = 0	102	102	204
Participants with ECOG Score = 1	154	152	306
Participants with ECOG Score = 2	19	17	36
Primary tumor resection [2] [units: participants]			
Yes	40	39	79
No	235	232	467

[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] Whether the participant had prior pancreatectomy.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Overall Survival (OS)
Measure Description	OS is the time interval from the date of randomization to the date of death due to any cause. If death was not observed during the study, data on OS were censored at the earlier of the last date participant was known to be alive, or the study data cutoff date (11 September 2009). OS time was estimated from Kaplan-Meier Plots.
Time Frame	From the first randomization until the end of study data cutoff date (approximately 2 years)
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population, which included all randomized participants.

Reporting Groups

	Description
Placebo and Gemcitabine	• Placebo: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.
Aflibercept and Gemcitabine	• Aflibercept: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

Measured Values

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
Number of Participants Analyzed	275	271
Number of OS Event (Death) Analyzed	142	142
Overall Survival (OS) [units: months] Median (95% Confidence Interval)	7.75 (6.768 to 8.575)	6.54 (5.552 to 7.852)

2. Secondary Outcome Measure:

Measure Title	Progression Free Survival (PFS) Based on Response Evaluation Criteria in Solid Tumors [RECIST] Criteria
Measure Description	PFS was the time interval from the date of registration to the date of progression, or death from any cause if it occurs before tumor progression is documented. Tumor progression was assessed using RECIST criteria, by which progression was a pre-defined increase in the size of existing tumors or appearance of one or more new tumors. If a participant did not progress or die, the progression was censored to the date of the last valid tumor assessment or data cut-off, whichever was earlier. Median PFS time was estimated from Kaplan-Meier Plots.
Time Frame	From the first randomization until the end of study data cutoff date (approximately 2 years)
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population, which included all randomized participants.

Reporting Groups

	Description
Placebo and Gemcitabine	• Placebo: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.
Aflibercept and Gemcitabine	• Aflibercept: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

Measured Values

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
Number of Participants Analyzed	275	271
Number of PFS Events Analyzed	189	182
Progression Free Survival (PFS) Based on Response Evaluation Criteria in Solid Tumors [RECIST] Criteria [units: months] Median (95% Confidence Interval)	3.71 (3.515 to 4.567)	3.71 (3.450 to 4.468)

3. Secondary Outcome Measure:

Measure Title	Objective Response Rate (ORR) Assessed by the Investigators According to RECIST Criteria
Measure Description	Objective response (OR) included complete response [CR] and partial response [PR]. OR was to be assessed by the Investigators according to RECIST criteria, and confirmed by repeating tumor imaging at least 4 weeks after the first radiological documentation of response. CR would reflect the disappearance of all tumor lesions and PR would reflect a defined reduction of tumor burden. However, OR analysis was not performed, as the study was terminated due to futility.
Time Frame	From the first randomization until the end of the study data cutoff date (approximately 2 years)
Safety Issue?	No

Analysis Population Description

Since the study was terminated due to futility, this analysis was not performed.

Reporting Groups

	Description
Placebo and Gemcitabine	• Placebo: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.
Aflibercept and Gemcitabine	• Aflibercept: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

Measured Values

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

4. Secondary Outcome Measure:

Measure Title	Clinical Benefit
Measure Description	Clinical benefit was to be assessed in all participants by time to symptom worsening (TTSW), evaluated from the time of randomization to symptom worsening, as well as by improvement in tumor related symptoms. However, this analysis was not performed, as the study was terminated due to futility.
Time Frame	From the first randomization until the end of the study data cutoff date (approximately 2 years)
Safety Issue?	No

Analysis Population Description

Since the study was terminated due to futility, analysis for this endpoint was not performed.

Reporting Groups

	Description
Placebo and Gemcitabine	• Placebo: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

	Description
Aflibercept and Gemcitabine	• Aflibercept: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

Measured Values

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

5. Secondary Outcome Measure:

Measure Title	Safety-Number of Participants With Adverse Events (AE)
Measure Description	All AEs regardless of seriousness or relationship to study treatment, spanning from the signature of informed consent until 30 days after the last administration of study treatment, were recorded. 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	up to 30 days after treatment discontinuation. SAEs and related AEs were followed till resolved or stabilized.
Safety Issue?	Yes

Analysis Population Description

The safety population included all randomized participants who were administered at least 1 dose of study medications (placebo, aflibercept, or gemcitabine). For safety analyses, participants were analyzed according to the treatment received.

