AMENDED CLINICAL TRIAL PROTOCOL 2

COMPOUND: AVE0005

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

STUDY NUMBER: EFC10547

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CLINICAL STUDY DIRECTOR: [redacted], MD

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address: Tel: Fax:	
APPLICANT/SPONSOR REPRESENTATIVE	Company: Address: Tel: Fax:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: Aflibercept STUDY No : EFC10547

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
INVESTIGATOR/TRIAL LOCATION	Multicenter / Worldwide except Japan
STUDY OBJECTIVE(S)	Primary objective: To demonstrate improvement in overall survival (OS) with aflibercept by comparison to placebo in patients treated with gemcitabine for metastatic pancreatic cancer. Secondary objectives: - To compare in the two treatment arms (by sequential order of statistical analysis): • Progression Free Survival (PFS), • Clinical Benefit assessed by Time to symptoms worsening (TTSW) and improvement in tumor related symptoms, • Overall Response Rate (ORR) in patients with measurable disease at study entry (as per RECIST criteria). - To assess the overall safety in the two treatment arms. - To assess immunogenicity of **iv** aflibercept. - To perform population pharmacokinetic **evaluation**.
STUDY DESIGN	This is a prospective, multicenter, multinational, randomized (1:1), double-blind, placebo-controlled, parallel-group study comparing the efficacy of aflibercept in term of overall survival *versus* placebo administered on top of gemcitabine in patients with metastatic pancreatic cancer (MPC). Each patient will be treated until disease progression, unacceptable toxicity, or patient's refusal. Following documentation of progressive disease patients will be followed-up for survival status. An Executive Steering Committee will be responsible for supervising the trial. This committee will include the Study Chairman, 2 main investigators and sponsor representatives. An independent Data Monitoring Committee (DMC) will ensure patient protection with regards to the safety and will give appropriate recommendation to the Executive Steering Committee regarding the study modification, continuation or termination. The DMC will also be in charge of reviewing the formal statistical interim analysis of OS planned during the course of the study (see statistical considerations). Treatment assignment will be done centrally via an Interactive Voice Response System (IVRS) using a permuted-block randomization stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1 vs 2), to prior curative surgical therapy (pancreatectomy yes vs. no) and to geographical region. All eligible patients will be randomly assigned to either the control arm or the experimental arm in a 1:1 ratio.
STUDY POPULATION	

Main selection criteria:	Inclusion criteria - Cytologically or histologically confirmed evidence of epithelial cancer (adenocarcinoma) of the exocrine pancreas. - Metastatic disease. Patients with measurable and with non-measurable disease (as per RECIST criteria) are eligible. - No prior chemotherapy for pancreatic disease. Prior **treatment** with 5-fluorouracil, **capecitabine or gemcitabine**, in **which the chemotherapy** was used as a radio-sensitizing agent, is allowed if the treatment-free interval is of at least 3 **months (time between last chemotherapy dose and randomization).** Main Exclusion criteria: - **Related to the methodology :** • Chemotherapy or other systemic therapy for pancreatic cancer. • Less than 42 days elapsed from prior major surgery (28 days from other prior surgery) to the time of randomization. Less than 28 days elapsed from prior radiation therapy. • Prior treatment with anti-VEGF or VEGF-Receptor-inhibitors. • Age < 18 years. • ECOG performance status (PS) of 3-4. • History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease. • History of another neoplasm. Adequately treated basal cell or squamous cell skin cancers, carcinoma in situ of the cervix, or any other cancer from which the patient has been disease free for > 5 years are allowed. • Participation in other clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization. • Any of the following events within the 3 months prior to randomization: treatment resistant peptic ulcer disease, erosive oesophagitis or gastritis, grade 3 or 4 gastrointestinal bleeding/hemorrhage, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event. • Any of the following events within the 6 months prior to randomization: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft surgery, NYHA class III or IV congestive heart failure, stroke or transient ischemic attack. • Occurrence of deep vein thrombosis within 4 weeks prior to randomization. • Known human immunodeficiency virus (HIV) infection requiring antiretroviral treatment or acquired immunodeficiency-syndrome (AIDS)-related illness. • Other severe acute or chronic medical condition, which could impair the ability of the patient to participate to the study or to interfere with interpretation of study results. • Absence of signed and dated Institutional Review Board (IRB)-

	/Independent Ethical Committee (IEC)-approved patient informed consent form prior to enrollment into the study. • Pregnant or breast-feeding woman. Positive serum or urine pregnancy test for women of reproductive potential prior to randomization. • Patient with reproductive potential (male, female) who do not agree to use accepted and effective method of contraception during the study treatment period and for at least **6** months after the completion of the study treatment. The definition of "effective method of contraception" will be based on the investigator's judgment. - **Related to aflibercept** • Urine Protein-Creatinine Ratio (UPCR) > 1 on morning spot urinalysis or proteinuria > 500 mg/24h. • Serum Creatinine > 1.5 x upper limit of normal (ULN). If creatinine 1.0 - 1.5 x ULN, creatinine clearance, calculated according to Cockcroft-Gault formula < 60 mL/min will exclude the patient. • Uncontrolled hypertension defined as blood pressure > 150/100 mmHg (≥ grade 2 according to NCI CTCAE v. 3.0), or systolic blood pressure >180 mmHg if diastolic blood pressure < 90 mmHg, on at least 2 repeated determination on separate days within 3 months prior to study enrollment. • Patients on anticoagulants therapy with unstable dose of warfarin and/or having an out-of-therapeutic range INR (>3) within the 4 weeks prior to randomization. • Evidence of clinically significant bleeding diathesis, non-healing wound or underlying coagulopathy (e.g. INR>1.5 without vitamin K antagonist therapy…). **- Related to Gemcitabine** • Inadequate bone marrow function: absolute neutrophil counts (ANC) < 1,500/mm3, platelets < 100,000/mm3, hemoglobin < 9.0 g/dL, • Inadequate liver function tests: total bilirubin > 1.5 x ULN, transaminases (SGOT/SGPT) > 2.5 x ULN (unless liver metastasis are present, 5 x ULN in that case), AP > 3 x ULN (unless liver metastasis are present, 5 x ULN in that case). Full criteria are described in Section 7.3.
Total expected number of patients:	Approximately 630 patients.
Expected number of sites:	Approximately 150 sites.
INVESTIGATIONAL PRODUCT(S) **Formulation(s):**	Aflibercept in 5 mM sodium phosphate, 5 mM sodium citrate, 100 mM sodium chloride, 20% (w/v) sucrose, and 0.1% (w/v) polysorbate 20, pH 6.0, supplied in sealed, sterile, single-use 5.0 mL vials filled with 4.4 mL content, with a withdrawable content of 4.0 mL at a concentration of 25 mg/mL. Placebo for aflibercept: Sterile aqueous buffered vehicle pH 6.0, containing 5 mM sodium phosphate, 5 mM sodium citrate, 100 mM sodium chloride, 0.1% (w/v) polysorbate 20 and 20% (w/v) sucrose. The content of the vials must be diluted prior to infusion with 0.9%

	sodium chloride or 5% dextrose solution. For gemcitabine, see manufacturer's product information.
Route(s) of administration:	Aflibercept and placebo for aflibercept will be administered by the intravenous route.
Dose regimen:	A cycle is defined as a 4-week or 28-day period in both arms. Next cycle is started on day 29. All cycles but first cycle include 3 gemcitabine infusions (Day 1, 8, 15) every 4 weeks. First cycle includes one additional gemcitabine infusion on Day 22 and no week rest. Patients will be randomly assigned to receive either Arm A or Arm B: • **Arm A:** Aflibercept 4 mg/kg over 1 hour I.V. every 2 weeks. • **Arm B:** Placebo over 1 hour I.V. every 2 weeks. Administration of investigational study drug (either aflibercept or placebo) will immediately be followed by gemcitabine, in both arms: Gemcitabine 1000 mg/m^2 IV administered over 30 minutes. This should be repeated once weekly on Days 1, 8, 15, 22 of cycle 1 (28-day) and on Days 1, 8, and 15 of subsequent 28-day cycles. In case of BSA > 2.1 m², the actual dose of gemcitabine should be adjusted to a maximum BSA of 2.1 m² for safety reasons. Dose reduction and/or treatment delay and/or treatment discontinuation are planned in case of severe toxicity.
PRIMARY ENDPOINT(S) AND MAIN SECONDARY ENDPOINT(S)	Primary end-point: - Overall Survival, defined as the time interval from the date of randomization to the date of death due to any cause. Main Secondary End-points: - Efficacy: • Progression free survival (PFS) is defined as the time interval from the date of randomization to the date of first observation of disease progression or the date of death (due to any cause), whichever comes first. • Clinical Benefit will be based on a composite score of pain severity assessed by Visual Analog Scale (VAS), analgesic consumption as morphine equivalents, ECOG PS and weight change from baseline. The Clinical Benefit will be assessed by time to symptom worsening (TTSW) evaluated from randomization to symptom worsening, and improvement in tumor related symptoms. • Objective responses (CR and PR) as assessed by investigators according to RECIST criteria (for patients with measurable disease at study entry). Confirmation of objective responses will be performed by repeating tumor imaging (CT scans, MRI) at least 4 weeks after the first radiological documentation of response. -Safety profile of the study treatment in terms of AEs/ SAE's and laboratory parameters: • Type, frequency, severity, seriousness, and relatedness of study treatment-emergent adverse events will be assessed

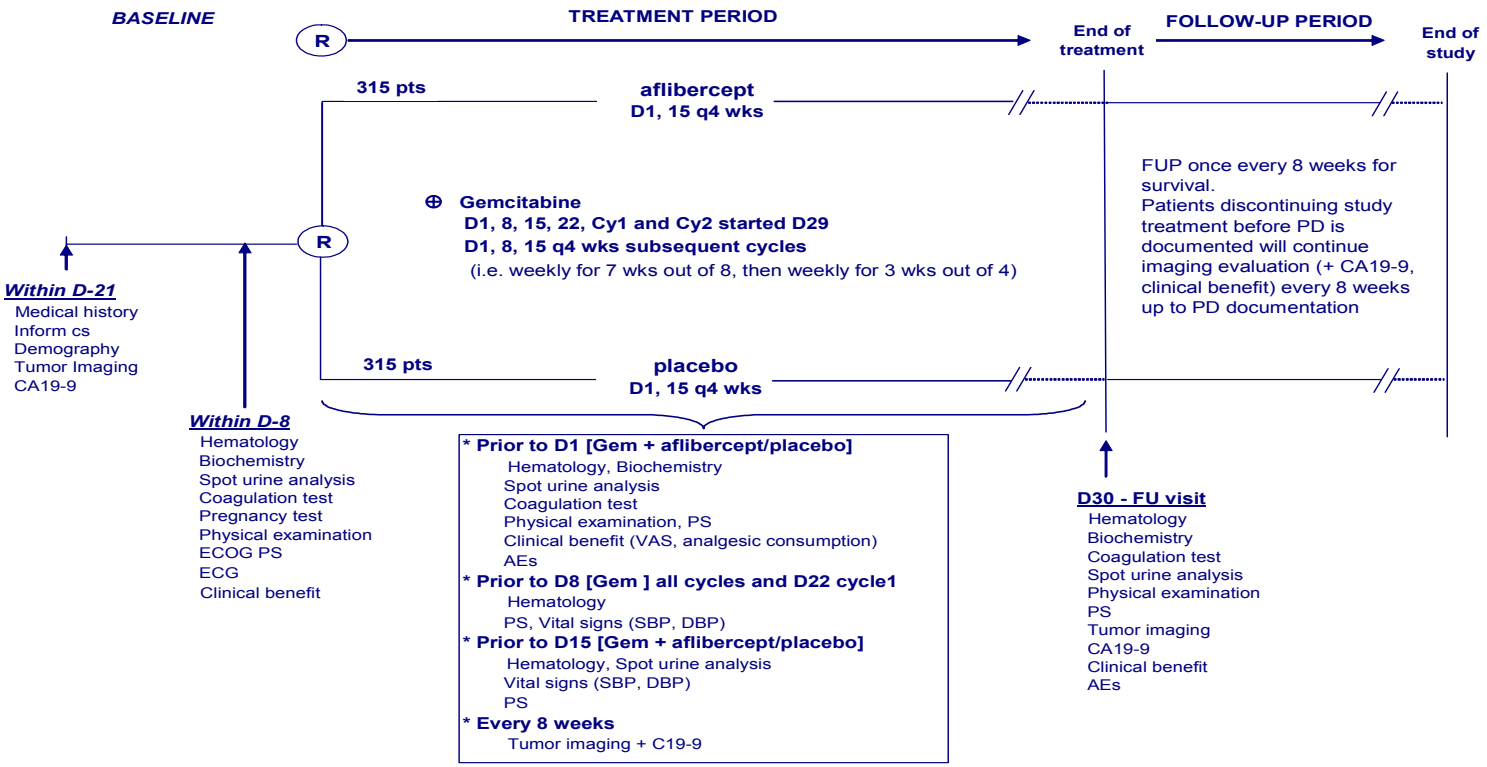
	according to NCI CTCAE v.3.0. • Laboratory abnormalities will be assessed according to the NCI CTCAE v.3.0. - Immunogenicity test: • Blood sampling for anti-aflibercept antibody detection will be performed prospectively at specified time points during the study in all patients. In addition, event-driven sampling for immunogenicity evaluation and pharmacokinetic measurement will be performed. - Pharmacokinetic parameters: • Blood sampling will be performed at specified time points during the study treatment. Pharmacokinetic parameters will include both free aflibercept and aflibercept:VEGF complex.
ASSESSMENT SCHEDULE	Clinical examinations (including vital signs, ECOG PS) and laboratory safety tests (including complete blood counts, serum chemistries and urine analyses) will be obtained prior to each cycle (i.e. every 4 weeks) and at the 30-days Follow-up (FU) visit. ECOG PS, vital signs assessment, hematological tests and urine analyses will be repeated within each cycle. Signs/symptoms that are present, or occurred, from the time the patient has signed the informed consent form to first study drug administration will be recorded as AEs, at cycle 1, if present at the time of first administration of study treatment. SAEs will be recorded from the time the patient has signed the inform consent. During the treatment period AEs will be collected at each visit (28-day cycle) up to the 30-day FU visit. During the FU period (i.e. after 30-day FU visit), only related ongoing, or new related, AEs will be recorded. SAEs, regardless of relationship with study treatment, ongoing at the end of study treatment, will be followed during the FU period until resolution or stabilization. For all **randomized and treated** patients, samples for detecting anti-aflibercept antibodies will be collected at baseline (before cycle 1), **at through [prior to every other aflibercept/placebo infusion, i.e. prior to third aflibercept/placebo infusion cycle 2, fifth aflibercept/placebo infusion cycle 3, seventh aflibercept/placebo infusion cycle 4, ninth aflibercept/placebo infusion cycle 5, etc….],** then approximately 30 days and 90 days after the last administered dose of aflibercept/placebo. Pharmacokinetic blood samples will be collected at the same time points, **with an additionnal sample at peak (end of aflibercept/placebo infusion 1 of cycle 1).** Samples for antibody detection and pharmacokinetic measurement should also be collected in patients who develop certain adverse events. For all patients **who are randomized at study sites equipped with a 4°C centrifuge (needed for preparation of the samples),** one additional blood sample will be collected at baseline to measure endogenous VEGF. Tumor assessments (abdominal CT scan, chest X-ray or CT scan in case of thoracic target lesion, and any other exams as clinically indicated), using the same method used at baseline, will be performed every 8 weeks until disease progression, even if the patient discontinued study treatment before disease progression

	and/or even if the patient receive further anti-cancer therapy before disease progression. After disease progression is documented, patients will be followed every 8 weeks until death, withdrawal of patient consent or study cut-off date whichever comes first. Further anticancer treatment will be collected. CA19-9 evaluation will be performed at the same timepoints imaging is performed. CA19-9 levels will not be used for making decision on study treatment discontinuation.
STATISTICAL CONSIDERATIONS	**Statistical hypotheses and sample size calculation:** [redacted] **Analysis populations:** • Intent-to-Treat (ITT) population: This population includes all randomized patients who have given their informed consent. Patient is randomized if there is confirmation of successful allocation of a randomization number through the study treatment allocation system (IVRS). This population is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned by IVRS. • Evaluable Patient (EP) population for tumor response: This population will consist of all randomized and treated patients, with cytologically or histologically confirmed pancreatic cancer, with metastatic and measurable disease at study entry, in first line setting and evaluable for response (i.e. patients with at least one tumoral evaluation while on treatment, except for early disease progression/cancer-related death). The EP for tumor response will be used for the RR analysis (secondary population for RR analysis, knowing that primary population will be ITT). All analyses using this population will be based on the treatment actually received. • All-Treated (AT) population: The AT population is a subset of the ITT population that took at least one dose of study medication. This population is for safety analyses. All analyses using this population will be based on the treatment actually received. • PK population: the PK population will include all treated patients with at least one PK assessment on treatment.

	Primary Analysis of the primary endpoint OS is defined as the number of months from the date of randomization to the date of death. If death is not observed during the study, OS data will be censored at the earlier of the last date patient is known to be alive and the cut-off date. OS will be compared between the two treatments groups by the log-rank test procedure stratified by stratification factors as specified at the time of randomization: ECOG PS (0 vs 1 vs 2), prior curative surgical therapy (pancreatectomy, yes vs no), and geographical region. The estimates of the hazard ratio and corresponding 95% confidence interval will be provided using a Cox proportional hazard model stratified by the same stratification factors as those used for the log-rank test described above. The survival curves will be estimated using Kaplan-Meier estimates. **Interim and final analyses** One interim analysis of OS is planned for the purpose of futility and overwhelming efficacy when approximately 205 OS events (40% information fraction) have occurred. Calculations are based on an O'Brien-Fleming alpha spending function for efficacy boundaries and a gamma (-4) spending function for futility boundaries and assuming that the interim look will actually be carried out after the 205th event. The one-sided nominal significance level to consider study termination for overwhelming efficacy is 0.0004 at the interim analysis. Futility will be considered if the hazard ratio is $\geq$ 1.05 in favor of the placebo arm. The interim analysis will be carried out under the supervision of the DMC. The final OS analysis will be conducted when 513 deaths have been observed. The one-sided nominal significance level to declare superiority of aflibercept at the final analysis is 0.0249.
DURATION OF STUDY PERIOD (per Patient)	Study treatment is intended to be administered until disease progression. Patients will be followed for disease progression until PD is documented. Patients will be followed for survival until death or study cut-off date, whichever comes first.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOWCHART

Evaluation	Study Phase					
	Baseline	Treatment Period			End of Treatment/ withdrawal	Post treatment Follow-up Until Death
DAY		Before each cycle	Day 8- Day15	Every 2 cycles (8 weeks)		
Informed Consent [a]	Before any study protocol specific procedure					
Inclusion/Exclusion Criteria [b]	Within 8 days *					
Patient Demography	Within 21 days *					
Prior Medical/Surgical and Cancer History [c]	Within 21 days *					
Prior anticancer treatment [d]	Within 21 days *					
Physical Examination / ECOG Performance Status [e]	Within 8 days *	X	X		X	X
Hematology [f]	Within 8 days *	X	X		X	
Blood Chemistry [g]	Within 8 days *	X			X	
Urine Analyses [h]	Within 8 days *	X	Only on Day 15		X	
Coagulation [i]	Within 8 days *	X			X	
Pregnancy test [j]	Within 8 days *	X				
Electrocardiogram	Within 8 days *		To be repeated as clinically indicated.			
Randomization [k]	First cycle within 3 days after randomization					
Study Drug Administration [l]		Aflibercept/placebo administered every 2 weeks (twice a cycle)				
Adverse Events Assessment [m]		X			X	X
Prior/Concomitant/Post Medications [n]	Within 21 days	X				
Other investigations	As clinically indicated					
Tumor assessment [o]	Within 21 days *			Every 8 weeks	X	X
CA19-9 [p]	Within 21 days *			Every 8 weeks	X	X
Clinical benefit [q]	Within 8 days *	X			X	X
Survival status [r]		X				X
Pharmacokinetic samples [s]	Cycle 1 (before and after **the end of** aflibercept/placebo infusion 1), **every cycle (prior to the first aflibercept/placebo infusion of each cycle),** approximately 30 and 90 days after the last aflibercept/placebo infusion.					
Anti-aflibercept antibody detection [t]	Cy 1 (before aflibercept/placebo inf 1), **every cy (prior to the first aflibercept/placebo inf of each cy),** and approximately 30 and 90 days after the last aflibercept/placebo inf.					
Endogenous VEGF level		Sample **prior to aflibercept/placebo infusion 1 of Cycle1**				