Reporting Groups

	Description
Placebo and Gemcitabine	• Placebo: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.
Aflibercept and Gemcitabine	• Aflibercept: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

Measured Values

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
Number of Participants Analyzed	271	270
Safety-Number of Participants With Adverse Events (AE) [units: participants]		
Treatment Emergent Adverse Event (TEAE)	257	266
Treatment Emergent Serious Adverse Event	122	148
TEAE leading to death	43	55
TEAE leading to permanent discontinuation	32	76

6. Secondary Outcome Measure:

Measure Title	Number of Participants With Anti-drug Antibodies
Measure Description	Anti-drug antibodies in the participants blood sample were detected using a validated immunoassay. The validated lower limit of detection (LLOD) for the assay was about 5.4 ng/mL in the absence of aflibercept and about 25.2 ng/mL in the presence of 20 µg/mL of aflibercept.
Time Frame	Up to 90 days post last dose of study drug
Safety Issue?	No

Analysis Population Description

Safety population with samples available for analysis

Reporting Groups

	Description
Placebo and Gemcitabine	• Placebo: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.
Aflibercept and Gemcitabine	• Aflibercept: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

Measured Values

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
Number of Participants Analyzed	202	201
Number of Participants With Anti-drug Antibodies [units: participants]	5	5

Reported Adverse Events

Time Frame	From treatment initiation up to November 26, 2010
Additional Description	[Not specified]

Reporting Groups

	Description
Placebo and Gemcitabine	• Placebo: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.
Aflibercept and Gemcitabine	• Aflibercept: 4 mg/kg was administered IV over 1 hour once every 2 weeks, on Days 1 and 15 of each 28-day cycle. • Gemcitabine: 1000 mg/m^2 administered IV over 30 minutes on Days 1, 8, 15, and 22 of Cycle 1 (28 days), and then Days 1, 8, and 15 of subsequent 28-day cycles.

Serious Adverse Events

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Total	122/271 (45.02%)	148/270 (54.81%)
Blood and lymphatic system disorders		
Anaemia [A] †	2/271 (0.74%)	4/270 (1.48%)
Anaemia of malignant disease [A] †	1/271 (0.37%)	1/270 (0.37%)
Disseminated intravascular coagulation [A] †	1/271 (0.37%)	0/270 (0%)

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Febrile neutropenia [A] †	1/271 (0.37%)	1/270 (0.37%)
Neutropenia [A] †	0/271 (0%)	2/270 (0.74%)
Splenic infarction [A] †	1/271 (0.37%)	0/270 (0%)
Splenic vein thrombosis [A] †	1/271 (0.37%)	1/270 (0.37%)
Thrombocytopenia [A] †	1/271 (0.37%)	2/270 (0.74%)
Cardiac disorders		
Acute myocardial infarction [A] †	1/271 (0.37%)	1/270 (0.37%)
Atrial fibrillation [A] †	0/271 (0%)	2/270 (0.74%)
Atrial flutter [A] †	0/271 (0%)	1/270 (0.37%)
Cardiac failure [A] †	0/271 (0%)	2/270 (0.74%)
Cardiac failure congestive [A] †	0/271 (0%)	1/270 (0.37%)
Extrasystoles [A] †	0/271 (0%)	1/270 (0.37%)
Left ventricular failure [A] †	0/271 (0%)	1/270 (0.37%)
Myocardial ischaemia [A] †	0/271 (0%)	1/270 (0.37%)
Sinus bradycardia [A] †	1/271 (0.37%)	0/270 (0%)
Ventricular extrasystoles [A] †	1/271 (0.37%)	0/270 (0%)
Ventricular fibrillation [A] †	1/271 (0.37%)	0/270 (0%)
Endocrine disorders		
Inappropriate antidiuretic hormone secretion [A] †	0/271 (0%)	1/270 (0.37%)
Gastrointestinal disorders		
Abdominal distension [A] †	1/271 (0.37%)	1/270 (0.37%)
Abdominal pain [A] †	11/271 (4.06%)	6/270 (2.22%)