*Assessment must be performed prior to randomization rather than prior to initial dose for eligibility determination.

a. Prior any protocol study procedures.

b. All assessments should be performed prior to dosing with study drug unless otherwise indicated. Acceptable time windows for performing the assessments are noted below each scheduled treatment day in the Study Flowchart, unless otherwise noted in the footnotes below. Time between biological work-up, physical examination or clinical benefit at baseline and first infusion should not exceeds 8 days. If time exceeds 8 days, biological tests, clinical benefit and physical examination should be repeated prior first administration of study treatment.

c. **Medical, Surgical and Cancer History:** including cancer diagnosis (primary tumor characteristics and metastatic sites) and concurrent illness.

d. **Prior Anticancer Treatment:** includes previous surgery for cancer, radiation therapy, chemotherapy and potential investigational antitumor therapy.

e. **Physical Examination:** Examination of major body systems, blood pressure, height (Baseline visit only), body weight, and ECOG PS. Weight, ECOG performance status and blood pressure will be assessed **prior to every study treatment dosing**.

f. **Hematology:** Hemoglobin, WBC, ANC, platelet count, prior **to every study treatment dosing**.

g. **Blood Chemistry:** Sodium, potassium, calcium, phosphorous, BUN, magnesium, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, and glucose. For patients with extensive liver involvement, a marked increase in liver function test results warrants radiological tumor assessment to verify or refute disease progression.

h. **Urine analyses:** dipstick (WBC, RBC); urine protein, urine creatinine, and UPCR will be calculated on morning urine spot **prior to each aflibercept/placebo infusion**. During study treatment, 24-h urine collection should be performed to quantify proteinuria when UPCR>1; ; **in case UPCR>2 or** in case of proteinuria of renal origin (according to urine protein electrophoresis) is associated with hematuria then **a blood** work-up **in search for hemolytic anemia of microangiopathic origin should be initiated and a nephrologist consultation should be considered. This work up could include** LDH, haptoglobin, schistocytes and orosomucoid **whenever possible**.

i. **Coagulation**: prothrombin time, expressed as international normalized ratio, will be assessed in patients under treatment with Vitamin K antagonist.

j. **Pregnancy Test:** Women of reproductive potential must have a negative pregnancy test result (serum or urine) within 8 days prior to randomization. To be repeated as clinically indicated.

k. **Randomization:** All eligible patients will be randomly assigned to one of the two treatment groups (either aflibercept + gemcitabine or placebo + gemcitabine) using an Interactive Voice Response System (IVRS). Study treatment should be started within 3 days from randomization.

l. **Study Drug Administration:** Aflibercept /placebo will be administered every 2 weeks immediately followed by gemcitabine administered on Days 1 and 15 of each 28-day cycle. In addition, gemcitabine will be administered alone on Day 8 of each 28-day cycle and on Day 22 of Cycle 1. Basically gemcitabine will be administered weekly for 7 weeks followed by 1 week rest, and then weekly for 3 weeks followed by 1 week rest.

m. **Adverse Event Assessment:** The period of safety observation starts from the time the patient gives informed consent. Whenever possible, symptoms should be reported as a single syndrome or diagnosis. Laboratory abnormalities are to be recorded as AE only if they are serious, and/or if they lead to study treatment modification (dose reduction, cycle delay, infusion temporary interrupted), or study treatment discontinuation. Signs/symptoms that are present, or occurred, from the time the patient has signed the ICF to first study drug administration will be recorded as AEs, at cycle 1, if present at the time of first administration of study treatment. SAEs will be recorded from the time the patient has signed the inform consent. During the treatment period AEs will be collected at each visit up to the 30-day FU visit. During the FU period -i.e. after 30-day FU visit-, only related ongoing, or new related, AEs will be recorded. SAEs, regardless of relationship with study treatment, ongoing at the end of study treatment, will be followed during the FU period until resolution or stabilization.

n. **Assessment of Concomitant Medications:** Concomitant medications and treatments will be recorded from 21 days prior to the start of study treatment, before every cycle during the study treatment period, and up to 30 days after the final dose of study treatment. Once the patient has withdrawn from study treatment, concomitant medication should only be recorded if used to treat new or unresolved study treatment related adverse events.

o. **Tumor Assessment:** abdominal CT-Scan or MRI, Chest X-Ray (or chest CT-Scan or MRI in case of thoracic target lesion) and other exams as clinically indicated to assess target and non target lesions to be performed at baseline, then every 8 weeks during study treatment, and at the end of study treatment visit, using the same method for each assessment. For the purpose of analysis, a CR or PR will be considered a confirmed response if a subsequent assessment has been performed 4 – 6 weeks after the first assessment and the results confirm the initial finding. If patients discontinue study treatment without documented disease progression, then tumor assessments must continue to be performed every 8 weeks until disease progression is documented.

p. **CA19-9** will be performed using commercially available assay at the same timepoints than tumor assessments, and will not drive the decision making in term of study treatment continuation or discontinuation.

q. **Clinical Benefit:** Tumor related symptoms will be based on a composite score of pain severity assessed by VAS, analgesic consumption as morphine equivalents, ECOG PS and weight change from baseline. During the follow-up period, patients who went off study treatment prior to documented disease progression will be evaluated for clinical benefit every 8 weeks until disease progression or start of other anticancer therapy.

r. **Survival Status:** During the follow-up period, once disease progression is documented, patients will be followed to collect his/her survival status (dead, alive, or lost to follow-up) until death or study cut-off date.

s. **Pharmacokinetics intended for all randomized and treated patients**: Blood sample for measurement of free aflibercept and aflibercept:VEGF complex to be collected pre-dose and at the end of aflibercept/placebo infusion 1 on Day 1 (cycle 1), then at pre-dose on day 1 of **each cycle (i.e. aflibercept/placebo infusion 3 cycle 2, infusion 5 cycle 3, infusion 7 cycle 4, infusion 9 cycle 5, etc…),** at approximately 30 days and 90 days after the last aflibercept/placebo administration. Refer to Appendix G for collection, handling, and shipping instructions. **In all patients that are randomized at study sites that are equipped with 4°C centrifuge,** one sample will be collected pre-dose of **aflibercept/placebo** infusion 1 Cycle 1 to measure endogenous VEGF.

t. Serum for detection of **anti- aflibercept antibodies** (in **all randomized and treated patients**) will be collected at pre-dose of Cycle 1 (before first aflibercept/placebo infusion), **then at pre-dose on day 1 of each cycle (i.e. aflibercept/placebo infusion 3 cycle 2, infusion 5 cycle 3, infusion 7 cycle 4, infusion 9 cycle 5, etc…),** at approximately 30 days and 90 days after last aflibercept/placebo infusion, and in all patients in specific circumstances detailed in section 8.5.1. Refer to Appendix G for collection, handling, and shipping instructions.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

Ab	Antibody
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
AS	Analgesic Score
AST	Aspartate Aminotransferase
AT	All Treated
AUC	Area Under the Time Concentration Curve
BSA	Body Surface Area
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Response
CHO	Chinese Hamster Ovary
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
D, d	Day
DBP	Diastolic Blood Pressure
DEHP	Di (2-ethylhexyl) phthalate
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DRF	Discrepancy Resolution Form
DVT	Deep Veinous Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme linked Immunosorbent Assay
EOT	End of treatment
EP	Evaluable Patient
FDA	Food and Drug Administration
FDR	Fixed-Dose Rate
5-FU	5-Fluorouracil
GCP	Good Clinical Practice
HBP	High Blood Pressure
HIV	Human Immunodeficiency Virus

HR	Hazard ratio
h	Hour
IA	Interim analysis
ICF	Informed consent form
ICH	International Conference on Harmonization
IFL	Irinotecan 5-Fluorouracil Leucoverin
Ig	Immunoglobulin
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
LD	Longest diameter
LDH	Lactate Dehydrogenase
MBC	Metastatic Breast Cancer
MCRC	Metastatic Colorectal Cancer
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial Infarction
Min	Minutes
mm	Millimeters
MPC	Metastatic Pancreatic Cancer
MRI	Magnetic Resonance Imaging
NA	Not available
NCI	National Cancer Institute
NS	Not significant
NSCLC	Non Small Cell Lung Cancer
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Pulmonary embolism
PEFG	cisplatin, epirubicin, fluorouracil, gemcitabine
PFS	Progression Free Survival
PI	Package Insert
PIGF	Placental Growth Factor
PK/PD	Pharmacokinetic/Pharmacodynamic
Plts	Platelets
PO	Per os
PR	Partial Response
PT	Prothrombin Time
PS	Performance Status
PVC	Polyvinyl Chloride
Q	Every
RBC	Red Blood Cells

RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible Posterior Leuko-encephalopathy Syndrome
RPTD	Recommended Phase II Dose
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SD	Stable Disease
SD	Standard Deviation
SGOT	Serum Glutamate-Oxalate Transferase
SGPT	Serum Glutamate-Pyruvate Transferase
SmPC	Summary Product Characteristics
T	Temperature
TEAE	Treatment Emergent Adverse Event
TMA	Thrombotic microangiopathy
TOTM	Tri-2-Ethylhexyl Trimellitate
TTSW	Time To Symptom Worsening
ULN	Upper Limit of Normal
UPCR	Urine Protein Creatinine Ratio
US	Ultra sound
V, v	Version
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor
VEGFR	VEGF Receptor
VPF	Vascular Permeability Factor
W	Week
WBC	White Blood Cell

4 INTRODUCTION AND RATIONALE

4.1 PANCREATIC CANCER

Pancreatic cancer is one of the most lethal cancers and continues to be a major unsolved health problem at the start of the 21st century. Pancreatic cancer represents the fourth leading cause of cancer mortality in the Unites States with an estimated 32,300 deaths attributed to this disease and about 45,600 deaths in the European Community in 2002 (1). This number has been quite steady over the past 3-5 years. This aggressive malignancy is typically diagnosed at an advanced stage (around 80% of patients have an unresectable disease at presentation) and lack of effective therapy are resulting in a dramatically poor survival, 20% after two years and only 3% after five years, the lowest of any cancer site (2).

4.1.1 Chemotherapy in pancreatic cancer

Due to the advanced stage of the disease at diagnosis, chemotherapy becomes the primary therapeutic modality, the objectives of which are palliation of symptoms (clinical benefit), improvement of quality of life, and extended survival. The majority of patients with advanced pancreatic cancer have a high burden of symptoms at the time of diagnosis, including pain, fatigue, weight loss, and jaundice. Pain is the most common symptom and is observed in many as 80% of patients.

Chemotherapy options for non operable advanced pancreatic cancer are limited. For the past decade, gemcitabine has been considered the standard chemotherapeutic agent in the treatment of locally advanced and metastatic pancreatic cancer based on a prospective clinical trial, that demonstrated a statistically significant improvement in clinical benefit response (CBR) (as measured by weight gain, decreased pain medication need, or increased performance status; 22.2% vs 4.8%, P=.0022) and 5-week gain in median survival over that achieved with bolus 5-Fluorouracil (5-FU) for clinically symptomatic patients (3-4). In that and subsequent studies, gemcitabine monotherapy resulted in median survivals and 1-year survival rates of approximately 6 months and 20% respectively. Subsequently gemcitabine was tested in combination with various cytotoxic (including platinum analogs, topoisomerase inhibitors, taxanes, antifolates and oral fluoropyrimidines) and targeted agents in various attempts to improve outcomes. Although endpoints, including response rates and progression free survival, were improved significantly in some studies, a significant survival advantage was not demonstrated until the results of gemcitabine plus erlotinib trial became available in 2005 (see Table 1) (4-21).

One phase III comparing the combination of gemcitabine and capecitabine with gemcitabine alone has shown a significantly improved median and 1-year survival in favor of the combination arm: 7.4 months *versus* 6.0 months and 26% *versus* 19%, respectively, with a favorable safety profile (10). Other studies with gemcitabine, with or without IV 5-FU, all failed to show a difference between gemcitabine monotherapy and combination treatment (7-9).

The first agent that has shown a survival benefit for patients with advanced pancreatic cancer is the oral EGFR TKI erlotinib (Tarceva®). When combined with gemcitabine, the hazard ratio for survival is 0.81, which reflects a 19% reduction in the rate of death for this disease (5). On the subgroup analysis, patients with metastatic cancer showed a better effect (hazard ratio = 0.80, median OS improvement from 5.1 to 5.9 months) compared to the population with locally advanced cancer (hazard ratio = 0.93). Given the statistically significant but clinically modest survival benefit, some may question whether use of erlotinib and gemcitabine constitutes a new standard of care. The standard treatment for patients with advanced pancreatic cancer remains controversial and the choice of the reference treatment in clinical trials is difficult. It is therefore reasonable to use gemcitabine alone as a backbone regimen for the addition of other targeted agent such as aflibercept. In addition, an add-on design, double-blind versus placebo, will allow to isolate the potential effect of aflibercept on safety and efficacy as compared to the control therapy.

Table 1 – Selected phase II / III trials of gemcitabine monotherapy versus gemcitabine-containing combination regimen

Drug	References	No of pts	Pts with locally advanced disease (%)	Survival (months)		p
				Gemcitabine combination	Gemcitabine alone	
5-FU	Berlin, 2002 [7]	326	10	6.7	5.4	.09
Infusional 5-FU	Riess, 2005 [8]	466	23	5.8	6.2	.68
Infusional 5-FU	De Constanzo, 2005 [9]	91	27-33	7.0	7.2	NS
Capecitabine	Herrmann, 2005 [6]	316	20-21	8.4	7.3	.31
Capecitabine	Cunnimgham, 2005 [10]	533	29	7.4	6.0	.026
Cisplatin	Heinemann, 2003 [11]	195	NA	8.3	6.0	.12
Oxaliplatin and FDR gemcitabine	Louvet, 2005 [12]	313	30-32	9.0	7.1	.13
Oxaliplatin	Poplin [13]	555	-	5.9	4.9 (Gem FDR 6.0)	NS
Erlotinib	Moore, 2005 [5]	569	24-25	6.4	5.9	.025 (HR, P=.81)
Irinotecan	Rocha Lima, 2004 [14]	342	24-27	6.3	6.6	.79
Irinotecan	Stathopoulos, 2006 [17]	145	14-22	6.4	6.5	NS
Exatecan	O'Reilly, 2004 [15]	349	21-22	6.7	6.2	.52
Pemetrexed	Oettle, 2006 [16]	330	NA	6.3	6.2	.85
Marimastat	Bramhall, 2002 [18]	239	NA	5.5	5.5	.95
BAY 12-9566	Moore, 2003 [19]	377	NA	3.74	6.6	<.001

Drug	References	No of pts	Pts with locally advanced disease (%)	Survival (months)		p
				Gemcitabine combination	Gemcitabine alone	
						(favoring gemcitabine)
Tipifarnib	Van Cutsem, 2004 [20]	688	23-24	6.5	6.0	.75
PEFG	Reni, 2005 [21]	99	29-30	38% at 1Year	21% at 1 Year	.1119

5-FU 5-fluorouracil; FDR fixed-dose rate; HR hazard ratio; NS not significant; NA not available; PEFG combined cisplatin, epirubicin, fluorouracil, and gemcitabine; Pts patients

4.1.2 Tumor angiogenesis

Several malignant tumors are dependent on angiogenesis to maintain a source of nutrition and oxygen from the body to support their growth and metastasis [22]. VEGF, also known as Vascular Permeability Factor (VPF), is a cytokine that was discovered in the late 1970s [23]. It is a homodimeric protein which binds to and activates two high-affinity receptors, Flt-1 (VEGFR1) and Flk-1 (VEGFR2), predominantly located on the vascular endothelium. VEGF is a powerful mitogen for endothelial cells, thus promoting formation of new vessels that are required for normal and neoplastic tissue growth. In addition, VEGF very potently increases vessel permeability [24]. Therefore, VEGF become a major target for anti-angiogenic therapy because its overexpression in several tumor types has been associated with increased tumor vascularity, proliferation, progression, invasion, metastasis, and poor prognosis [25-27].

Several studies in animal models and, more recently, human clinical trials, have demonstrated the efficacy of anti-VEGF approaches to cancer treatment. By additionally “normalizing” tumor vasculature and reducing tumor interstitial fluid pressure, VEGF antagonists may enhance intratumoral delivery of traditional cytotoxic agents thereby improving their antitumor efficacy without overlapping toxicity [28]. Convincing clinical evidence in support of this therapeutic approach was first demonstrated by the humanized anti-VEGF monoclonal antibody, bevacizumab (Avastin®), which was granted FDA approval in February 2004 in combination with IV 5-FU-based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon or rectum. This was followed by full approvals in Switzerland, Israel, and the European Union. Avastin® significantly improved the progression-free and overall survival of previously untreated metastatic colorectal cancer (MCRC) patients in combination with irinotecan/bolus 5-FU/LV (IFL) chemotherapy as compared to patients treated with IFL alone [29], the approved standard first-line MCRC treatment control.

Aflibercept (also refers as AVE0005 or VEGF Trap in other related documents) is a novel anti-angiogenic protein, which interferes with the biological actions of VEGF by complexing VEGF and preventing it from interacting with its receptors on endothelial cells. Further details can be found in the Investigator’s Brochure [30], which contains comprehensive information on aflibercept.

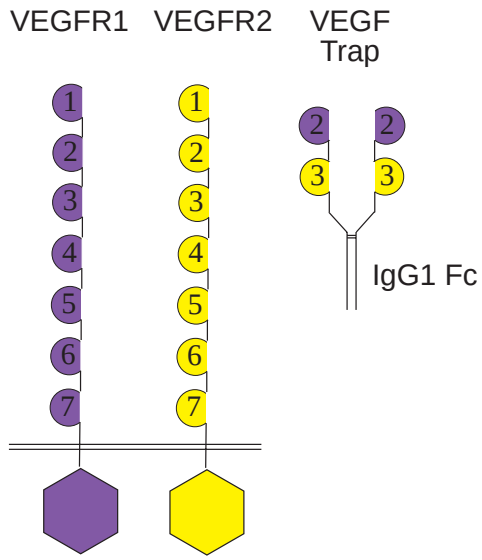
4.1.3 Angiogenesis and pancreatic cancer

Although pancreatic adenocarcinoma is not a grossly vascular tumor, this malignancy often exhibits enhanced foci of endothelial cell proliferation and frequently overexpresses vascular endothelial growth factor (VEGF), a potent angiogenic factor that is secreted by many tumor cell lines. Vascular endothelial growth factor (VEGF) is commonly overexpressed in pancreatic cancer, and high levels of VEGF correlate with both advanced-stage disease and poorer patient survival [31]. The inhibition of VEGF and VEGF receptor signaling suppressed pancreatic cancer growth in vitro and in animal models [32] suggesting that VEGF blockade may be an interesting therapeutic approach.

4.2 INVESTIGATIONAL PRODUCT

Aflibercept is a recombinantly-produced fusion protein consisting of human VEGF receptor extracellular domains fused to the Fc portion of human IgG1. It contains sequences encoding Ig domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of the human IgG1 Fc domain. Aflibercept is a dimeric glycoprotein with a molecular weight of 115 kDa. Aflibercept is made recombinantly in Chinese hamster ovary (CHO) cells.

Figure 1 - Aflibercept structure



- Aflibercept is a specific antagonist that binds and inactivates circulating VEGF in the bloodstream and in the extravascular space. Aflibercept was designed to prevent the growth of primary and metastatic tumors by reducing tumor vascularity and vascular permeability with several potential advantages over other VEGF blockers:
    - Aflibercept has a much higher VEGF-A binding affinity (0.5 pM dissociation constant for VEGF165 and VEGF121) than a humanized monoclonal antibody (~800 pM),

- Aflibercept also binds VEGF-B plus the related factors PlGF1 and PlGF2 which may be advantageous in certain disease settings (e.g., malignant ascites where PlGF may mediate vascular permeability),
- Aflibercept has a longer circulating half-life compared to other soluble receptor constructs that have been studied in animals.

4.3 OVERVIEW OF PRECLINICAL INFORMATION

Detailed information regarding the *in vitro* and *in vivo* pharmacology of aflibercept, including the results of preclinical efficacy, safety and pharmacokinetic studies, can be found in the Investigator's Brochure [30]. In particular, compound-related microscopic findings in primates were observed in the bone, kidney, and ovary. Most kidney findings were very slight or slight and aflibercept was not highly immunogenic in monkeys. In all animal species evaluated, free aflibercept was characterized by a low clearance, a low volume of distribution, and a long apparent elimination half-life. Aflibercept inhibition of tumor growth in mouse xenograft models was observed at $\geq$ 2.5 mg/kg twice weekly dose, which corresponded to a pharmacological exposure where free aflibercept increases approximately linearly in excess of plateauing aflibercept complex (i.e., bound aflibercept) levels.

The ability of systemically administer aflibercept to prevent the vascular leak induced by VEGF was evaluated in a model of ascites formation. Human ovarian cancer cells (OVCAR-3) were implanted into the peritoneum of nude mice. These animals developed significant tumor burden and ascites over a period of approximately 8 weeks. Treatment with aflibercept initiated 2 weeks after tumor cell inoculation prevented the formation of ascites and decreased tumor burden in these mice by >50% [33].

Fukasawa M et al [34] reported that aflibercept suppresses the s.c. growth of four distinct pancreatic cell lines in athymic nude mice and that this effect is associated with a marked decrease in microvesel density. In addition, using an orthotopic model, aflibercept is shown to attenuate intrapancreatic tumor growth and regional and distant metastasis. These findings support the hypothesis that VEGF-A has an important role in pancreatic cancer in vivo and raise the possibility that may ultimately provide a novel therapeutic option for management of this disease.

4.4 SUMMARY OF PREVIOUS HUMAN EXPERIENCE

Sofar, around 600 patients have been treated with aflibercept, either in monotherapy or combined with various chemotherapies (oxaliplatin, 5-FU, irinotecan, gemcitabine, docetaxel, docetaxel/cisplatin and docetaxel/cisplatin/5-FU). In general, aflibercept has an accepatble safety profile at the dose levels evaluated to date, as the majority of adverse events encountered have been mild to moderate in severity. Adverse reactions linked with VEGF blockade have been reported with consistent incidences and severity, across all the studies. Detailed information regarding the clinical safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of aflibercept can be found in the Investigator's Brochure [30].

4.4.1 Summary of clinical experience of aflibercept in monotherapy

Study TED6115/6116 is an ongoing open-label dose-escalation study of aflibercept given in monotherapy in patients with various advanced cancers. Doses, ranging from 0.3 mg/kg to 7.0 mg/kg iv, administered once every 2 weeks, were investigated for a median of 3 to 7 cycles. Overall 46 patients have been enrolled and have received 1 to 50 cycles.

Six out of 46 (13%) patients experienced dose limiting toxicity (ies) (DLT) within the first 4 weeks of study treatment, influencing dose escalation or cohort extension decision. One patient at the 1.0 mg/kg dose experienced grade 3 arthralgia associated with grade 3 dysphonia, at the 2.0 mg/kg dose, 1 patient experienced grade 3 dyspnea (patient with preexisting COPD). At 4.0 mg/kg dose, 1 patient experienced grade 3 hypertension and another patient had grade 2 proteinuria (>2.0 g/24hours) associated with grade 3 manageable hypertension. Two patients at the 7.0 mg/kg dose level reported DLTs, 1 grade 3 rectal ulcer and the other patient developed grade 3 proteinuria that recovered and continued treatment at the 4 mg/kg dose.

Treatment emergent adverse events, consisting mostly of low grade events, were reported in most of the patients (Table 2). No evident particular pattern, in frequency or in severity of the adverse events, could be identified across the investigated doses. The five most frequent TEAEs reported were fatigue (84.8%), nausea (65.2%), constipation (54.3%), dysphonia (50.0%) and dyspnea (50.0%).

Adverse events that may be related to VEGF blockade, were observed across all dose levels. Overall incidences for these events were: dysphonia (50.0%), hypertension (41.3%), proteinuria (19.6%), epistaxis (13.0%). No arterial ischemic event was reported.

Table 2 – Most common TEAEs (all grades) in studies TED6115/6116 (in at least 10% of treated patients), regardless of relationship to study medication

	Dose Level							
MedDRA Preferred Term	0.3 mg/kg (N=3) N	1.0 mg/kg (N=7) N	2.0 mg/kg (N=6) N	3.0 mg/kg (N=7) N	4.0 mg/kg (N=7) N	5.0 mg/kg (N=4) N	7.0 mg/kg (N=12) N	Total Doses (N=46) N
Subjects With at Least 1 TEAE	3	7	6	7	7	4	10	44
Subjects Without Any TEAEs	0	0	0	0	0	0	2	2
Fatigue	3	6	6	7	7	2	8	39
Nausea	3	5	2	7	6	2	5	30
Constipation	1	4	6	5	4	1	4	25
Dysphonia	1	2	3	6	3	2	6	23
Dyspnoea	1	4	5	6	3	0	4	23
Vomiting	2	3	3	6	3	2	2	21
Hypertension	0	2	2	1	4	3	7	19
Abdominal pain	2	3	1	4	3	1	3	17
Anorexia	1	3	3	4	4	1	1	17
Arthralgia	1	3	2	3	2	2	4	17
Back pain	1	1	1	4	3	3	4	17
Headache	0	3	3	1	3	3	3	16

	Dose Level							
MedDRA Preferred Term	0.3 mg/kg (N=3) N	1.0 mg/kg (N=7) N	2.0 mg/kg (N=6) N	3.0 mg/kg (N=7) N	4.0 mg/kg (N=7) N	5.0 mg/kg (N=4) N	7.0 mg/kg (N=12) N	Total Doses (N=46) N
Diarrhea	2	3	1	4	3	0	2	15
Pyrexia	1	3	3	3	2	1	2	15
Shoulder pain	0	3	1	1	3	3	3	14
Cough	0	3	3	2	2	0	1	11
Myalgia	0	2	2	2	1	1	3	11
Pain in extremity	0	1	2	2	0	2	4	11
Pharyngolaryngeal pain	0	2	2	2	1	1	2	10

The most frequently reported grade 3**-4** AE was HBP in 15/**46** (32.6%) of the patients (Table 3). At doses of 4 mg/kg or above, **half of the patients (11 out of 23 treated patients) experienced a a grade 3-4 blood pressure increase.** Grade 3 HBP seems to occur earlier in the treatment as the dose is escalated from 4 mg/kg. Hypertension is reported within 2 weeks of the first drug administration. Severe proteinuria (grade 3) was observed in 2 (4.3%) patients. Fatigue was the only other grade 3 AE to be reported in more than 5 patients.

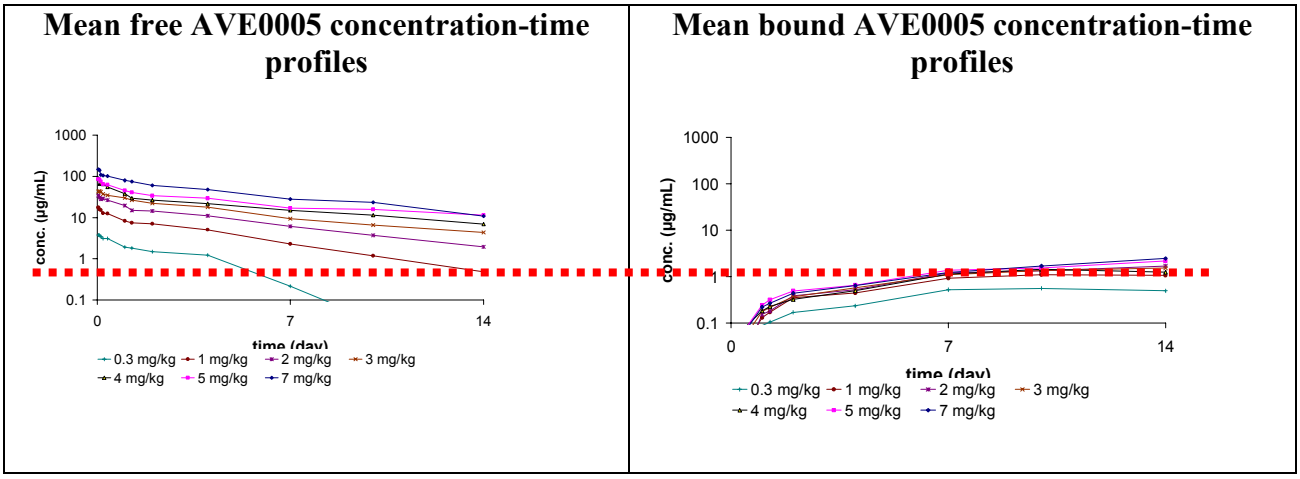
Table 3 – Most common Grade 3-4 TEAEs in studies TED6115/6116 (in at least 2 treated patients), regardless of relationship to study medication

	Dose Level							
MedDRA Preferred Term	0.3 mg/kg (N=3) N	1.0 mg/kg (N=7) N	2.0 mg/kg (N=6) N	3.0 mg/kg (N=7) N	4.0 mg/kg (N=7) N	5.0 mg/kg (N=4) N	7.0 mg/kg (N=12) N	Total Doses (N=46) N
Subjects With at Least One Grade 3-4-5 TEAE	1	6	4	5	5	4	8	33
Subjects Without Any Grade 3-4-5 TEAEs	2	1	2	2	2	0	4	13
Hypertension	0	1	2	1	3	3	5	15
Fatigue	0	2	1	2	2	0	0	7
Dyspnoea	0	2	2	0	0	0	0	4
Abdominal pain	0	1	0	1	0	0	1	3
Nausea	0	0	0	1	0	2	0	3
Vomiting	0	0	0	1	0	2	0	3
Anorexia	0	0	0	1	0	1	0	2
Arthralgia	0	1	0	0	0	0	1	2
Blood alkaline phosphatase	0	1	0	1	0	0	0	2
Blood alkaline phosphatase increased	0	0	0	1	1	0	0	2
Blood sodium decreased	0	0	0	0	1	0	1	2
Colon cancer metastatic	0	0	0	0	1)	0	1	2
Hyperbilirubinaemia	0	0	0	1	0	0	1	2
Pleural effusion	0	1	0	0	0	1	0	2
Proteinuria	0	0	1	0	0	1	0	2

Three patients had a partial response. Responses were observed in a patient with a malignant thymoma, and 2 other patients with ovarian cancer had a partial response. All these tumor responses were observed in heavily pretreated patients.

The pharmacokinetics of free aflibercept appeared to be linear between the 2 and 7 mg/kg dose levels while bound aflibercept increased with dose between 0.3 and 2 mg/kg, then plateaued between 2 and 7 mg/kg, suggesting that free aflibercept was present in sufficient amount to bind all endogenous VEGF at these higher dose levels. Free aflibercept levels have remained in excess of bound levels (ratio >1) throughout the dosing intervals at ≥ 2.0 mg/kg dose levels.

Figure 2 – Intravenous free versus bound aflibercept concentration time profile (Cycle 1)



Based on the above adverse events, thought to be related to VEGF blockade or not, formal DLTs as well as AEs resulting in discontinuation, safety profile, pharmacokinetic results, and clinical benefit across dose levels, it was recommended to select 4 mg/kg every 2 weeks for aflibercept administered as a single agent. This is independently supported by the safety experience from currently ongoing phase II studies of aflibercept administered as single agent, in the indications of non small cell lung adenocarcinoma and advanced ovarian carcinoma (either at doses of 2 or 4 mg/kg every 2 weeks). The safety profile in these trials is similar to the phase I study described above with most adverse events being grade 1 or 2. The adverse events most frequently reported are: hypertension, proteinuria, epistaxis, dysphonia/hoarseness, pain (including abdominal pain and back pain), asthenia/ fatigue, nausea, vomiting, headache, constipation, increase in liver enzymes, myalgia, arthralgia, dyspnea, decreased appetite and diarrhea.

4.4.2 Phase I Combination studies

A total of 5 combination phase 1 studies of aflibercept (every 2 or 3 weeks) have started with the primary objectives of evaluating DLT and determining an RPTD in combination with standard cytotoxic chemotherapy agents/regimens administered at a fixed dose based on safety, pharmacokinetics, and pharmacodynamics.

So far, in all combination tested, aflibercept has been well tolerated with acute and reversible adverse reactions (mainly high blood pressure), no cumulative or late toxicity have been observed. In addition, no evidence of exacerbation of background chemotherapy-related toxicities was observed. The adverse events thought to be associated with VEGF blockade such as HBP, epistaxis, hoarseness/dysphonia, proteinuria are presented in Table 4.

The dose selection in each combination took into account the combination of DLTs/overall safety profile and pharmacokinetics together with observation of DLTs at these doses. The selected dose in each study was based on the aflibercept free/bound ratio >1. This ratio should be >1 during the two- or three-week period and approaching 1 at the end of the cycle for all the patients. The aflibercept dose of 6 mg/kg every 3 weeks (in combination with docetaxel) and the dose of 4 mg/kg every 2 weeks (in combination with irinotecan/LV5FU2, FOLFOX or gemcitabine) have been selected, which allows a same dose intensity of aflibercept whatever the schedule (every 2 or 3 weeks) and is also consistent with the single agent dose selected (4.0 mg/kg q2w).

Table 4 – Adverse events thought to be associated to VEGF Blockade

	Single Agent TCD6115/6116 Q2wk N = 46		+ FOLFOX TCD6117 Q2wk N = 15		+ irinotecan-LV5FU2 TCD6118 Q2wk N = 31		+ docetaxel TCD6120 Q3wk N = 27		+ gemcitabine TCD6121 Q2wk N = 18	
	All Gr	Gr3-4	All Gr	Gr3-4	All Gr	Gr3-4	All Gr	Gr3-4	All Gr	Gr3-4
HBP	19 (41.3%)	15 (32.6%)	9 (60%)	3 (20%)	17 (55%)	6 (20%)	15 (56%)	2 (7%)	10 (55.6%)	6 (33.3%)
Epistaxis	6 (13%)	-	6 (40%)	-	11 (35.5%)	-	20 (74%)	-	1 (5.6%)	-
Hoarseness/Dysphonia	23 (50%)	1 (2%)	5 (33%)	-	20 (64.5%)	-	20 (74%)	1 (4%)	2 (11.1%)	-
Thromboembolic events	1 (2%)	1 (2%)	-	-	2 (6%)	-	2 (7%)	-	2 (11.1%)	2 (11.1%)
Proteinuria	9 (19.6%)	2 (4.3%)	15 (100%)	1 (7%)	10 (32%)	4 (13%)	5 (18.5%)	1 (4%)	10 (55.6%)	2 (11.1%)

HBP: high blood pressure, Folfox: 5-fluorouracile combined with oxaliplatin

4.4.3 clinical study of aflibercept in combination with gemcitabine

Study TCD6121 is an ongoing open-label, phase 1, dose-escalation, investigating intravenous aflibercept administered every 2 weeks in combination with weekly intravenous gemcitabine (1000 mg/m², 7 weeks on/1 week off x 1, then 3 weeks on/1 week off every 4 weeks) in subjects with advanced solid malignancies. Based on the preliminary results of other ongoing phase I combination studies, the 4.0 mg/kg dose level was the starting dose level of aflibercept. From April 18, 2006 to December 30, 2006, a total of 18 patients were enrolled and treated in the escalation step of the study across 2 dose levels: 6 patients at 4.0 mg/kg and 12 patients at 6.0 mg/kg.

Patient demographics were as follows: mean age 62.5 years (with 6 subjects ≥ 65 years), predominantly female (83%). With respect to cancer history, primary tumors were mostly pancreas (n = 8, with 2 and 6 patients at 4.0 and 6.0 mg/kg dose levels, respectively). Other primary tumor types include lung cancer, head and neck cancer, sarcoma and melanoma. The median duration since cancer diagnosis was 33.8 months. All patients with pancreatic cancer

except one were first-line patients, whereas all other patients had received prior chemotherapy (median of 3.0 prior lines of chemotherapy, range: 1-11).

The median number of aflibercept doses administered was 3 (range: 2-9) and 2 (range: 1-8) at the 4.0 and 6.0 mg/kg dose levels, respectively. The median number of gemcitabine doses administered was 6 (range: 4-14) and 5 (range: 1-16) at the aflibercept 4.0 and 6.0 mg/kg dose levels, respectively. The median aflibercept relative dose-intensity (RDI) was 0.92 (range: 0.73 – 1.0) and 0.95 (range: 0.53 - 1.0) at the aflibercept 4.0 and 6.0 mg/kg dose levels, respectively. At the 4.0 mg/kg dose level, out of the 6 patients enrolled, 3 (50%) had at least one cycle delayed, and 2 (33%) experienced at least one dose reduction of gemcitabine. At the 6.0 mg/kg dose level, 6 (50%) patient had a cycle delay, and 3 (25%) had their dose of gemcitabine reduced. There was no dose-reduction of aflibercept, at any of the dose levels, but one dose omitted at 6.0 mg/kg. Gemcitabine dosing was omitted twice (one patient in each dose level).

One patient experienced a DLT within the first 4 weeks of study treatment at the 6 mg/kg dose level: grade 3 thrombocytopenia ($25x10^9$/L) associated with grade 2 hematuria was observed on day 15 after the first infusion of aflibercept and gemcitabine. Platelet count returned to grade ≤ 1 within a week.
Treatment emergent adverse events, mostly of low grades, were reported in 100% of the patients. Hypertension was observed with an incidence of 55.6% overall (50.0% and 58.3% at 4.0 and 6.0 mg/kg, respectively). The incidence of Grade > 3 hypertension is 33% overall (16.7% and 41.7% at 4.0 and 6.0 mg/kg). One patient at 6.0 mg/kg discontinued the treatment due to hypertension grade 3, poorly controlled despite treatment. The incidence of proteinuria is 55.6% overall (33.3 and 66.7% at 4.0 and 6.0 mg/kg, respectively). Two patients reported grade 3 proteinuria.

Table 5 – Main TEAEs (all grade) observed in TCD6121 study

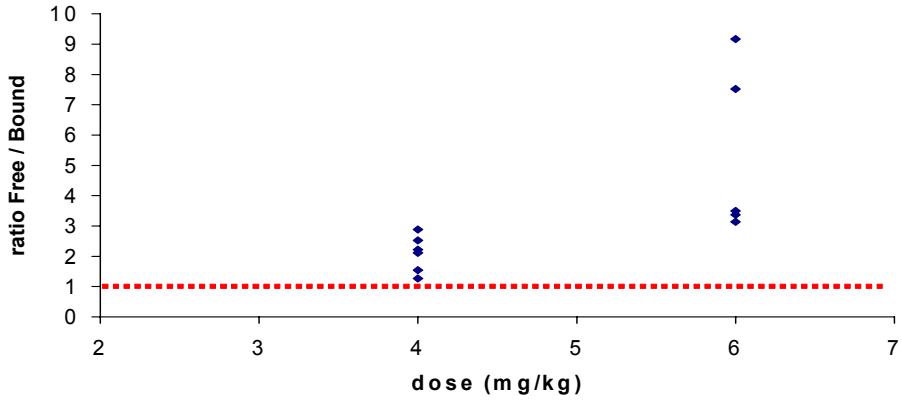
	Initial planned aflibercept dose level		
	4 mg/kg	**6 mg/kg**	**All**
Total number of treated patients [N]	6	8	18
Total patients with any TEAE [N (%)]	6 (100)	12 (100)	18 (100)
Fatigue	3 (50.0)	9 (75.0)	12 (66.7)
Nausea	5 (83.3)	6 (50.0)	11 (61.1)
Constipation	3 (50.0)	9 (75.0)	12 (66.7)
Vomiting	5 (83.3)	4 (33.3)	9 (50.0)
Diarrhea	3 (50.0)	5 (41.7)	8 (44.4)
Hypertension	3 (50.0)	7 (58.3)	10 (55.6)
Anorexia	3 (50.0)	6 (50.0)	9 (50.0)
Headache	2 (33.3)	4 (33.3)	6 (33.3)

In conclusion, preliminary TCD6121 data suggest that the safety profile is quite similar across the 2 dose levels explored, which is consistent with the preliminary conclusion of other combination phase I studies. However even if the incidence of hypertension is similar in both dose levels, there is more severe hypertension at the 6 mg/kg dose level. In addition, there is more patients experiencing proteinuria at the 6 mg/kg dose level. Therefore the dose of 4.0 mg/kg every 2 weeks in combination with gemcitabine has been selected.