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Abdominal pain upper [A] †	0/271 (0%)	2/270 (0.74%)
Ascites [A] †	2/271 (0.74%)	4/270 (1.48%)
Colonic obstruction [A] †	1/271 (0.37%)	0/270 (0%)
Constipation [A] †	1/271 (0.37%)	0/270 (0%)
Diarrhoea [A] †	2/271 (0.74%)	1/270 (0.37%)
Duodenal obstruction [A] †	1/271 (0.37%)	3/270 (1.11%)
Duodenal stenosis [A] †	1/271 (0.37%)	3/270 (1.11%)
Duodenal ulcer haemorrhage [A] †	0/271 (0%)	1/270 (0.37%)
Dysphagia [A] †	1/271 (0.37%)	0/270 (0%)
Enteritis [A] †	0/271 (0%)	1/270 (0.37%)
Enterocutaneous fistula [A] †	0/271 (0%)	1/270 (0.37%)
Gastric ulcer haemorrhage [A] †	0/271 (0%)	1/270 (0.37%)
Gastrointestinal haemorrhage [A] †	1/271 (0.37%)	4/270 (1.48%)
Gastrointestinal ischaemia [A] †	1/271 (0.37%)	0/270 (0%)
Gastrointestinal obstruction [A] †	1/271 (0.37%)	1/270 (0.37%)
Gastrointestinal oedema [A] †	1/271 (0.37%)	0/270 (0%)
Haematemesis [A] †	1/271 (0.37%)	0/270 (0%)
Ileus [A] †	3/271 (1.11%)	1/270 (0.37%)
Ileus paralytic [A] †	0/271 (0%)	1/270 (0.37%)
Intestinal obstruction [A] †	4/271 (1.48%)	4/270 (1.48%)
Intestinal perforation [A] †	0/271 (0%)	1/270 (0.37%)
Melaena [A] †	0/271 (0%)	2/270 (0.74%)

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Nausea [A] †	3/271 (1.11%)	3/270 (1.11%)
Oesophageal stenosis [A] †	0/271 (0%)	1/270 (0.37%)
Oesophagitis haemorrhagic [A] †	1/271 (0.37%)	0/270 (0%)
Pancreatitis [A] †	1/271 (0.37%)	0/270 (0%)
Pancreatitis chronic [A] †	0/271 (0%)	1/270 (0.37%)
Peritonitis [A] †	0/271 (0%)	1/270 (0.37%)
Small intestinal obstruction [A] †	1/271 (0.37%)	1/270 (0.37%)
Stomatitis [A] †	0/271 (0%)	1/270 (0.37%)
Thrombosis mesenteric vessel [A] †	1/271 (0.37%)	0/270 (0%)
Upper gastrointestinal haemorrhage [A] †	0/271 (0%)	1/270 (0.37%)
Vomiting [A] †	6/271 (2.21%)	10/270 (3.7%)
General disorders		
Asthenia [A] †	1/271 (0.37%)	3/270 (1.11%)
Death [A] †	4/271 (1.48%)	0/270 (0%)
Device dislocation [A] †	0/271 (0%)	1/270 (0.37%)
Device occlusion [A] †	2/271 (0.74%)	3/270 (1.11%)
Disease progression [A] †	25/271 (9.23%)	38/270 (14.07%)
Fatigue [A] †	5/271 (1.85%)	1/270 (0.37%)
Malaise [A] †	0/271 (0%)	1/270 (0.37%)
Non-cardiac chest pain [A] †	1/271 (0.37%)	1/270 (0.37%)
Pain [A] †	1/271 (0.37%)	0/270 (0%)
Performance status decreased [A] †	0/271 (0%)	1/270 (0.37%)