Reported free and bound aflibercept concentrations are comparable to those observed in the monotherapy study, suggesting that the gemcitabine do not influence the pharmacokinetics of aflibercept.

In order to maintain endogenous free VEGF at very low levels (< 20 pg/mL, corresponding approximately to median value of endogenous VEGF in healthy subjects.) at the end of a cycle, a free / bound ratio higher than 1 is needed. At steady-state, mean free / bound trough ratios are 2.1 and 5.3 following every 2 weeks infusion of 4 and 6 mg/kg, respectively. In this phase I study, at the steady state 6/6 patients had free > bound at the 4 mg/kg dose level as depicted in Figure 3.

Figure 3 – Individual free/bound Aflibercept ratios at steady state vs dose



4.5 STUDY RATIONALE

Since 1997, gemcitabine has remained the standard of care for the treatment of advanced pancreatic cancer. However, this treatment is not curative, and thus new therapeutic options for patients with this disease are still desperately needed. The outcome of patients with locally advanced and metastatic pancreatic cancer is different. Many trials have combined both groups of patients and some trials have suggested a benefit for one of the subgroups for the investigational treatment arm. Therefore, the target population in the current trial is patients with metastatic disease only.

The recent modest survival benefit observed with erlotinib associated with gemcitabine over gemcitabine has validated targeted therapy as a rational approach for therapy of pancreatic cancer. VEGF is in addition a legitimate target. Aflibercept is a novel anti-VEGF agent that has a high affinity for binding VEGF and other related pro-angiogenic factors.

Convincing clinical evidence in support of this therapeutic approach may be independent of tumor type with emerging reports of bevacizumab efficacy in combination with different chemotherapy regimens for the first-line treatment of MCRC, NSCLC, and MBC [26, 35, 36], and for the second-line treatment of MCRC [37]. However, the randomized phase III trial (CALGB 80303) of bevacizumab in combination with gemcitabine compared to gemcitabine plus placebo as a first-line therapy for advanced pancreatic cancer did not meet its primary endpoint for overall survival. Therefore, the clinical evidence in support of this study in the first-line treatment of MPC may be

made by extrapolation from the favorable results of Phase III clinical trials of Avastin® in combination with standard chemotherapy in MCRC, NSCLC, and MBC and by higher VEGF-A binding affinity compared to a humanized monoclonal antibody.

The present randomized placebo-controlled study has been designed to evaluate the efficacy and safety of the addition of aflibercept at the dose of 4 mg/kg (Section 4.4.2) to the registered doses of gemcitabine in the first-line treatment of patients with MPC. Stratification will be done according to ECOG PS (0 vs 1 vs 2), to prior curative surgery (pancreatectomy, yes vs no) and to geographical region. Overall survival will be the primary efficacy endpoint, which will be analyzed after approximately 513 patients have died.

5 STUDY OBJECTIVES

5.1 PRIMARY

- The primary objective of this study is to demonstrate improvement in overall survival (OS) with aflibercept by comparison to placebo in patients treated with gemcitabine for metastatic pancreatic cancer.

5.2 SECONDARY

The secondary objectives are:

- To compare in the two treatment arms (by sequential order of statistical analysis):
  - progression free survival (PFS),
  - clinical benefit, which will be based on the measurement of tumor related symptoms including a composite score of pain severity assessed by visual analog scale (VAS), analgesic consumption as morphine equivalents, ECOG PS and weight change from baseline. Clinical benefit will be assessed by time to symptom worsening (TTSW) evaluated from randomization to symptom worsening as well as improvement in tumor related symptoms.
  - and overall response rate (RR) according to RECIST criteria (Appendix C),
- To assess the overall safety in the two treatment arms.
- To assess immunogenicity of **iv** aflibercept.
- To perform population pharmacokinetic **evaluation**.

6 STUDY DESIGN

This is a prospective, multicenter, multinational, randomized (1:1), double-blind, parallel-group study comparing the efficacy of aflibercept (Arm A) in terms of OS *versus* placebo (Arm B) administered on top of gemcitabine in patients with metastatic pancreatic cancer.

6.1 DESCRIPTION OF THE PROTOCOL

Each patient will be treated every 4 weeks, in the absence of definitive treatment discontinuation criteria outlined in Section 11.1.1.

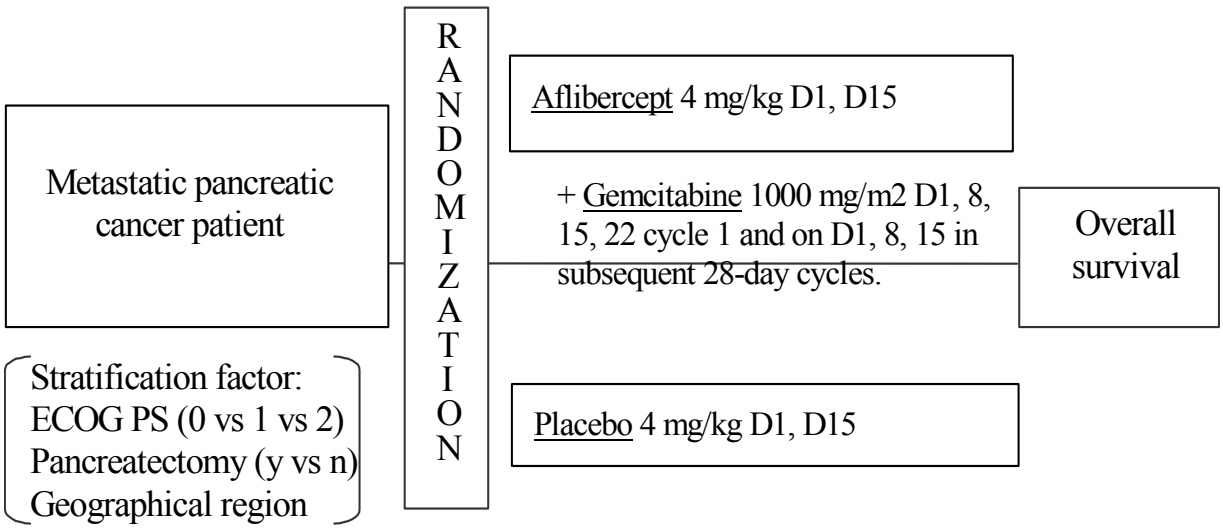
An Executive Steering Committee will be responsible for supervising the trial.

An independent Data Monitoring Committee (DMC) will periodically assess the progress of the trial, the safety data and will advise the Executive Steering Committee, as necessary. In addition the DMC will review the efficacy data from the planned survival interim analysis (IA).

Treatment assignment will be done centrally via an Interactive Voice Response System (IVRS) using a permuted-block randomization stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0 *vs* 1 *vs* 2), prior curative surgery (pancreatectomy yes vs no), and geographical region. All eligible patients will be randomly assigned to either the control arm or the experimental arm in a 1:1 ratio.

- The study design is summarized in Figure 4.

Figure 4 – Study design



6.2 DURATION OF STUDY PARTICIPATION

Patients will be considered on study upon signing the informed consent form. As described in the study flow chart and graphic study design (see Section 1.1 and 1.2), the study consists of a maximum of 21-day period prior to randomization (baseline), followed by a treatment period, consisting of 28-day treatment cycles which will end by a 30-day Follow-up visit, which in turn will be followed by a post study treatment follow-up period (follow-up visit every 8 weeks).

All baseline procedures (see Sections 1.1 and 1.2) will have to be performed within defined timelines, including review of eligibility criteria (see Section 7.2 and 7.3).

The first study treatment administration will take place within 3 days of randomization.

During the treatment period, the study treatment, either aflibercept or placebo, will be administered every 2 weeks unless a definitive treatment discontinuation criterion is met and then patients will remain on study until death or the study cutoff date. A cycle is defined as a 4-week or 28-day period in both arms and includes 2 aflibercept/placebo infusions. Cycle lengths may be extended in case of unresolved toxicity (see Section 8.5).

Imaging to document progressive disease will take place every 8 weeks and will continue to be done during the follow-up phase in case of early study treatment discontinuation (i.e. prior to documented progression).

Once disease progression is documented, patients will be followed every 8 weeks for survival status and collection of data regarding further anticancer therapy, until death or until the study cut-off date, whichever comes first.

The patients will be followed for safety for a minimum of 30 days following the last administration of the study treatment (30-day Follow-up visit). Beyond this date, all study drug-related AEs and all SAEs should be followed until resolution/stabilization. Study drug-related Aes and SAEs brought to the attention of the investigator at any time after the 30-day Follow-up visit should be recorded in the case report form (CRF).

- The termination of the study and the final data cut-off date for survival will be the date when it is determined that approximately 513 deaths have occurred.

6.3 INTERIM ANALYSIS

One interim analysis (IA) of overall survival is planned to stop for futility or overwhelming efficacy when approximately 205 OS events (40% information fraction) have occurred. Statistical operating characteristics of this analysis e.g. stopping boundaries and α- and β- spending functions to maintain the type I and type II error rates are described in the statistical considerations (see section 13.6).

The interim analysis will be reviewed by the DMC.

6.4 STUDY COMMITTEES

An **Executive Steering Committee** will include the Study Chairman, 2 main investigators and Sponsor representatives and be responsible for:

- Supervising the progress of the trial towards its overall objectives,
- Reviewing at regular intervals relevant information that may affect the study conduct,
- Discussing and supervising implementation of the recommendations of the independent Data Monitoring Committee.
- This committee will not have access to unblinded data sets before completion of the study, except if released by the DMC at the time of IA for overall survival (see Section 9.4).

An independent **Data Monitoring Committee (DMC)** consisting of at least 3 external independent members not associated with the conduct of the study or other study committees will meet regularly to:

- Review the progress of the trial,
- Review the unblinded safety and efficacy data,
- Review unblinded results of the IA for OS,
- Advise the sponsor and the Executive Steering Committee on potential modifications or communications that may be necessary to ensure the patient safety or protect the scientific integrity of the trial.

The first formal safety review of the trial by the DMC will be the earlier of either 6 months after the first patient has been enrolled, or the time when 100 patients will have been treated for a minimum of at least 2 treatment cycles. The DMC meeting will be set up semiannually. Ad-hoc DMC meetings may also be held if a significant safety issue or any other issue deemed important for the conduct of the trial arise, on this or on any other studies with aflibercept. After each meeting, the DMC will advise the Executive Steering Committee and the Sponsor's representatives regarding the patients' safety, as well as the course of action regarding the conduct of the trial.

The DMC procedures will be detailed in the DMC charter and will have to be approved by the DMC members.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS PLANNED

A total of approximately 630 patients (315 per arm) is planned to be randomized in this study, from approximately 150 investigational sites, over a 24 months accrual period. Enrollment will be stopped when the anticipated or actual patient numbers have been achieved across all study sites. No patient may be randomized into the study more than once.

7.2 INCLUSION CRITERIA

1. Cytologically or histologically confirmed evidence of epithelial cancer (adenocarcinoma) of the exocrine pancreas.

2. Metastatic disease. Patients with measurable and with non-measurable disease, as per RECIST criteria (41) are eligible (Appendix C).

3. No prior chemotherapy for pancreatic disease. Prior **treatment** with 5-fluorouracil, **capecitabine or gemcitabine**, in which the **chemotherapy** was used as a radio-sensitizing agent, is allowed if the treatment-free interval is of at least 3 months **(time between last chemotherapy dose and randomization)**.

7.3 EXCLUSION CRITERIA

Related to the methodology

1. Chemotherapy or other systemic therapy for pancreatic cancer.

2. Less than 42 days elapsed from prior major surgery (28 days from other surgery) to the time of randomization. Less than 28 days elapsed from prior radiation therapy.

3. Prior treatment with anti-VEGF or VEGF-Receptor-inhibitors.

4. Age < 18 years.

5. ECOG performance status (PS) of 3-4 (Appendix B).

6. History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease.

7. History of another neoplasm. Adequately treated basal cell or squamous cell skin cancers, carcinoma in situ of the cervix, or any other cancer from which the patient has been disease free for > 5 years are allowed.

8. Participation in other clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization.

9. Any of the following events within the 3 months prior to randomization: treatment resistant peptic ulcer disease, erosive oesophagitis or gastritis, grade 3 or 4 gastrointestinal bleeding/hemorrhage, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event.

10. Any of the following events within the 6 months prior to randomization: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft surgery, NYHA class III or IV congestive heart failure (Appendix H), stroke or transient ischemic attack.

11. Occurrence of deep vein thrombosis within 4 weeks prior to randomization.

12. Known human immunodeficiency virus (HIV) infection requiring antiretroviral treatment or acquired immunodeficiency-syndrome (AIDS)-related illness.

13. Other severe acute or chronic medical condition, which could impair the ability of the patient to participate to the study or to interfere with interpretation of study results.

14. Absence of signed and dated Institutional Review Board (IRB)-/Independent Ethical Committee (IEC)-approved patient informed consent form prior to enrollment into the study.

15. Pregnant or breast-feeding woman. Positive serum or urine pregnancy test for women of reproductive potential prior to randomization.

16. Patient with reproductive potential (male, female) who do not agree to use accepted and effective method of contraception during the study treatment period and for at least **6** months after the completion of the study treatment. The definition of "effective method of contraception" will be based on the investigator's judgment.

Related to aflibercept

17. Urine Protein-Creatinine ratio (UPCR) > 1 on morning spot urinalysis (38) or proteinuria > 500 mg/24 hours.

18. Serum Creatinine > 1.5 x ULN. If creatinine 1.0 - 1.5 x ULN, creatinine clearance calculated according to Cockcroft-Gault formula (39) < 60 mL/min will exclude the patient (Appendix A).

19. Uncontrolled hypertension defined as blood pressure > 150/100 mmHg (≥ grade 2 according to NCI CTCAE v. 3.0), or systolic blood pressure >180 mmHg if diastolic blood pressure < 90 mmHg, on at least 2 repeated determination on separate days, within 3 months prior to study enrollment.

20. Patients on anticoagulants therapy with unstable dose of warfarin and/or having an out-of-therapeutic range INR (>3) within the 4 weeks prior to randomization.

21. Evidence of clinically significant bleeding diathesis, non-healing wound or underlying coagulopathy (e.g. INR >1.5 without vitamin K antagonist therapy…).

Related to gemcitabine

22. Inadequate bone marrow function:
    - Absolute neutrophil counts (ANC) < 1,500/mm3
    - Platelet count < 100,000/mm3
    - Hemoglobin < 9.0 g/dL

23. Inadequate liver function tests:
    - Total bilirubin > 1.5 ULN
    - Transaminases (SGOT/SGPT) > 2.5 x ULN (unless liver metastasis are present, 5 x ULN in that case).
    - Alkaline phosphatase > 3 x ULN (unless liver metastasis are present, 5 x ULN in that case).

8 TREATMENTS

8.1 DETAILS OF TREATMENTS

Study treatment details are summarized in Table 6 below.

Table 6 – Details of treatments

Drug code	**AVE0005 (VEGF Trap)**	**Placebo for aflibercept**	**-**
INN	**Aflibercept**	**Not applicable**	**Gemcitabine**
Trade name	**-**	**Not applicable**	**Gemzar®**
Formulation	aflibercept in 5 mM sodium phosphate, 5 mM sodium citrate, 100 mM sodium chloride, 20% (w/v) sucrose, and 0.1% (w/v) polysorbate 20, pH 6.0, supplied in sealed, sterile, single-use 5.0 mL vials containing 4.4 mL in order to withdraw 4.0 mL aflibercept at a concentration of 25 mg/mL.	Sterile aqueous buffered vehicle pH 6.0, containing 5 mM sodium phosphate, 5 mM sodium citrate, 100 mM sodium chloride, 0.1% (w/v) polysorbate 20 and 20% (w/v) sucrose, supplied in sealed, sterile, single-use 5-mL vials containing 4.4-mL in order to withdraw 4.0 mL of placebo.	Either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder (hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment), supplied in a sterile form for intravenous use only. Marketed formulation (refer to the local labeling)
Storage conditions	aflibercept must be refrigerated at 2–8°C (36-46°F) in a locked area with restricted access and handled in accordance with the manufacturer's instructions.	placebo must be refrigerated at 2–8°C (36-46°F) in a locked area with restricted access and handled in accordance with the manufacturer's instructions.	Refer to the local labeling.

8.2 INVESTIGATIONAL PRODUCT

8.2.1 Description of aflibercept

Aflibercept is formulated as a sterile liquid to a final concentration of 25 mg/mL. Aflibercept in 5 mM phosphate, 5 mM sodium citrate, 100 mM sodium chloride, 20% (w/v) sucrose, and 0.1% (w/v) polysorbate 20, pH 6.0, is supplied in sealed, sterile, single-use 5.0 mL vials containing 4.4 mL in order to withdraw 4.0 mL.

8.2.2 Description of placebo

Placebo for aflibercept is formulated in bulk aqueous buffered solution, pH 6.0, containing 5 mM phosphate, 5 mM sodium citrate, 100 mM sodium chloride, 0.1% (w/v) polysorbate 20, and 20% (w/v) sucrose, supplied in sealed, sterile, single-use 5-mL vials containing 4.4 mL placebo in order to withdraw 4.0 mL.

8.2.3 Preparation, reconstitution and administration for aflibercept

Aflibercept and placebo vials will be supplied by the Sponsor.

Aflibercept/placebo must be diluted in 0.9% NaCl (normal saline) or 5% dextrose prior to IV administration. The dilution must be carried out under aseptic conditions.

Diluted aflibercept/placebo solution at 0.6 to 8.0 mg/ml can be stored up to 24 hours under refrigerated conditions (2° to 8°C) or for up to 8 hours at ambient temperature (approximately 25°C) in polypropylene syringe or in infusion bags made of the following materials:

- PVC containing DEHP,
- Polyolefin (PVC free DEHP free).

Diluted solution of aflibercept can be administered using infusion tubing made of the following materials:

- PVC containing DEHP,
- DEHP-free PVC containing TOTM,
- Polypropylene,
- Polyethylene lined PVC.

The infusion sets must contain a 0.2 μm polyethersulfone filter.

The research pharmacist or designee at the study site will prepare all aflibercept/placebo infusion solutions according to the instructions contained in protocol supporting documents. Multiple vials may be required in the preparation of each dose depending on the patient's weight **and the aflibercept/placebo intended dose**.

The volume of aflibercept/placebo to be administered to each patient, and hence the rate of infusion, will be based on each patient's weight. The pharmacist or designee will prepare the dosing solution as follows:

- Calculate the number of aflibercept/placebo vials needed according to the patient's body weight, and the aflibercept intended dose,

Then either:

- Dilute the entire volume of each vial in the infusion bag of 0.9% NaCl or 5% dextrose, **to obtain the final concentration of the diluted solution ranging from 0.6 mg/ml to 8.0 mg/ml,**
- Retrieve the excess of the diluted solution in order to obtain the exact amount of aflibercept/**placebo** to be administered to the patient.