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Pyrexia [A] †	5/271 (1.85%)	3/270 (1.11%)
Sudden death [A] †	0/271 (0%)	1/270 (0.37%)
Hepatobiliary disorders		
Bile duct obstruction [A] †	1/271 (0.37%)	2/270 (0.74%)
Bile duct stenosis [A] †	0/271 (0%)	2/270 (0.74%)
Cholangitis [A] †	4/271 (1.48%)	5/270 (1.85%)
Cholangitis acute [A] †	1/271 (0.37%)	1/270 (0.37%)
Cholecystitis acute [A] †	0/271 (0%)	1/270 (0.37%)
Hepatic failure [A] †	2/271 (0.74%)	0/270 (0%)
Hyperbilirubinaemia [A] †	2/271 (0.74%)	3/270 (1.11%)
Jaundice [A] †	2/271 (0.74%)	3/270 (1.11%)
Jaundice cholestatic [A] †	2/271 (0.74%)	0/270 (0%)
Portal hypertension [A] †	1/271 (0.37%)	0/270 (0%)
Portal vein thrombosis [A] †	0/271 (0%)	2/270 (0.74%)
Infections and infestations		
Abdominal abscess [A] †	1/271 (0.37%)	1/270 (0.37%)
Anal abscess [A] †	1/271 (0.37%)	0/270 (0%)
Bacterascites [A] †	0/271 (0%)	2/270 (0.74%)
Biliary sepsis [A] †	2/271 (0.74%)	1/270 (0.37%)
Bronchopneumonia [A] †	0/271 (0%)	1/270 (0.37%)
Cellulitis [A] †	1/271 (0.37%)	0/270 (0%)
Cholecystitis infective [A] †	1/271 (0.37%)	0/270 (0%)

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Clostridium difficile colitis [A] †	0/271 (0%)	1/270 (0.37%)
Device related infection [A] †	3/271 (1.11%)	0/270 (0%)
Enterocolitis infectious [A] †	0/271 (0%)	1/270 (0.37%)
Escherichia sepsis [A] †	2/271 (0.74%)	0/270 (0%)
Escherichia urinary tract infection [A] †	0/271 (0%)	1/270 (0.37%)
Febrile infection [A] †	0/271 (0%)	1/270 (0.37%)
Fungal oesophagitis [A] †	1/271 (0.37%)	0/270 (0%)
Influenza [A] †	0/271 (0%)	1/270 (0.37%)
Liver abscess [A] †	0/271 (0%)	1/270 (0.37%)
Peritoneal infection [A] †	0/271 (0%)	1/270 (0.37%)
Pharyngitis [A] †	0/271 (0%)	1/270 (0.37%)
Pneumonia [A] †	3/271 (1.11%)	2/270 (0.74%)
Pyelonephritis [A] †	1/271 (0.37%)	0/270 (0%)
Sepsis [A] †	2/271 (0.74%)	2/270 (0.74%)
Skin infection [A] †	0/271 (0%)	1/270 (0.37%)
Subdiaphragmatic abscess [A] †	0/271 (0%)	1/270 (0.37%)
Urinary tract infection [A] †	3/271 (1.11%)	0/270 (0%)
Urosepsis [A] †	1/271 (0.37%)	0/270 (0%)
Injury, poisoning and procedural complications		
Anastomotic leak [A] †	0/271 (0%)	1/270 (0.37%)
Fall [A] †	0/271 (0%)	1/270 (0.37%)
Hip fracture [A] †	0/271 (0%)	1/270 (0.37%)

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Therapeutic agent toxicity [A] †	0/271 (0%)	1/270 (0.37%)
Investigations		
Blood glucose fluctuation [A] †	1/271 (0.37%)	0/270 (0%)
Ejection fraction decreased [A] †	0/271 (0%)	1/270 (0.37%)
Gamma-glutamyltransferase increased [A] †	1/271 (0.37%)	0/270 (0%)
Hepatic enzyme increased [A] †	0/271 (0%)	1/270 (0.37%)
Weight decreased [A] †	1/271 (0.37%)	0/270 (0%)
Metabolism and nutrition disorders		
Decreased appetite [A] †	2/271 (0.74%)	1/270 (0.37%)
Dehydration [A] †	5/271 (1.85%)	5/270 (1.85%)
Diabetes mellitus [A] †	0/271 (0%)	1/270 (0.37%)
Failure to thrive [A] †	0/271 (0%)	1/270 (0.37%)
Hyperglycaemia [A] †	0/271 (0%)	1/270 (0.37%)
Hyperkalaemia [A] †	0/271 (0%)	1/270 (0.37%)
Hypoalbuminaemia [A] †	0/271 (0%)	1/270 (0.37%)
Hypoglycaemia [A] †	2/271 (0.74%)	0/270 (0%)
Hyponatraemia [A] †	1/271 (0.37%)	1/270 (0.37%)
Musculoskeletal and connective tissue disorders		
Bone pain [A] †	0/271 (0%)	1/270 (0.37%)
Groin pain [A] †	0/271 (0%)	1/270 (0.37%)
Musculoskeletal chest pain [A] †	0/271 (0%)	1/270 (0.37%)
Musculoskeletal pain [A] †	0/271 (0%)	1/270 (0.37%)