Or:

- **Withdraw the exact volume of aflibercept/placebo needed from each vial,**
- **And dilute directly into the infusion bag (0.9% NaCl or 5% dextrose) to obtain a final concentration of the diluted solution ranging from 0.6 mg/ml to 8.0 mg/ml.**

Infusion can be conducted by gravity or, with an IV infusion pump, or with a syringe pump using administration sets made of above listed materials.

The infusion should not exceed 2 hours at ambient temperature (approximately 25°C).

8.2.3.1 Precautions

All drug packages are to be inspected upon receipt at the study site and the individual vials inspected prior to being drawn up. If a vial is chipped or any particulate matter or cloudiness is detected, the vial is not to be used. Cloudy or damaged vials are to be reported to the sponsor and returned to the refrigerator until instructions have been given. As aflibercept is a protein, the study vials are not to be shaken.

Given the investigational nature of the product and to provide the patients with the maximum level of safety in case of an unexpected event, the following requirements must be fulfilled before any administration of the investigational product can start and for a minimum of 1 hour following the completion of the infusion:

- Immediate access to appropriate resuscitative equipment,
- Personnel appropriately qualified and trained to use the above equipment (see also Section 15.1 for delegation of investigator duties).

Aflibercept/placebo should not be administered less than 48 hours following minor surgical procedures (e.g., fine needle biopsy/aspiration, placement of a central venous access device, or removal/biopsy of a skin lesion), or until evidence of wound healing (e.g., scab formation) is observed, whichever is longer. A peripheral venous catheter may be inserted prior to and removed immediately after individual study drug doses, for the purpose of study drug administration.

Infusion and hypersensitivity reactions may occur during or shortly after intravenous administration of protein therapeutics. If infusion or hypersensitivity reactions occur in a given patient, institutional treatment guidelines for similar therapeutic agents or protocol guidelines should be followed (see Table 10). In case of severe reaction (grade ≥ 3), aflibercept/placebo should be permanently discontinued. **Blood samples for anti-aflibercept antibodies detection should be collected within 2 weeks for event of Grade ≥ 2 and then every 2-3 months, up to 6 months following aflibercept/placebo discontinuation. Simultaneously to each antibodies detection, circulating free and bound aflibercept will be measured** (see Appendix G for sample collection, handling methods and shipping procedures).

8.3 ASSOCIATED PRODUCTS: GEMCITABINE

Marketed formulation of gemcitabine will be used. Refer to the package insert or summary of product characteristics for details on description, preparation, administration, and precautions for use.

Gemcitabine is a deoxycytidine analogue, a pyrimidine antimetabolite related to cytarabine, which is formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder (hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment), supplied in a sterile form for intravenous use only.

8.4 DOSAGE SCHEDULE

Within 3 days after randomization, patients will be administered either aflibercept or placebo, depending on arm assigned. Immediately after, patients will receive gemcitabine.

8.4.1 Aflibercept / placebo

Arm A, aflibercept: 4 mg/kg will be administered IV over 1 hour once every 2 weeks, i.e. on Day 1 and 15 of each 28-day cycle, prepared and administered as described in Section 8.2.3.

OR

Arm B, placebo: 4 mg/kg will be administered IV over 1 hour once every 2 weeks, i.e. on Day 1 and 15 of each 28-day cycle, prepared and administered as described in Section 8.2.3.

Dose adjustment will be permitted for subsequent treatment cycles based on individual patient tolerance.

8.4.2 Gemcitabine

Gemcitabine 1000 mg/m^2 IV will be administered IV over 30 minutes on Day 1, 8, 15, 22, of 28-day cycle 1, and then Day 1, 8, 15 of subsequent 28-day cycles.

Dosage for gemcitabine is described below using the Body surface area (BSA).

BSA will be calculated from body weight in kg, recorded **prior to every gemcitabine dosing**, and height in cm, recorded at baseline. The preferred Dubois and Dubois equation is below:

BSA in units of m^2 = wgt. in kg $^{0.425}$ x hgt. in cm $^{0.725}$ x 0.007184

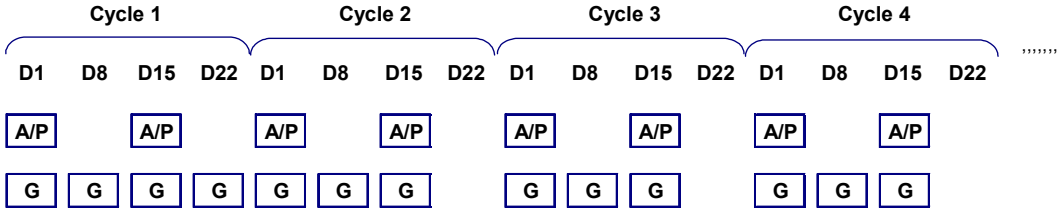
Patients with a BSA >2.1 m^2 will use 2.1 m^2 for the determination of gemcitabine dose.

Dose adjustment will be permitted for subsequent treatment cycles based on individual patient tolerance.

As a summary, patients will receive study treatment as follows (see Figure 5):

- on Day 1: aflibercept/placebo followed by gemcitabine,
- on Day 8: gemcitabine,
- on Day 15: aflibercept/placebo followed by gemcitabine,
- on Day 22 of cycle 1 only: gemcitabine.
- Treatments will be repeated in the same manner at 4-week intervals (or 28-day cycles).

Figure 5 – Study treatment administration



D: day; A/P: aflibercept/placebo; G: gemcitabine

8.4.3 Premedication

The use of any premedication is left to the current hospital practices. For gemcitabine, refer to the package insert or summary of product characteristics for details on administration and precautions.

8.4.4 Schedule modification

For both arms, it is a 4 weekly schedule. Plus or minus 3-day time windows are permitted, as are cycle delays of up to 2 weeks in case of unresolved toxicity at the time of planned re-administration. In addition, infusion of aflibercept/placebo or gemcitabine may be omitted within a treatment cycle, in case of unresolved toxicity at the time of planned re-administration, for a maximum of 2 consecutive aflibercept/placebo or 4 consecutive gemcitabine infusions. As a consequences 2 infusion of aflibercept/placebo may be given at a 6-week interval. Doses may be modified or infusion delayed for toxicity as described in Section 8.5. New cycles of therapy may not begin until any study drug-related toxicities have been adequately resolved. Study treatment will continue until a definitive treatment discontinuation criterion is met (see section 11.1).

Details of the exact dose, and time of administration of medication (day/month/year, and h:min for patients participating to the pharmacokinetics evaluation) and the labeling on the investigational product containers (including batch and/or lot numbers) will be documented in the CRF. In addition, complete Drug Accountability Records must be maintained at each site.

8.5 DOSAGE MODIFICATION:

Dose adjustment and/or cycle delay are planned in case of toxicity. Dose adjustments will be made according the worst grade of toxicity observed within a cycle. Toxicities will be graded according the NCI-CTC AE version 3.0 scale (40). Patient will receive the next cycle after recovery of the toxicity as describe below. Patient may have dose omitted (aflibercept/placebo or gemcitabine) within a cycle if toxicity occurred and does not recover the theoretical day of infusion.

The toxicities observed with gemcitabine are myelotoxicity (neutropenia, anemia and thrombocytopenia), nausea, vomiting, reversible ALT/AST increase, hypersensitivity (rash, pruritis, bronchospasm), cutaneous reactions in previously irradiated area.

If a patient experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended (dose reduction/omission appropriate to the most severe toxicity) should be followed. Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

No more than 1 dose reduction as well as no more than 2 infusions omitted of aflibercept/placebo per patient are permitted. Aflibercept/placebo will be discontinued in patients requiring > 1 dose reduction of aflibercept or > 2 dose omission due to aflibercept toxicity.

If gemcitabine is permanently discontinued, then aflibercept / placebo can be continued until disease progression or unacceptable toxicity or patient's refusal of further treatment. The end of study treatment will be the date of the last aflibercept or placebo administration.

If aflibercept / placebo is permanently discontinued, then gemcitabine can be continued until disease progression or unacceptable toxicity or patient's refusal of further treatment. The end of study treatment will be the date of the last gemcitabine administration.

In both cases the end of the study is death, cut off date for final analysis, or patient denied consent, whichever comes first.

8.5.1 Aflibercept / Placebo

Aflibercept / placebo doses will be modified according to the dose level described in Table 7 below.

Table 7 – Aflibercept dose reduction level

	Initial dose (mg/kg)		Dose reduction 1 (mg/kg)
aflibercept / placebo	4	→	2

Actions to be taken for aflibercept / placebo according the type of toxicity are described in Table 8, Table 10 and Table 9 below.

Table 8 – Dose modifications for aflibercept/placebo and impact on study treatment

Toxicity	Grade	Action to be taken
Hypertension	**Grade ≤ 2**	Initiate antihypertensive drug therapy (see recommendation below) and close monitoring of BP for further adjustment, as needed. No aflibercept/placebo dose modification and no treatment delay.
	Grade 3 (requiring more than one drug or more intensive therapy than previously)	Modify antihypertensive drug therapy (see recommendation below). *1st episode of grade 3 HBP unresponsive to antihypertensive drug therapy:* • On Day 8 (any cycle) or 22 (cycle 1): o Administer gemcitabine as planned • On Day 15 or 28: o Omit aflibercept/placebo and administer gemcitabine alone o At next aflibercept/placebo theoretical infusion (+2 weeks) - BP controlled: administer aflibercept/placebo at the same dose - BP uncontrolled: omit aflibercept/placebo and administer gemcitabine alone and at the next aflibercept/placebo theoretical infusion (+2 weeks): ▪ BP controlled: reduce aflibercept/placebo by one dose level* ▪ BP uncontrolled: permanently discontinue aflibercept/placebo and administer gemcitabine alone *2nd episode of grade 3 HBP unresponsive to antihypertensive drug therapy:* • On Day 8: o Administer gemcitabine as planned • On Day 15 or 28: o Omit aflibercept/placebo and administer gemcitabine alone o At next aflibercept/placebo theoritical infusion (+2 weeks) - BP controlled: reduce aflibercept/placebo by one dose level* - BP uncontrolled: permanently discontinue aflibercept/placebo and administer gemcitabine alone *3rd episode of grade 3 HBP unresponsive to antihypertensive drug therapy:* • On Day 8: o Administer gemcitabine as planned • On Day 15 or 28: o Permanently discontinue aflibercept/placebo and administer gemcitabine alone
	Grade 4	Permanently discontinue aflibercept/placebo, administer gemcitabine alone and seek cardiologist opinion.

Toxicity	Grade	Action to be taken
Arterial thrombo-embolic events (e.g. : MI or stroke..) (Documented by appropriate tests)	**Grade 3-4**	Permanently discontinue aflibercept/placebo
Hemorrhage	**Grade 3[a]-4**	Permanently discontinue aflibercept/placebo
Gastrointestinal perforation or Fistula formation	**Any grade**	Withdrawn from study treatment
Reversible Posterior Leuko-encephalopathy syndrome (Documented by appropriate tests)	**Any grade**	Withdrawn from study treatment
Venous Thromboembolic Event (Documented by appropriate tests)	**Grade 3 (DVT)**	*1st episode:* • Treat DVT with heparins • **and** Administer gemcitabine and aflibercept/placebo as planned** *2nd episode despite appropriate anticoagulation* • Permanently discontinue aflibercept/placebo
	Grade 4 (PE)	Withdrawn from study treatment ***

BP blood pressure; DVT deep vein thrombosis; PE pulmonary embolism
* Dose reduction levels provided in Table 7
** Based on investigator's judgement in assessing potential risk of extension and/or embolization.
*** Continuation of aflibercept/placebo may be considered, depending on individual benefit/risk assessment in case of incidental discovery of asymptomatic pulmonary embolism in a patient with a US evidence of DVT.
[a] In case of grade 3 hemorrhage, continuation of aflibercept/placebo may be considered depending on individual Benefit/risk assessment

Hypertension therapy recommendations

For patients without prior antihypertensive therapy, at the time of the hypertensive episode the initiation of calcium-channel blockers should be considered as a first-intent treatment. A close monitoring of the BP should be initiated for further adjustment in treatment, as needed. Ultimately, antihypertensive treatment must be individualized based on the presence of comorbidity factors such as diabetes, cardiovascular or renal disease, additionally taking into account the safety and the efficacy of any prior antihypertensive therapy received. In addition, oral and/or intravenous sodium intake should be carefully monitored in these patients.

For patients already under anti-hypertensive therapy, efforts should be done to optimize the existing therapy before adding other agents as required to control the BP.

When hypertension is accompanied by signs or symptoms of end organ damage such as hypertensive retinopathy, kidney function abnormalities (like progressive proteinuria), or any signs or symptoms of cardiovascular morbidity or central nervous system (CNS) morbidity, treatment with aflibercept/placebo should be interrupted.

Proteinuria:

Prior to administration of aflibercept/placebo, an UPCR and dipstick urinalysis should be performed.

Urinary protein creatinine ratio (UPCR) corresponds to the ratio of urinary protein and urinary creatinine concentrations (expressed in mg/dL). There is a high correlation between morning UPCR and 24-hour proteinuria in patients with normal or reduced renal function. UPCR demonstrated very good to excellent performance for the diagnosis of both abnormal and nephrotic proteinuria at all renal function levels. This ratio provides an accurate quantification of 24-hours urinary protein excretion [38].

UPCR to detect proteinuria, will be done on morning urine spot. If UPCR > 1, 24-hour urine collection to grade proteinuria will be performed. In addition, **in case UPCR>2 or** in case of proteinuria of renal origin (according to urine protein electrophoresis) is associated with hematuria (microscopic or macroscopic), then a **blood** work-up **in search for hemolytic anemia of microangiopathic origin should be initiated and a nephrologist consultation should be considered.** as detailed in Table 9.

This work up could include LDH, haptoglobin, schistocytes and orosomucoid **whenever possible. Delay in availabilty of part of the results should not delay consultation to the nephrologist.**

Proteinuria should always be assessed taking into account the presence or absence of hematuria and the blood pressure status of the patient.

Table 9 summarizes the course of action with regard to aflibercept/placebo dosing, which will depends on the presence of hematuria and the level of 24h proteinuria results. Only one dose level reduction is permitted for aflibercept/placebo.

Anti-aflibercept antibody detection as well as concomitant pharmacokinetics evaluation and subsequent FU should also be performed in patients reporting proteinuria >3.5 g/24h, or protenuria from renal origin associated with hematuria (Section 12.1.3.3)

Table 9 – Management of proteinuria

UPCR performed on day 1 and 15 of each cycle	aflibercept/placebo + gemcitabine (A/P) Day 1 infusion N	24h urine collection	Week 1 (gemcitabine)	Week 2 (aflibercept/placebo + gemcitabine)	Week 3 (gemcitabine)	Week 4 (aflibercept/placebo + gemcitabine)	Week 5 (gemcitabine)	Week 6 (aflibercept/placebo + gemcitabine)
UPCR [0-1]	No delay and no dose reduction are required for A/P and/or gemcitabine.	No 24 hour urine collection is required	-					
UPCR]1-2] without hematuria	No delay and no dose reduction are required for A/P and/or gemcitabine. **Perform** 24h urine collection to grade proteinuria. 24h urine collection or UPCR will be repeated as necessary	**≤3.5g/24h Grade 1-2**	Omit gemcitabine if applicable	If Prot U ≤ 2 g/24h dose both gemcitabine and A/P at the same dose				
				If Prot U > 2 g/24h omit gemcitabine and A/P	Omit gemcitabine	If Prot U ≤ 2 g/24h reduce both gemcitabine and A/P by one DL		
						If Prot U > 2 g/24h omit gemcitabine and A/P.	Omit gemcitabine	If Prot U > 2 g/24h withdrawn from study trt If Prot U ≤ 2 g/24h reduce both gemcitabine and A/P by one DL
		>3.5g/24h Grade 3[a]	Omit gemcitabine if applicable	If Prot U ≤ 2 g/24h reduce both gemcitabine and A/P by one DL				
				If Prot U >2g – ≤ 3.5	Omit gemcitabine	If Prot U ≤ 2 g/24h reduce both gemcitabine and A/P by one dose level		

UPCR performed on day 1 and 15 of each cycle	aflibercept/placebo + gemcitabine (A/P) Day 1 infusion N	24h urine collection	Week 1 (gemcitabine)	Week 2 (aflibercept/placebo + gemcitabine)	Week 3 (gemcitabine)	Week 4 (aflibercept/placebo + gemcitabine)	Week 5 (gemcitabine)	Week 6 (aflibercept/placebo + gemcitabine)
				g/24h omit gemcitabine and A/P,		If Prot U > 2 g/24h omit gemcitabine and A/P	Omit gemcitabine	If Prot U ≤ 2 g/24h reduce both gemcitabine and A/P by one DL If Prot U > 2 g/24h withdrawn from study trt
				If Prot U >3.5 g/24h: Nephorologist consultation Withdrawn from study treatment				
If **UPCR > 2** or If **UPCR]1-2]** With Hematuria **Perform** Biological work-up** **Perform** 24h urine collection to grade proteinuria. 24h urine collection or UPCR will be repeated as necessary **Nephrologist** consultation		**If TMA is diagnosed** **Or nephrotic syndrome**		Withdrawn from study trt				
		If **TMA is ruled out**		Omit both A/P and gemcitabine for a maximum of 4 weeks and dose modification according to 24h urine protein value				

DL dose level; D day, Trt treatment
[a] Collect blood samples for detection of anti aflibercept antibody and for PK measurement
* Dose reduction levels provided in Table 7 and Table 11
** Perform: urinary protein electrophoresis & 24H urine collection to assess proteinuria rate & collect blood samples for haptoglobin + orosomucoid + schistocytes + LDH + detection of anti aflibercept antibodies/pharmacokinetics evaluation

Hypersensitivity reaction

In case of hypersensitivity reaction, institutional treatment guidelines for this type of adverse event, or the following proposed guideline in Table 10 can be applied. Venous blood samples for anti- aflibercept antibody detection and for concomitant pharmacokinetics evaluation should be collected in any patient developing grade ≥ 2 systemic immunologic adverse event considered at least possibly related to study drug.

Table 10 – Acute infusion reaction management

Symptom Severity	Intervention Recommendation
Mild-Moderate e.g., NCI CTCAE grade ≤ 2 cutaneous reaction, pruritus, flushing, rash, dyspnea, tachycardia, anxiety, headache, myalgias, edema, nausea	Stop aflibercept/placebo infusion; Give diphenhydramine 50 mg IV and/or IV dexamethasone 10 mg; For grade 2 event: Collect blood sample for detection of anti-aflibercept antibody and for pharmacokinetics evaluation within a maximum of 2 weeks, and then every 2-3 months for follow up, **up to 6 months from last aflibercept/placebo dose.** Resume aflibercept/placebo infusion after subject recovery.
Severe e.g., symptomatic bronchospasm, generalized urticaria, systolic BP ≤ 80 mm Hg, angioedema, anaphylaxis	Stop aflibercept/placebo infusion; Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg and/or epinephrine as needed; Collect blood sample for detection of anti-aflibercept antibodies and for pharmacokinetics evaluation within 2 weeks, and then every 2-3 months for follow up, **up to 6 months from last aflibercept/placebo dose**. Discontinue aflibercept/placebo

Reversible posterior leuko-encephalopathy (RPLS) or clinical symptoms related to vasogenic edema of the white matter:

Clinical presentations are variable and may include headache, altered mental status, seizure and cortical visual deficit. Hypertension is a risk factor. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypodensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure, or other CNS findings. RPLS is potentially reversible with early recognition of symptoms and timely correction of the underlying causes, including control of blood pressure and interruption of the offending drug, which are important in order to prevent progression to irreversible tissue damage.

Gastro-intestinal Perforation

In case a patient reported abdominal pain or increase in severity of pre-existing abdominal pain, with or without associated symptoms (such as nausea, vomiting, constipation), he/she should be evaluated by a physician for possible gastro-intestinal perforation, as this has been reported with anti-VEGF agents.