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Myositis [A] †	2/271 (0.74%)	0/270 (0%)
Pain in extremity [A] †	1/271 (0.37%)	0/270 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bladder neoplasm [A] †	0/271 (0%)	1/270 (0.37%)
Cancer pain [A] †	1/271 (0.37%)	2/270 (0.74%)
Malignant ascites [A] †	2/271 (0.74%)	0/270 (0%)
Paraneoplastic syndrome [A] †	1/271 (0.37%)	0/270 (0%)
Tumour associated fever [A] †	2/271 (0.74%)	0/270 (0%)
Tumour haemorrhage [A] †	1/271 (0.37%)	0/270 (0%)
Tumour pain [A] †	2/271 (0.74%)	1/270 (0.37%)
Nervous system disorders		
Cerebellar syndrome [A] †	0/271 (0%)	1/270 (0.37%)
Cerebral haemorrhage [A] †	0/271 (0%)	1/270 (0.37%)
Cerebral infarction [A] †	0/271 (0%)	1/270 (0.37%)
Convulsion [A] †	1/271 (0.37%)	0/270 (0%)
Diabetic ketoacidotic hyperglycaemic coma [A] †	0/271 (0%)	1/270 (0.37%)
Hepatic encephalopathy [A] †	1/271 (0.37%)	0/270 (0%)
Intracranial pressure increased [A] †	1/271 (0.37%)	0/270 (0%)
Ischaemic stroke [A] †	2/271 (0.74%)	1/270 (0.37%)
Monoplegia [A] †	1/271 (0.37%)	0/270 (0%)
Spinal cord compression [A] †	1/271 (0.37%)	0/270 (0%)
Syncope [A] †	0/271 (0%)	1/270 (0.37%)

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Psychiatric disorders		
Completed suicide [A] †	0/271 (0%)	1/270 (0.37%)
Confusional state [A] †	0/271 (0%)	2/270 (0.74%)
Mental status changes [A] †	2/271 (0.74%)	0/270 (0%)
Renal and urinary disorders		
Haematuria [A] †	0/271 (0%)	1/270 (0.37%)
Nephrotic syndrome [A] †	0/271 (0%)	2/270 (0.74%)
Proteinuria [A] †	0/271 (0%)	1/270 (0.37%)
Renal failure [A] †	0/271 (0%)	1/270 (0.37%)
Renal failure acute [A] †	1/271 (0.37%)	1/270 (0.37%)
Reproductive system and breast disorders		
Epididymitis [A] †	0/271 (0%)	1/270 (0.37%)
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease [A] †	0/271 (0%)	1/270 (0.37%)
Dyspnoea [A] †	3/271 (1.11%)	2/270 (0.74%)
Epistaxis [A] †	0/271 (0%)	2/270 (0.74%)
Hypoxia [A] †	1/271 (0.37%)	0/270 (0%)
Interstitial lung disease [A] †	2/271 (0.74%)	1/270 (0.37%)
Pleural effusion [A] †	0/271 (0%)	2/270 (0.74%)
Pleuritic pain [A] †	1/271 (0.37%)	0/270 (0%)
Pneumonia aspiration [A] †	1/271 (0.37%)	1/270 (0.37%)
Pneumothorax [A] †	0/271 (0%)	1/270 (0.37%)
Pulmonary embolism [A] †	11/271 (4.06%)	4/270 (1.48%)

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory failure [A] †	1/271 (0.37%)	0/270 (0%)
Tachypnoea [A] †	0/271 (0%)	1/270 (0.37%)
Skin and subcutaneous tissue disorders		
Dermatitis [A] †	0/271 (0%)	1/270 (0.37%)
Skin ulcer [A] †	0/271 (0%)	1/270 (0.37%)
Urticaria [A] †	0/271 (0%)	1/270 (0.37%)
Vascular disorders		
Deep vein thrombosis [A] †	2/271 (0.74%)	3/270 (1.11%)
Embolism arterial [A] †	0/271 (0%)	1/270 (0.37%)
Hypertension [A] †	0/271 (0%)	4/270 (1.48%)
Hypertensive crisis [A] †	0/271 (0%)	2/270 (0.74%)
Jugular vein thrombosis [A] †	0/271 (0%)	1/270 (0.37%)
Thrombophlebitis superficial [A] †	1/271 (0.37%)	1/270 (0.37%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.1

Other Adverse Events

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

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Total	239/271 (88.19%)	249/270 (92.22%)
Blood and lymphatic system disorders		
Neutropenia [A] †	71/271 (26.2%)	85/270 (31.48%)
Thrombocytopenia [A] †	17/271 (6.27%)	47/270 (17.41%)
Gastrointestinal disorders		

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Abdominal pain [A] †	61/271 (22.51%)	54/270 (20%)
Abdominal pain upper [A] †	28/271 (10.33%)	33/270 (12.22%)
Constipation [A] †	73/271 (26.94%)	64/270 (23.7%)
Diarrhoea [A] †	57/271 (21.03%)	65/270 (24.07%)
Nausea [A] †	124/271 (45.76%)	102/270 (37.78%)
Stomatitis [A] †	16/271 (5.9%)	43/270 (15.93%)
Vomiting [A] †	77/271 (28.41%)	82/270 (30.37%)
General disorders		
Asthenia [A] †	42/271 (15.5%)	51/270 (18.89%)
Fatigue [A] †	103/271 (38.01%)	97/270 (35.93%)
Oedema peripheral [A] †	43/271 (15.87%)	33/270 (12.22%)
Pyrexia [A] †	47/271 (17.34%)	51/270 (18.89%)
Infections and infestations		
Urinary tract infection [A] †	17/271 (6.27%)	16/270 (5.93%)
Investigations		
Weight decreased [A] †	43/271 (15.87%)	81/270 (30%)
Metabolism and nutrition disorders		
Decreased appetite [A] †	72/271 (26.57%)	78/270 (28.89%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	10/271 (3.69%)	15/270 (5.56%)
Back pain [A] †	23/271 (8.49%)	27/270 (10%)
Pain in extremity [A] †	4/271 (1.48%)	14/270 (5.19%)
Nervous system disorders		

	Placebo and Gemcitabine	Aflibercept and Gemcitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Dysgeusia [A] †	8/271 (2.95%)	15/270 (5.56%)
Headache [A] †	19/271 (7.01%)	51/270 (18.89%)
Psychiatric disorders		
Anxiety [A] †	13/271 (4.8%)	16/270 (5.93%)
Depression [A] †	8/271 (2.95%)	19/270 (7.04%)
Insomnia [A] †	18/271 (6.64%)	28/270 (10.37%)
Renal and urinary disorders		
Proteinuria [A] †	6/271 (2.21%)	30/270 (11.11%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	14/271 (5.17%)	14/270 (5.19%)
Dysphonia [A] †	6/271 (2.21%)	40/270 (14.81%)
Dyspnoea [A] †	16/271 (5.9%)	26/270 (9.63%)
Epistaxis [A] †	5/271 (1.85%)	37/270 (13.7%)
Skin and subcutaneous tissue disorders		
Rash [A] †	19/271 (7.01%)	17/270 (6.3%)
Vascular disorders		
Deep vein thrombosis [A] †	16/271 (5.9%)	9/270 (3.33%)
Hypertension [A] †	17/271 (6.27%)	96/270 (35.56%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.1

Limitations and Caveats

As the study was terminated due to futility, some changes were made to the planned analyses, and the analyses for the following outcome measures were not performed:

- Objective Response Rate (ORR)
- Clinical Benefit

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).

Results Point of Contact:

Name/Official Title: International Clinical Development Study Director
Organization: Sanofi
Phone:
Email: Contact-Us@sanofi.com