8.5.2 Gemcitabine

The dose of gemcitabine will be modified in case of severe toxicity according to the dose level described in Table 11.

Table 11 – Gemcitabine dose reduction schedule (mg/m^2)

	Initial dose		Dose Reduction 1		Dose Reduction 2
Gemcitabine	1000	→	800	→	650

Dose modifications within cycle (dose omission or reduction) and across cycles (dose delay or reduction) are summarized in Table 9 for management of proteinuria and Table 12.

Table 12 – Dose modifications for gemcitabine

Toxicity	Grade 2	Grade 3	Grade 4
Neutropenia if concomitant with infection or T ≥ 38.5°C, or T ≥ 38.1°C x 3 during a 24-hour period.	- On D28, delay** D1 of next cycle until ANC ≥ 1.5 x 10^9/L. - On D8, D15 or D22, no dose reduction, no infusion delay required.	On Day 28, delay** next cycle until ANC ≥ 1.5 x 10^9/L On D8, D15 or D22, omit gemcitabine infusion. Administer next cycle or infusion at reduced dose: - 1st episode: Reduce gemcitabine at next cycle/Infusion by 1 dose level*. - 2nd episode: Reduce gemcitabine at next cycle/Infusion by a second dose level*. - 3rd episode [a]: Discontinue gemcitabine.	
Thrombocytopenia	- On D28, delay** D1 of next cycle until plts ≥ 75 x 10^9/L. - On D8, D15 or D22, no dose reduction, no infusion delay required.	On Day 28, delay** next cycle until platelets ≥ 75 x 10^9/L. On D8, D15 or D22, omit gemcitabine infusion. Administer next cycle or infusion at reduced dose: - 1st episode: Reduce gemcitabine at next cycle/Infusion by 1 dose level*. - 2nd episode: Reduce gemcitabine at next cycle/Infusion by a second dose level*. - 3rd episode [a]: Discontinue gemcitabine.	
Diarrhea **Stomatitis**	- On D28, delay** D1 of next cycle until recovery (grade ≤1). - On D8, D15 or D22, no dose reduction, no infusion delay required.	On day 28, delay** next cycle until recovery (grade ≤1). On D8, D15 or D22, omit gemcitabine infusion. Administer next cycle or infusion at reduced dose: - 1st episode: Reduce gemcitabine at next cycle/Infusion by 1 dose level*. - 2nd episode: Reduce gemcitabine at next cycle/Infusion by a second dose level*. - 3rd episode: Discontinue gemcitabine.	
Cutaneous Reactions	No dose reduction, no infusion delay required.	On day 28, delay** next cycle until recovery (grade ≤1). On D8, D15 or D22, omit	Withdraw from study treatment.

Toxicity	Grade 2	Grade 3	Grade 4
		gemcitabine infusion. Administer next cycle or infusion at reduced dose: - 1st episode: Reduce gemcitabine at next cycle/Infusion by 1 dose level*. - 2nd episode: Discontinue gemcitabine.	
Bilirubin	On day 28, delay** next cycle until recovery to bilirubin ≤ 1.0 x ULN. No dose reduction. On D8, D15 or D22, omit gemcitabine infusion.		
Transaminases	Reduce gemcitabine by 1 dose level*.	Discontinue gemcitabine.	
Alkaline Phosphatase Elevation	No dose reduction, no infusion delay required.	Reduce gemcitabine by 1 dose level*.	Withdraw from study treatment.
Hypersensitivity	No dose reduction. Management of hypersensitivity according to local practice. Withdraw from study treatment in case of 2nd grade 3 episode.		Withdraw from study treatment.

[a] **In case of 3rd episode, continuation or omission of gemcitabine infusion (s) may be considered depending on individual Benefit/risk assessment.**
* Dose reduction levels provided in Table 11.
** Delay cycle by maximum of 2 weeks between cycles, until recovery to grade ≤ 1 otherwise gemcitabine will be permanently discontinued. Apply dose reduction according to worst grade observed.

8.5.3 Other toxic effects

Any other dose modifications in study treatment that are not described above may be performed at the discretion of the investigator, provided that criteria for patient withdrawal from study treatment described in Section 11.1 have not been met. Treatment cycle should be delayed (for a maximum of two weeks from the planned date of reinfusion) or dosing should be omitted (for a maximum of 2 consecutive aflibercept/placebo or 4 consecutive gemcitabine infusions) or until resolution to ≤ grade 1, then reinstituted, if medically appropriate. A dose reduction of subsequent doses would be considered. These patients will be withdrawn from study treatment if >2 dose reductions for gemcitabine are needed.

8.6 DESCRIPTION OF BLINDING METHODS

Aflibercept and placebo will be supplied in indistinguishable sealed vials.

See also Section 8.10 - Access to the randomization code during the study and Section 9.4 - Measures to protect the blinding of the trial.

8.7 METHOD OF ASSIGNING PATIENTS TO TREATMENT ARM

For detailed information, refer to the IVRS user manual.

8.7.1 Randomization

After each patient has completed the necessary baseline visit procedures, the corresponding baseline CRFs have been completed and the patient is deemed eligible for study entry by the investigator or designee, the study site will contact the IVRS.

Treatment assignment will be done centrally via an Interactive Voice Response System (IVRS) using a permuted-block randomization stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1 vs 2), curative surgery (pancreatectomy, yes vs no) and geographical region. All eligible patients will be randomly assigned to either the control arm or the experimental arm in a 1:1 ratio.

The site will need to enter the following information regarding the clinical site and study patient:

- Personal site identification number
- Patient's gender and date of birth
- ECOG performance status
- Prior curative surgery
- Weight

The information above will be used to identify the study treatment arm assigned for the patient according to predefined randomization scheme.

A confirmation fax or e-mail will be sent to the site detailing the patient's initial kit number(s) assignment. A copy of the confirmation fax or e-mail should be retained in the patient's records.

Study treatment should begin within 3 days after randomization.

The investigational product will be administered only to patients included in this study following the procedures set out in this clinical trial protocol. Patients withdrawn from the study retain their patient number, and new patients must always be allotted a new patient number.

8.7.2 Treatment period (treatment re-allocation)

Before each dosing of investigational product during the treatment period, the IVRS will need to be accessed again in order to receive another kit number(s) (1 or 2 depending on patient's weight) containing the same investigational product as the one assigned at the time of randomization, as described in Section 8.7.1.

The site will need to enter the following information regarding the clinical site and study patient:

- Personal site identification number
- Patient's identification number (received at randomization)
- Patient's gender and date of birth
- Weight and aflibercept/placebo intended dose in mg/kg

8.8 PACKAGING AND LABELING

Please also refer to Section 8.1.

8.8.1 Aflibercept or Placebo

Aflibercept or placebo vials will be supplied in identical boxes corresponding to patient kits. Each kit will be labelled with a unique kit number.

- Aflibercept or placebo, as described in Section 8.1, will be packaged by the Sponsor or an approved contractor, in sealed, sterile, single-use vials. The vials containing either aflibercept or placebo will be labeled in accordance with the local regulatory specifications.

Packaging reference (packaging number, batch number, or lot number) and quantity of vials dispensed to each patient must be recorded in the CRF/drug accountability form.

8.8.2 Gemcitabine

Commercially available gemcitabine vials will be used.

Batch reference (packaging number, batch number, or lot number) and quantity of gemcitabine dispensed to each patient must be recorded in the CRF/drug accountability form.

8.9 STORAGE CONDITIONS

- Aflibercept or placebo must be refrigerated at 2 - 8°C (36 - 46°F) in a locked area with restricted access and handled in accordance with the manufacturer's instructions.
- Gemcitabine: refer to the package insert (PI) or summary product characteristics (SmPC).

8.10 ACCESS TO THE RANDOMIZATION CODE DURING THE STUDY

Please also refer to Section 9.4.

In case of an AE, the code can be broken only in exceptional circumstances when knowledge of the investigational product is essential for treating the patient. If possible, a contact should be initiated with the Monitoring Team before breaking the code.

The IVRS center should be called if code breaking is necessary. Only if this fails, code-breaking material can be opened.

For each patient, code-breaking material is supplied, containing the name of the treatment. Each treatment box will be labeled with a 3-panel label. The third panel, which is masked by a scratch off laminate, contains emergency and treatment (aflibercept or placebo) information. It will be kept in a safe place on site throughout the Clinical Trial. The Sponsor will retrieve all code-breaking material (opened or sealed) on completion of the Clinical Trial.

If the blind is broken, the Investigator will document the date, time of day and reason for code breaking **and** the patient will permanently discontinue the investigational product (see Section 11.1).

8.11 RESPONSIBILITIES

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense aflibercept/placebo will be responsible for ensuring that aflibercept/placebo used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All aflibercept/placebo shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of aflibercept/placebo issued and returned is maintained.

Any quality issue noticed with the receipt or use of aflibercept/placebo (deficient IP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply aflibercept/placebo to a third party, allow the aflibercept/placebo to be used other than as directed by this Clinical Trial Protocol, or dispose of aflibercept/placebo in any other manner.

8.12 RETRIEVAL AND/OR DESTRUCTION OF TREATMENTS

All used treatments vials (aflibercept/placebo, gemcitabine) will be destroyed by the study site after an accurate accountability has been performed and signed by the investigator.

The Sponsor will retrieve all partially used or unused vials of aflibercept/placebo treatments. A detailed treatment log of the returned aflibercept/placebo will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy the partially used or unused vials of aflibercept/placebo unless the Sponsor provides written authorization.

A potential defect in the quality of aflibercept/placebo may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall aflibercept/placebo and eliminate potential hazards.

8.13 CONCOMITANT TREATMENT

All treatments being taken by the patient on entry to the study or at any time during the study in addition to the study treatments are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF (as defined in the flow chart, Section 1.1).

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the investigational product, they may be given at the discretion of the investigator and recorded in the CRF.

The following concomitant treatments <u>are not permitted</u> during this study:

- Systemic anticancer agents other than aflibercept /placebo and other than gemcitabine.
- Concurrent treatment with other investigational drugs or devices.
- Concomitant radiation therapy, immunotherapy, targeted therapy or biological therapies.

The following concomitant treatments <u>should be administered with caution</u>:

- Vitamine K antagonist therapy.

The following concomitant treatments <u>are permitted</u> during this study:

- Ancillary treatment must be given as medically indicated; they must be specified in the CRF.
- Therapeutic or secondary prophylactic use of hematopoietic growth factors may be given at the investigator's discretion and should follow American Society of Clinical Oncology guidelines for their use (42).
- Appropriate prophylactic anti-emetic therapy will be left to the current hospital practices. The addition of a benzodiazepine, e.g., lorazepam IV or orally, may also be considered if clinically indicated.
- Medications for chronic pain management, including narcotic analgesics, are permitted as clinically indicated.
- Medications for managing diarrhea, including loperamide.
- Antihypertensive medications are permitted as described in Section 8.5.1.
- Heparin medications are permitted as clinically indicated.
- All supportive measures (including blood transfusions and erythropoietin) consistent with optimal patient care will be given throughout the study and should be documented in the CRF.

8.14 POST-STUDY TREATMENT

Patients will continue to be treated as long as they are benefiting from study treatment and have not met study withdrawal criteria as defined in Section 11.1. After withdrawal from study treatment, further treatment, if any, is at the discretion of the investigator. Please note that in the absence of documented progressive disease, patients should be followed every 8 weeks until progression or study cutoff date, whichever comes first. Then, all patients will be followed for survival and vital status information will be collected at 8 weeks intervals until death or the study cutoff date, whichever comes first.

8.15 TREATMENT ACCOUNTABILITY AND COMPLIANCE

- The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the aflibercept/placebo. Aflibercept/placebo must be kept in a locked area with restricted access. Aflibercept/placebo must be stored and handled in accordance with the manufacturer's instructions.
- Administration of the study drugs will be supervised by the investigator or subinvestigator.
- The person responsible for drug dispensing is required to maintain adequate records of all study drugs. The labels of the aflibercept/placebo vials administered or dispensed to patients must be completed (patient number, and date of infusion, respectively). The packaging reference of aflibercept/placebo and the lot number of gemcitabine must be recorded in the CRF/drug accountability form, as well as the total number of vials per cycle.
- The person responsible for drug administration to the patient will record precisely the date when the drug is administered to the patient. Interruption of the 1-hour aflibercept/placebo infusion or 30 minutes infusion of gemcitabine will be recorded in the CRF.

The study monitor will periodically check the supplies of aflibercept/placebo held by the investigator or pharmacist to verify accountability. All unused or partially used aflibercept/placebo and all medication containers will be returned to the sponsor unless other arrangements have been approved by the sponsor (see Section 8.12). The sponsor will verify that a final report of drug accountability to the unit dose level is prepared and maintained in the investigator study file.

9 ASSESSMENT OF INVESTIGATIONAL PRODUCT

9.1 EFFICACY

9.1.1 Primary criteria

The primary efficacy endpoint is overall survival (OS) defined as the time interval from the date of randomization to the date of death due to any cause. In absence of confirmation of death, survival time will be censored at the earlier of the last date the patient is known to be alive and the study cutoff date.

9.1.2 Secondary criteria

The secondary and exploratory efficacy parameters will be assessed as follows:

9.1.2.1 Progression Free Survival

- Progression free survival (PFS) will be evaluated from the date of randomization to the date of tumor progression or death (from any cause).

9.1.2.2 Overall Response Rate

- Tumor response will be assessed by investigators according to RECIST criteria (Appendix C).
- At baseline, a CT or MRI scan of the abdomen, or other relevant organ system with target lesion(s) is required. Chest X-ray will be performed and chest CT scan/MRI in case target lesion in the lung(s)/thorax is/are identified.
- Imaging on study will be then performed every 8 weeks, using the same technologies, up to documentation of disease progression and whenever disease progression is suspected.
- These tests will be repeated to confirm a partial or complete response (at least 4 weeks after initial documentation of response) and at the end of study treatment. The investigator at the site will be responsible for the assessment and collection of the radiographic information in compliance with the schedule of evaluations presented in this protocol.
- Disease progression will be determined by at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter since the treatment started, or unequivocal increase in the size of non-target lesions or the appearance of one or more new lesions.
- Hepatomegaly alone is not sufficient to assess progression. In the presence of evidence suggestive of progression, such as rising tumor marker, increasing liver enzymes, declining performance status, weight loss or increasing pain, every reasonable effort should be made to document the nature of progressive disease by appropriate imaging studies. The investigator may remove a patient from the study either for clinical progression when it is not possible to obtain an imaging study or for any other reason it is determined that it is in the best interest of

the patient to do so; however, the rationale for this decision must be recorded in the patient's medical chart and in the patient's CRF.

- Clear evidence of progression must be documented in the patient's medical record and this data will be recorded on the patient's CRF.
- Tumor evaluations will not be performed after progression is documented.
- During the follow-up period, patients who went off study treatment prior to documented disease progression will be evaluated by CT scan/MRI for tumor progression every 8 weeks from End of Study Treatment until disease progression or study cutoff date whichever comes first.
- The overall response rate will be defined as the proportion of patients with confirmed RECIST-defined complete response (CR) or partial response (PR) relative to the total number of patients in the analysis population considered.

9.1.2.3 Clinical benefit

- Clinical Benefit will be based on the measurement of tumor related symptoms including a composite score of pain severity assessed by VAS, analgesic consumption as morphine equivalents, ECOG PS and weight change from baseline. The VAS is a line of fixed length of 100 mm with words that anchor the scale at the extreme ends (no pain – worst possible pain) and no words describing intermediate positions. Patients will be instructed to place a mark on the line corresponding to their perceived state (average pain during the past 24-hour). Only validated translation in each local language for all participating countries is planned, but no conceptual framework is identified since this kind of scale was already used in the gemcitabine pivotal study. Clinical benefit will be assessed by time to symptom worsening (TTSW) evaluated from randomization to worsening of at least one symptom, as well as, improvement in any tumor related symptoms.

9.2 SAFETY

AE data will be collected at specified intervals throughout the study.The results of weight, performance status and vital signs will be recorded in the CRF. Laboratory safety work-up will be carried out according to standard operating procedures by the local laboratory. Abnormal, clinically significant results will be verified to rule out laboratory error. Persistent relevant abnormal values must be followed up until the cause is determined or until they return to the baseline value.

The study-specific and general safety criteria are developed in Section 10.

9.3 PHARMACOKINETICS AND IMMUNOGENICITY

Prospectively scheduled immunogenicity evaluations are intended to be performed **in all randomized and treated patients, at baseline, during treatment with aflibercept/placebo and after discontinuation of aflibercept/placebo. Pharmacokinetic sampling will be performed at**

the same time points with an additional sample at peak (end of aflibercept/placebo infusion 1, cycle 1).

For the purpose of of exploratory analyses, endogenous VEGF will be measured at baseline in all patients who are randomized at study sites equipped with a 4°C centrifuge (needed for preparation of the samples).

9.3.1 PK handling procedure

- Vacutainer tubes will be used to collect 4 mL of whole blood from patients for plasma preparation for the determination of circulating free aflibercept and VEGF: aflibercept complex levels for pharmacokinetic analysis at the sampling times described in Section 9.3.3. Refer to Appendix G for detailed pharmacokinetic blood sample collection, handling, and shipping procedures.

- Red-top vacutainer tubes will be used to collect 4 mL of whole blood from patients for serum preparation for the analysis of anti-aflibercept antibody levels. Detailed anti-aflibercept antibody blood sample collection, handling, and shipping procedures are provided in Appendix G.

- CPD (or ACD) tubes will be used to collect blood sample for the analysis of free endogenous VEGF levels. A total of one sample per patient (4 mL) of whole blood will be collected for this evaluation. All specimens must be stored frozen at -20°C until shipped to sanofi-aventis. Refer to Appendix G for detailed pharmacokinetic blood sample collection, handling, and shipping procedures

Blood samples should not be taken at the infusion site.

The analysis of free and bound aflibercept and anti-aflibercept antibody levels will be performed by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY).

The plasma free endogenous VEGF concentrations will be determined at sanofi-aventis, GMPK Alfortville under the responsibility of [redacted]

9.3.2 Sampling time for immunogenicity and pharmacokinetic evaluations

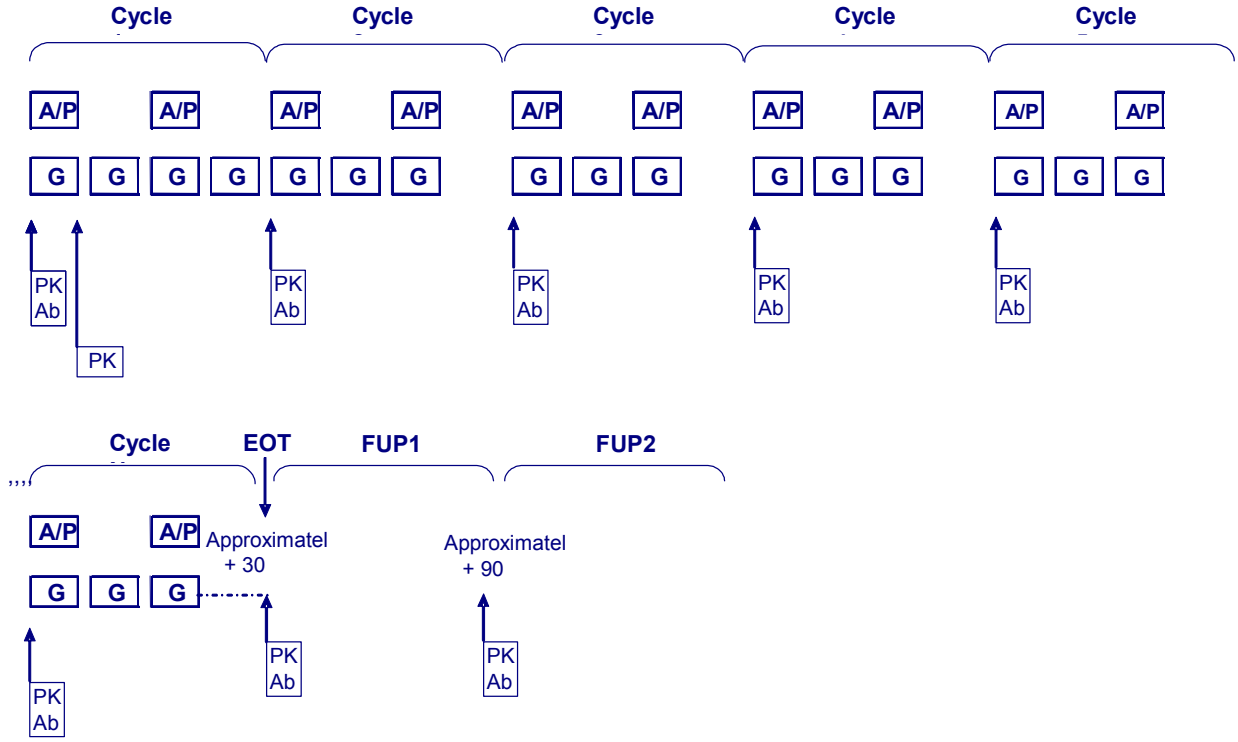
Blood samples for sytematic prospective detection of anti-aflibercept antibody levels will be collected as described in Figure 6 at baseline, i.e. **prior to** the start of the first aflibercept/placebo infusion (cycle 1, day 1), **then prior to each cycle (i.e. pre-dose of aflibercept/placebo infusion 3 -cycle2, infusion 5-cycle 3, infusion 7-cycle 4, infusion 9-cycle 5, etc…)**, then **approximately** 30 days and 90 days after last aflibercept/placebo administration. A **minimum** of 3 samples/patient corresponding to 12 mL of whole blood will be collected **in all randomized and treated patients (baseline, 30-day and 90-day follow-up visit).**

Pharmacokinetic sampling will be performed at the same time points. **In addition patients will be sampled at the end of infusion of aflibercept/placebo for cycle 1 for peak measurement of free and bound aflibercept.** A **minimum** of **4** samples/patient and **16** mL of whole blood will be collected for these evaluations (**baseline**, **end of aflibercept/placebo infusion 1, 30-day and 90-day follow-up visit).**

Sampling for anti-aflibercept detection will also be performed on an event driven basis (see Section 12.1.3.3). **The first evaluation (sampling for anti-aflibercept antibodies and circulating free and bound aflibercept) will be done within 2 weeks following the occurrence of the event (when this time point is not covered with the prospective evaluation). Follow-up will prolonged up to 6 months following discontinuation of aflibercept/placebo with sampling repeated every 2-3 months.**

Endogenous VEGF will be measured (4 mL of whole blood) on day 1 of cycle 1, prior to infusion of aflibercept/placebo (only when equipment for sample preparation is available on site, i.e. 4°C centrifuge).

Figure 6 – Immunogenicity and PK sampling



A/P: aflibercept/placebo; G: gemcitabine infusion; Ab: antibody detection

9.3.3 Bioanalytical methods

Free aflibercept concentrations in plasma will be measured by a validated ELISA method. The ELISA microplates are coated with human VEGF, which specifically binds functional aflibercept, while the detection antibody is directed against the receptor domains of the aflibercept. By

requiring a vacant VEGF binding site, this ELISA specifically measures free aflibercept; it does not detect the VEGF: aflibercept complex.

The assay of VEGF: aflibercept complex will also be measured by a validated ELISA method. The ELISA captures the complex with an antibody selective for VEGF coated on a plate. The captured complex is detected with an antibody selective for the receptor domains of aflibercept.

Human antibodies selective for aflibercept will be detected with an enzyme-linked immunosorbent assay that uses microplates coated with extracellular receptor domains of aflibercept. Immobilized receptor domain-antibody complexes are detected using peroxidase conjugated mouse anti-human IgG, F(ab')2 fragment specific antibody. The calibration standard is a mouse monoclonal antibody specific for the R1 domain of aflibercept that is detected with a peroxidase-conjugated goat anti-mouse IgG Fc fragment-specific antibody.

Free endogenous VEGF will be detected by sandwich enzyme immunoassay using an anti-VEGF monoclonal antibody coated on the plates. VEGF is detected using an enzyme-linked polyclonal antibody specific for free VEGF. The limit of detection is 15 pg/mL.

9.4 MEASURES TO PROTECT BLINDING OF THIS TRIAL

Please also refer to Section 8.10.

Patients, investigators, and other persons responsible for study conduct and data analyses will be blinded to treatment assignment.

All samples for PK evaluation will be assessed blindly (treatment arm and timing) and results will not be communicated to the study staff.

During the course of the study an external statician (independent from the sponsor) will perform unblinded safety and efficacy (IA) analyses for the purpose of the DMC data review. Access to these data and analyses will be restricted to the DMC members, unless decision is made by the DMC to release results to the Executive Steering Committee. Conditions to release unblinded results to the Executive Steering Committee and processes to protect the integrity of the study are described in the DMC charter.

In case of a SAE that is unexpected and reasonably associated with the use of the study treatment the code will be broken by the global safety officer in charge of the study for the purpose of regulatory reporting.

In case of an AE, the code can be broken at the investigator initiative only in exceptional circumstances, when knowledge of the investigational product is essential for treating the patient. The investigator or authorized person should follow the procedures outlined in Section 8.10.

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

Information on the following parameters will be collected by the investigator and reported in the CRF:

- Physical examination, including height (baseline only), body weight, ECOG PS (Appendix B) and blood pressure,
- Laboratory data,
  - Complete blood count and clinical chemistry.
  - Urinalysis and other tests as clinically indicated.
- Adverse events and serious adverse events.
- Concomitant medications and corrective treatments.
- Immunogenicity evaluation (see Section 9.3)

10.2 SAFETY INSTRUCTIONS

The NCI CTCAE v.3.0 will be used (Appendix D) to grade clinical and laboratory AEs.

Every attempt should be made to have the same study personnel to perform the assessment throughout the study for any given patient for consistency of grading.

Details and schedule of requested evaluations are given in Sections 1.1 and 1.2.

AEs will be recorded on the CRF, with all requested attributes.

If a finding meets the criteria for a SAE, then the appropriate procedures for reporting such events should be followed as described in Section 10.5.2.

Signs/symptoms that are present, or occurred, from the time the patient has signed the inform consent form to first study drug administration will be recorded as AEs, in the cycle 1 AE page of the CRF, if present at the time of first administration of study treatment. Height will be recorded at baseline only. Body weight will be assessed every 2 weeks. ECOG PS will be recorded prior to the start of each gemcitabine treatment (i.e. day 1, 8, 15, 22 of cycle 1 and day 1, 8, and 15 of subsequent 28-day cycles) and every 8 weeks during follow up period until progressive disease is documented, or cutoff date whichever comes first. Blood pressure will be recorded during study treatment period, i.e. prior to the start of each gemcitabine treatment (i.e. day 1, 8, 15, 21 of cycle 1 and day 1, 8, and 15 of subsequent 28-day cycles).

SAEs will be recorded from the time the patient has signed the inform consent.

During the treatment period AEs will be systematically collected at each visit up to the 30-day FU visit.

During the FU period (i.e. after 30-day FU visit), only related ongoing, or new related, AEs will be recorded. SAEs, regardless of relationship with study treatment, ongoing at the end of study treatment, will be followed during the FU period until resolution or stabilization.

10.3 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

10.4 DEFINITIONS OF ADVERSE EVENT (AE) AND SERIOUS ADVERSE EVENT (SAE)

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A priori, efficacy endpoints as specified in the protocol will not be considered as AEs.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Note: Examples of such medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, convulsions or asymptomatic ALT increase $\geq$ 10 ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Adverse Events

The period of safety observation starts from the time the patient gives informed consent.

All Adverse Events regardless of seriousness or relationship to Investigational Product, spanning from the signing of the informed consent form until 30 days after the last study treatment administration, are to be recorded on the corresponding page(s) included in the Case Report Form.

At baseline (i.e. even in the absence of any administration of study treatments), all signs and symptoms will be recorded as adverse event only if they are still present at the time of first study drug administration or if they are serious. They are to be recorded on the corresponding AE page (s) included in cycle 1 of the Case Report Form.

During the treatment period (i.e. until 30 days after the last administration of study drugs), all adverse events, regardless of seriousness or relationship to study treatments, are to be recorded on the corresponding page(s) included in the Case Report Form.

For follow-up period, refer to Section 10.5.3.

Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to study treatment, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the study treatment.

Vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to study treatment discontinuation/study drugs dose modification and/or fulfilling a seriousness criterion.

Laboratory abnormalities are to be recorded as Adverse Events only if they leads to study treatment discontinuation/study drugs dose modification and/or fulfills a seriousness criterion.

10.5.2 Serious Adverse Events

In the case of a Serious Adverse Event the Investigator must immediately:

- SEND (within 1 working day) by email (automatic sending activated by ticking “save complete” (for the initial report) or “save” (for follow-up reports) the electronic AE/SAE notification (html format) to the representatives of the Monitoring Team in the Clinical Research Unit (Clinical Safety Officer and Clinical Research Associates) who then forwards to Global Pharmacovigilance and Epidemiology and the Clinical Study Director. Before sending, please verify relationship to study drug has been indicated on the SAE complementary form.

- APPROVE the AE/SAE page in the electronic CRF immediately after automatic sending of the electronic Serious Adverse Event notification by entering, for a second time, “username and password”;
- If the mail connection is not functional or in case of any technical issue, SEND (within 1 working day, preferably by fax) the signed and dated corresponding page(s) in the Case Report Form to the representative of the Monitoring Team whose name, address and fax number appear on the Clinical Trial Protocol;
- ATTACH AND FAX photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient’s identity is protected and the patient’s identifiers in the Clinical Trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges;
- Follow-up of any SAE that is fatal or life threatening should be provided within one additional calendar week.

10.5.3 Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any related AEs (clinical signs, laboratory values or other, etc.) until the return to normal or consolidation of the patient's condition.
- In the case of SAE, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until evolution has been stabilized. This may imply that follow-up will continue beyond 30-day follow-up visit and that additional investigations may be requested by the Monitoring Team;
- In case of any Adverse event or Serious Adverse Event brought to the attention of the Investigator at any time after cessation of study treatment and considered by him/her to be caused by the study treatment with a reasonable possibility, should be reported to the Monitoring Team.

10.6 PREGNANCY

- Pregnancy will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfills SAE criteria.
- In the event of pregnancy, the study treatment should be discontinued and the Sponsor informed immediately (i.e. within 1 working day), even not fulfilling a seriousness criterion, using the AE form together with the SAE complementary form to be sent to the representative of the monitoring team whose name, address and fax number appear on the clinical trial protocol.
- Follow-up of the pregnancy will be mandatory until the outcome has been determined.

10.7 OVERDOSAGE

In case of accidental or intentional overdose with the IP, even not fulfilling a seriousness criterion, is to be reported to the sponsor immediately (within 1 working day) using the SAE complementary form to be sent to the representative of the monitoring team whose name, address and fax number appear on the clinical trial protocol.

No case of aflibercept overdose has been reported so far. The highest doses that have been administered so far are 7 mg/kg I.V. every 2 weeks and 9 mg/kg I.V. every 3 weeks.

For the purpose of safety reporting (as described above) dosing of gemcitabine above 1200 mg/m² per infusion should be considered as overdosage. There is no known antidote of gemcitabine. In case of overdosage, refer to gemcitabine labeling for appropriate supportive care.

10.8 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study treatment, to the Authorities, IECs / IRBs as appropriate and to the Investigators.

The determination of expectedness for SAEs, for regulatory reporting purposes, will be defined by the current Investigators' Brochure, in force at the time of event(s) occurrence.

In addition, the Sponsor may report in an expedited manner all SAEs that are expected and at least reasonably related to the study treatment to the Authorities, according to local regulations.

In this study, the SAEs considered related to the underlying condition will not be considered unexpected unless their course, intensity or other specific features are such that the Investigator, according to his/her best medical judgment, considers these events as exceptional in the context of this medical condition.

Any other AE not listed as an expected event in the Investigator’s Brochure for aflibercept and/or contained within the reference safety information for gemcitabine on file in the pharmacovigilance will be considered as unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the CSR.

11 HANDLING OF PATIENT DEFINITIVE TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

11.1 DEFINITIVE TREATMENT DISCONTINUATION

11.1.1 List of criteria for definitive study treatment discontinuation

The patients may discontinue study treatment under the following circumstances but will continue to be assessed and followed in the study unless the patient refuses:

- The patients may withdraw from study treatment if they decide to do so, at any time and irrespective of the reason (consent's withdrawal) or at the request of their legally authorized representative. "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research.
- If, in the investigator's opinion, continuation of the study treatment would be detrimental to the patient's well being, such as:
    - Disease progression as defined in Section 9.1.2.1,
    - Unacceptable adverse event(s) not manageable by symptomatic therapy, dose delay or dose modification (see section 8.5),
    - Intercurrent illness that prevents further administration of study treatment,
    - Non compliance to the study protocol.
- Patient is lost to follow-up.
- **Of note**, any investigational **agent** unblinding by the Investigator will lead to permanent investigational agent discontinuation.

In all cases, the reason for and date of withdrawal must be recorded in the CRF and in the patient's medical records. The patient must be followed up to establish whether the reason was an adverse event, and, if so, this must be reported in accordance with the procedures in Section 10.5.

11.1.2 Handling of patients after definitive treatment discontinuation

All definitive treatment discontinuation should be recorded by the Investigator in the appropriate pages when considered as confirmed.

After study treatment is discontinued, patients should perform 30-day FU visit and then will be followed for disease progression (every 8 weeks imaging) if discontinuation occurred prior to documented progression and for survival status (every 8 weeks) once progressive disease is documented.

Patients should be sampled 30 and 90 days following the last administration of aflibercept/placebo for immunogenicity and PK evaluation.

Following the 30-day follow-up visit, ongoing SAEs and new related AEs/SAEs should be recorded/followed as described in Section 10.5.

11.2 PROCEDURE FOR WITHDRAWAL OF PATIENTS FROM STUDY FOLLOW-UP SCHEDULE

The patients may withdraw from the study follow-up schedule, before study completion if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision.

All study withdrawals should be recorded by the Investigator in the appropriate CRF pages and in the patient's medical records when considered as confirmed (at least date of withdrawal and reason for).

- If possible, the patients are assessed using the procedure normally planned for the 30-day Follow-up visit as described in Section 12.1.4.

The investigator must make every effort to contact patients lost to follow-up. Attempts to contact such patients must be documented in the patient's records (e.g., dates of attempted telephone contact, receipt for sending a registered letter). Patients who did not complete the study and for whom no endpoint data are available will be considered as lost to follow-up. Patients lost to follow-up will be censored for overall survival analysis at the time they were last known to be alive (see primary endpoint definition in section 13.2.2.1).

11.3 CONSEQUENCE

Patients who have been withdrawn from the study cannot be reincluded in the study. Their inclusion must not be reused.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

12.1.1 Pretreatment evaluation (Baseline / Screening visit)

Each potential patient will be examined before the start of the study to determine his/her eligibility for participation.

The **written informed consent** will have to be signed by the patient before any protocol specific procedures are performed.

The following examinations will be performed within 21 days prior to randomization:

- **Demographics**: age (date of birth), gender, and race.
- **Medical, surgical and cancer history** including significant prior and concurrent illnesses, cancer diagnosis (primary tumor characteristics and metastatic sites).
- **Prior anticancer treatment** including previous surgery for cancer, radiation therapy, chemotherapy and potential investigational antitumor therapy.
- **Tumor imaging**: abdominal CT-Scan or MRI, chest X-Ray (or chest CT-Scan or MRI in case of thoracic target lesions), and all other exams as clinically indicated (e.g. brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions (measurable and non measurable). CT-Scan/MRI will be preferred to X-Ray for the purposes of efficacy assessment. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Minimum interval between 2 assessments must be of at least 28 days (4 weeks). When available, spiral CT acquisition should be done. Slice thickness should be adapted to the anatomical area and presumed size of the lesions. Slice thickness of 5 to 8 mm should be favored rather than 10 mm, especially during spiral acquisition. If limitations appear in volume acquisition, it is encouraged to choose a 1.5 pitch and thin slices, rather than a 1 pitch with thick slices. A centimeter scale should appear on films.
- **Prior medications** will be recorded from 21 days prior to the start of study treatment.
- **CA19-9** will be performed, for exploratory purpose, using commercially available assay.

The following examinations will be performed within 8 days prior to randomization:

- **Inclusion/Exclusion criteria**.
- **Physical examination** including major body systems examination, height and weight, ECOG performance status, blood pressure and other signs and symptoms.

- **12-lead ECG.**
- **Laboratory safety assessments**:
    - **Hematology**: hemoglobin, WBC, ANC, platelet count,
    - **Blood Chemistry**: sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, and glucose,
    - **Coagulation test:** prothrombin time expressed as INR in patients under treatment with Vitamine K antagonist,
    - **Urinalysis**: dipstick (WBCs, RBCs) and UPCR on morning urine spot or proteinuria assessed on 24-hour urine collection.
    - **Pregnancy test** in women of reproductive potential: serum or urine β-hCG.
- **Clinical benefit assessment**: pain severity assessed by VAS (Appendix E), analgesic consumption as morphine equivalents, assessed during the week prior to first dosing (Appendix F). The VAS is a line of fixed length of 100 mm with words that anchor the scale at the extreme ends (no pain – worst possible pain) and no words describing intermediate positions. Patients will be instructed to place a mark on the line corresponding to their perceived state.
- The procedures described above are not to be repeated before study treatment administration for Cycle 1, provided they were performed at baseline, within 8 days of the start of administration and provided they did not show significant abnormalities.

12.1.2 Randomization

Randomization will take place once the consented patient has completed all the necessary screening procedures and is deemed eligible for study entry by the investigator or designee. All eligible patients must be randomized by contacting the IVRS (see section 8.7).

The results of the baseline examinations will be recorded in each randomized patient's CRF. Source documentation to support the screening results must be maintained in the patient's medical record.

Treatment should begin within 3 days after randomization.

12.1.3 Study treatment

The Study treatment period begins when the patient receives the initial dose of study drugs (Cycle 1 Day 1). Each cycle consists of 28 days and assessments are scheduled on a every 2 or 4 weeks basis (Day 1, 15 each cycle) except for hematological tests assessed on a weekly basis (Day 1, 8, 15 and Day 22 cycle 1 and Day 1, 8, 15 for subsequent cycles) but may be repeated more often, as clinically indicated. Cycle length may be extended if additional time is required for resolution of study drug-related toxicities or other adverse events, but cycle shortening to less than 25 days is not permitted.

Sampling schedule for patients taking part to the pharmacokinetics evaluations is summarized in Section 12.1.3.3.

12.1.3.1 At Cycle 1

Day 1

The day on which the patient receives the initial dose of study medication is referred as Cycle 1 Day 1 (Day 1 of the study). The examinations described in section 12.1.1 are not to be repeated for cycle 1, provided they were performed within 8 days of the start of study treatment and provided that they did not show significant abnormalities.

- A total of 2 blood samples per patient will be collected just before the start of aflibercept/placebo for **detection of anti-aflibercept antibody** and pharmacokinetics respectively.

Day 8

- **Hematological test:** WBC, ANC, hemoglobin, platelet count.
- **ECOG** performance status and blood pressure.

Day 15

- **Hematological test:** WBC, ANC, hemoglobin, platelet count.
- **Clinical examination:** examination of the major body systems, ECOG performance status, BP, and body weight.
- **Urinalysis:** dipstick (WBCs, RBCs) and UPCR on morning urine spot .
    - If UPCR is >1 then 24 hour urine collection must be performed to assess the urine protein rate, as well as an urine protein electrophoresis.
    - **In case UPCR is greater than 2 or in case of proteinuria of renal origin (according to urinary protein electrophoresis) is associated with hematuria (microscopic or macroscopic), then a blood work-up in search for hemolytic anemia of microangiopathic origin should be initiated.**

Day 22

- **Hematological test:** WBC, ANC, hemoglobin, platelet count.
- **ECOG** performance status and blood pressure.

Day 29

Day 29 corresponds to Day 1 of the following cycle (see section 12.1.3.2).

12.1.3.2 At Cycles 2, 3, 4, 5, …

Day 1 of all cycles prior to study drug administration

- **Laboratory safety assessments**:
  - **Hematology**: WBC, ANC, hemoglobin, platelet count.
  - **Blood Chemistry** sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, creatinine clearance (calculated with Cockroft-Gault formula) if creatinine >ULN, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose.
  - **Coagulation test***:* prothrombin time expressed as INR in patients under treatment with Vitamine K antagonist.
  - **Urinalysis**: dipstick (WBCs, RBCs) and UPCR on morning urine spot.
    - If UPCR is >1 then 24 hour urine collection must be performed to assess the urine protein rate, as well as a urine protein electrophoresis.
    - **In case UPCR is greater than 2 or in case of proteinuria of renal origin (according to urinary protein electrophoresis) is associated with hematuria (microscopic or macroscopic), then a blood work-up in search for hemolytic anemia of microangiopathic origin should be initiated.**
- **Clinical examination**: examination of the major body systems, ECOG performance status, BP and body weight.
- **Clinical benefit assessment** (Tumor related symptoms):
  - pain severity assessed by VAS recorded daily via a patient diary. Patients will be instructed to place a mark on the line (fixed length of 100 mm) corresponding to their perceived state (average pain during the past 24-hour),
  - analgesic consumption as morphine equivalents (recorded daily via a patient diary). Both results will be recorded in the CRF.
- **Assessment of adverse events and concomitant medications.**
- **Other investigations if clinically indicated.**

Day 8 of all cycles

- **Hematological test:** WBC, ANC, hemoglobin, platelet count.
- **ECOG** performance status and BP.

Day 15 of all cycles

- **Hematological test:** WBC, ANC, hemoglobin, platelet count.

- **Clinical examination**: examination of the major body systems, ECOG performance status, BP and body weight.

- **Urinalysis:** dipstick (WBCs, RBCs) and UPCR on morning urine spot .
  - If UPCR is >1 then 24 hour urine collection must be performed to assess the urine protein rate, as well as an urine protein electrophoresis.
  - **In case UPCR is greater than 2 or in case of proteinuria of renal origin (according to urinary protein electrophoresis) is associated with hematuria (microscopic or macroscopic), then a blood work-up in search for hemolytic anemia of microangiopathic origin should be initiated.**

12.1.3.3 Pharmacokinetics and immunogenicity

Prospective evaluations

The evaluations are intended to be performed in all **randomized and treated** patients. All patients will be sampled for immunogenicity (anti-aflibercept Ab detection) and pharmacokinetics evaluations at baseline, **during aflibercept/placebo treatment period** and following aflibercept/placebo discontinuation:

- Baseline, prior to first administration of study treatment,
- just after the first administration of aflibercept/placebo (for PK only),
- **on treatment, prior to each cycle, i.e. pre-dose of aflibercept/placebo infusion 3 cycle 2, infusion 5 cycle 3, infusion 7 cycle 4, infusion 9 cycle 5, etc…,**
- approximately 30 days after the last infusion of aflibercept/placebo.
- approximately 90 days after the last infusion of aflibercept/placebo.

In addition, a sample for the determination of endogenous VEGF level will be collected just before the start of the first infusion of aflibercept/placebo in all patients from centres where equipment for samples preparation is available, i.e. 4°C centrifuge.

Event driven evaluations

Beside the per protocol prospectively scheduled immunogenicity evaluations, patients will be sampled for both anti-aflibercept Ab detection and pharmacokinetics in a symptom driven manner when the occurrence of Ab is suspected.

Patients experiencing infusion related reactions Grade ≥ 2 will be sampled for anti-aflibercept Ab detection and pharmacokinetics within a maximum of 2 weeks following the occurrence of the event, then every 2-3 months for FU, **up to 6 months from last aflibercept/placebo dose.**

Similarly, anti-aflibercept antibody detection and subsequent FU should also be performed in patients reporting proteinuria >3.5 g/24h, or protenuria of renal origin assosciated with hematuria.

12.1.3.4 Every 8 weeks

The following examinations will be performed every 8 weeks:

- **Tumor assessment**, every 8 weeks from first cycle or at any time in case of clinical suspicion of progression, to follow target and /or not target lesion present at baseline (see Section 9.1.2). To ensure comparability, the imaging should be performed *using identical techniques throughout the study* period (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

- **CA19-9** measurement for exploratory purpose.

12.1.4 End of study treatment (30-day Follow-up visit)

All patients must continue to be observed for at least 30 days after the final dose of study treatment (either aflibercept/placebo or gemcitabine).

The following procedures should be performed approximately 30 days following the final dose of study treatment:

- **Clinical examination**: examination of the major body systems, ECOG performance status, BP and body weight.
- **Laboratory safety assessments**:
  - *Hematology*: WBC, ANC, hemoglobin, platelet count.
  - *Blood Chemistry* sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, creatinine clearance (calculated with Cockroft-Gault formula) if creatinine >ULN, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose.
  - *Coagulation test:* prothrombin time expressed as INR. in patients under treatment with Vitamine K antagonist.
  - *Urinalysis*: dipstick (WBCs, RBCs) and UPCR on morning urine spot.
    - If UPCR is >1 then 24 hour urine collection must be performed to assess the urine protein rate, as well as a urine protein electrophoresis.
    - **In case UPCR is greater than 2 or in case of proteinuria of renal origin (according to urinary protein electrophoresis) is associated with hematuria (microscopic or macroscopic), then a blood work-up in search for hemolytic anemia of microangiopathic origin should be initiated.**
- **Tumor assessment**: CT/MRI scan if not performed within the prior 8 weeks.
- **CA19-9** measurement if not performed within the prior 8 weeks.
- **Assessment of adverse events** (to be reported in the last cycle pages of the CRF).
- **Assessment of concomitant treatments.**

- **Clinical benefit**: Assessment of tumor related symptoms including pain severity assessed by VAS, analgesic consumption as morphine equivalents (to be reported in the last cycle pages of the CRF).
- **Other investigations if clinically indicated**.
- **Blood sample collection**:
  - Blood sample for Pharmacokinetics: approximately 30 days after the last infusion of aflibercept/placebo.
  - Blood sample for anti-aflibercept antibody: approximately 30 days after the last infusion of aflibercept/placebo.

12.1.5 Post treatment Follow-up period

Following 30-day FU visit patients will be followed every 8 weeks for PFS (if study treatment has been discontinued prior to disease progression) and then every 8 weeks for OS, **until death** or study cut-off, which ever comes first.

The first follow up visit will occur approximately 90 days after the final dose of study treatment (i.e., 60 days after the 30-day Follow-up visit).

- The following evaluations should be performed:
- **Blood sample collection**:
  - For anti-aflibercept antibody detection: approximately 90 days after the last infusion of aflibercept/placebo.
  - For Pharmacokinetics: approximately 90 days after the last infusion of aflibercept/placebo.
- **Tumor assessment** (if applicable –i.e. if disease progression has not yet been documented) every 8 weeks.
- **CA19-9** measurement (if applicable –i.e. if disease progression has not yet been documented) every 8 weeks..
- **Clinical benefit**: Assessment of tumor related symptoms including pain severity assessed by VAS, analgesic consumption as morphine equivalents until disease progression or start of further anticancer therapy.
- **Related AEs and all SAEs, ongoing** at the end of the study treatment, or new related AE and SAE will be recorded until recovery, or until progression has been stabilized.
- **Post medications** if correspond to treatment of related AEs.
- **Further anticancer therapy:** After withdrawal from study treatment, further treatment, if any, is at the discretion of the investigator. No further antitumor therapy should be administered before disease progression unless the patient requests further antitumor therapy, or the investigator deems it necessary.

- **Survival status,** every 8 weeks. Following documented disease progression, all patients will be followed for survival and vital status information will be collected at 8 weeks intervals until death or the study cutoff date, whichever comes first.

12.1.6 Study procedures after stop of the trial for futility at the interim analysis

On 9 September 2009, the Data Monitoring Committee (DMC) requested to stop the EFC10547 trial for futility based on the predefined boundary rules. The following section describes procedures to be performed after this decision.

12.1.6.1 Patients in follow up period on 11 September 2009

The blood samples for detecting anti-aflibercept antibodies will be collected as planned in the protocol approximately 30 days and 90 days after the last administered dose of aflibercept. If these samples were already performed, no further follow up visit will be collected except for ongoing related AE and ongoing SAEs regardless of relationship, which will be followed until recovery or stabilization.

12.1.6.2 Patients in treatment period on 11 September 2009

- **Patient treated in placebo-gemcitabine arm**

Placebo should be stopped and all data related to ongoing cycle at the date of 11 September 2009 will be collected. The End of study treatment visit should be performed and the End of Treatment e-CRF page should be completed with the reason "Other, study stopped further to DMC recommendations" (if decision of stopping study treatment was not taken during the last ongoing cycle).

The investigator will have to perform the "permanent treatment discontinuation" call via IVRS to confirm that placebo treatment arm has been stopped. No more "reallocation call" should be performed via IVRS after unblinding, for those patients randomized in placebo/gemcitabine treatment arm.

If gemcitabine is then continued alone, the anti-cancer therapy page will be completed at the date of the subsequent follow up visit.

If no related AE or SAE regardless of relationship is ongoing, the data collection will then be stopped.

If a related AE or SAE regardless of relationship is ongoing at the end of this last cycle, the AE/SAE(s) will be collected in the AE FUP page until recovery or stabilization.

Tumor assessment (CT Scan/MRI) will be performed at the discretion of the investigator but the corresponding tumor measurement are no more collected in the e-CRF after the last study treatment cycle.

- **Patient treated in aflibercept-gemcitabine**

If the patient does not want to continue to receive aflibercept, the recommendations are the same as for patients treated in the placebo-gemcitabine arm (see above) with the addition of blood samples for pharmacokinetics measurement and anti-aflibercept antibody detection (approximately 30 days and 90 days after the last administered dose of aflibercept) to be collected as per protocol pre-defined schedule.

If the patient wants to continue to receive aflibercept, patient will have to reconsent and can continue study treatment until disease progression, unacceptable toxicity, or the patient's refusal. Study drug(s) administration, SAE information and End of Treatment reason are to be captured in the e-CRF. Blood samples for pharmacokinetics measurement and anti-aflibercept antibody detection (approximately 30 days and 90 days after the last administered dose of aflibercept) are also be collected as per protocol pre-defined schedule and to be reported in the e-CRF accordingly.

Then the data collection will be stopped except if a related SAE is still ongoing: the SAE(s) will be collected in the AE FUP page until recovery or stabilization.

Patients will be followed as per institution's standard practice and investigator's judgment. Tumor assessment (CT Scan/MRI) will be performed at the discretion of the investigator but the corresponding tumor measurement are no more collected in the e-CRF in the study treatment cycle that start beyond 11 September 2009.

At the time the aflibercept treatment is stopped (for any of the reasons mentioned above), the investigator will have to perform the "permanent treatment discontinuation" call via IVRS to confirm that aflibercept treatment arm has been stopped.

12.2 DEFINITION OF SOURCE DATA

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided within a CRF.

The results of certain examinations or evaluations recorded in the CRF may be considered to be source data (such as patient's VAS, diary….).

13 STATISTICAL CONSIDERATIONS

The statistical considerations presented in this section forms the basis for the Statistical Analysis Plan (SAP), which will provide accurate definitions and detailed specifications for the analyses to be performed on the data collected from this study. A final SAP will be issued prior to the database lock of the interim analysis.

13.1 DETERMINATION OF SAMPLE SIZE

The primary endpoint of this study is overall survival. [redacted]

The cutoff date for the Overall Survival (OS) will be the date when the required 513 deaths have been observed.

13.2 ANALYSIS VARIABLES

13.2.1 Demographic and baseline characteristics

Standard demographic and baseline characteristics (including age, gender, race, height and weight), medical history, cancer diagnosis, prior anticancer therapy, prior medications (other than prior anticancer treatment for pancreatic cancer) will be reported at baseline.

Baseline efficacy and safety variables as well as other prognostic factors will also be assessed. These variables include tumor assessment, clinical benefit components (analgesic consumption, pain, PS, weight), CA19-9 marker, vital signs, ECG and major laboratory parameters.

In general, baseline value is defined as the last value or measurement taken before the first dose of study treatment. A mean value can be considered for certain variables if multiple observations are collected at baseline (e.g. baseline analgesic consumption will be defined as the daily morphine

equivalent measured during the week prior to first dosing. Baseline VAS will be defined as the average score during the week prior to first dosing).

13.2.2 Efficacy variables

13.2.2.1 Primary efficacy variable(s)

The primary efficacy endpoint is overall survival defined as the time interval from the date of randomization to the date of death due to any cause. If death is not observed during the study, data on OS will be censored at the earlier of the last date patient is known to be alive and the cutoff date.

13.2.2.2 Secondary efficacy variable(s)

Progression free survival (PFS) is defined as the time interval from the date of randomization to the date of first observation of progression or the date of death (due to any cause). If death or progression is not observed, data on PFS will be censored at the earlier of the date of last tumor assessment without evidence of progression and the cutoff date.

Objective response rate (RR) is defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR), defined by RECIST criteria, relative to the total number of patients in the considered analysis population (ITT or evaluable for response). Tumor assessments are performed at baseline, then every 8 weeks during the treatment and the follow-up period, up to disease progression. The analysis of RR will include tumoral assessments performed up to the initiation of an other anti-tumor treatment. In particular, for patients early stopping the study treatment without achieving a response, a tumoral response (CR or PR) achieved under a post-treatment anti-cancer therapy will not be considered.

Clinical benefit components are assessed at baseline, during the treatment and on-follow-up as defined below:

- Analgesic consumption (morphine equivalents (mg) per day): recorded daily via a diary completed by the patients,
- Pain intensity (VAS): recorded daily via a diary completed by the patients,
- Functional impairment assessed by ECOG Performance Status: recorded at baseline, and at day 1, 8, 15, 22 of cycle 1 and at day 1, 8, 15 of subsequent cycles and then every 8 weeks during follow up period,
- Weight change (kg): weight recorded at baseline, at day 1 and day 15 of each cycle and then every 8 weeks during follow up period

For each clinical benefit component the patients will be classified as positive, stable or negative as defined in the following table:

Table 13 - Classification of clinical benefit's components

Positive	Negative	Stable
	Analgesic consumption[a]	
≥ 50% reduction from baseline lasting at least 4 weeks	Any increase from baseline lasting at least 4 weeks	No change in narcotic analgesic usage (including Improvement/Worsening not confirmed)
	Pain intensity[b]	
≥ 50% reduction from baseline lasting at least 4 weeks	Any increase from baseline lasting at least 4 weeks	No change in pain intensity (including Improvement/Worsening not confirmed)
	ECOG performance Status	
≥ 1 point decrease from baseline lasting at least 4 weeks	≥ 1 point increase from baseline lasting at least 4 weeks	No change in ECOG PS (including Improvement/Worsening not confirmed)
	Weight	
≥ 7% increase (not due to fluid accumulation) from baseline lasting at least 4 weeks	≥ 5% decrease from baseline lasting at least 4 weeks	No change in weight (including Improvement/Worsening not confirmed)

a: Narcotic analgesic increase/decrease will be determined by the calculation of the average morphenic equivalent calculated every week
b: Pain increase/decrease will be determined by the calculation of the average pain calculated every week

Clinical benefit will be assessed by:

- Time to symptom worsening (TTSW) is defined as the time interval from the date of randomization to the date of symptom worsening. Date of symptom worsening is defined as the date of the first change from baseline which meets the definition of worsening for at least one clinical benefit component. If symptom worsening is not observed, data on TTSW will be censored at the earlier of the date of last assessment without evidence of symptom worsening, the date of initiation of an other anti-tumor treatment and the cutoff date.

- Improvement in tumor related symptoms is defined as the proportion of patients classified as clinical benefit responders, i.e. patient who has at least one positive component of clinical benefit (pain, performance status or weight) with none of the other components being negative relative to the total number of patients in the analysis population. Assessments performed up to the initiation of an other anti-tumor treatment will be taken into account in the analysis of improvement in tumor related symptoms.

13.2.3 Safety variables

The safety variables include:

- **AE**
  - On-treatment period: On-treatment period is the period from the first dose to 30 days after the last dose.
  - Treatment-emergent AEs (TEAEs): A TEAE is defined as an AE that is reported during the on-treatment period defined above.
- **Discontinuation**
  - Treatment discontinuation and reasons.
  - Treatment discontinuation due to AEs.
- **Vital signs** (blood pressure SPB, DBP) and ECOG performance status
- **Major laboratory safety parameters**
  - Hematology: WBC, neutrophil, platelets, and hemoglobin.
  - Selected Blood chemistry: total bilirubin, alkaline phosphatase, SGOT (AST), and SGPT (ALT), Creatinine.
  - Renal function and urinalysis: Dipstick protein (WBC, RBC), Urinary Protein-to-creatinine Ratio (UPCR), and 24-hour protein.

13.2.4 Pharmacokinetic variables

The PK analysis will include population pharmacokinetics of IV aflibercept and endogenous VEGF level.

13.3 ANALYSIS POPULATIONS

13.3.1 Efficacy populations

13.3.1.1 Intent-to-Treat (ITT) population

The Intent-to-Treat (ITT) population will include all patients who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number through the IVRS. Patients will be included in a treatment arm as randomized, regardless of whether patients received any study drug or received a different study drug from which they were randomized. Analysis of the primary efficacy endpoint will be performed using the ITT population. Secondary efficacy endpoints will also be analyzed in the ITT population, and in evaluable patients whenever applicable.

13.3.1.2 Evaluable Patient (EP) population for tumor response

Evaluable Patient (EP) population for tumor response will consist of all randomized and treated patients, with cytologically or histologically confirmed pancreatic cancer, with metastatic and measurable disease at study entry, in first line setting and evaluable for response (i.e. patients with at least one tumoral evaluation while on treatment, except for early disease progression/cancer-related death).

The EP population for tumor response will be used for the RR analysis (secondary population for RR analysis knowing that primary population will be ITT). Analyses using this population will be based on the treatment actually received.

Protocol deviations

During blinded review of the database, the compliance with the protocol will be examined with regard to inclusion/exclusion criteria, prohibited therapies, timing and availability of planned assessments. Protocol deviations will be identified by the clinical trial team before database lock and will be classified as minor or major deviations. The detailed definitions of protocol deviations will be provided in the final version of the SAP.

13.3.2 Safety population

The All-Treated (AT) population is a subset of the ITT population that took at least one dose of study medication. All analyses using this population will be based on the treatment actually received. Treatment administration/compliance and all clinical safety data will be summarized using the all treated population.

13.3.3 Other analysis populations

Clinical benefit population

A specific population will be defined for the clinical benefit analysis. The clinical benefit population will include randomized patients, with baseline clinical benefit available, with a minimum pain score ≥ 20 and a minimum analgesic consumption ≥ 10.

PK and immunogenicity population

All **randomized and** treated patients will be used to collect samples to perform the complete PK analyses. The pharmacokinetic analysis will be performed based on the all treated population with evaluable blood samples, at pre- and post-dose **of infusion 1** cycle 1, pre-dose **every cycle (prior to aflibercept/placebo infusion 3 cycle 2, infusion 5 cycle 3, infusion 7 cycle 4, etc…)** and then at approximately 30 days and 90 days following the last aflibercept/placebo infusion e.g. whom had pre-dose and at least one post dose assessment performed. Peak analysis will be performed at cycle 1 (post-dose cycle 1) and trough analysis will be performed **at each cycles.**

All treated patients will be used in the analysis of anti-aflibercept antibody measurement.

13.3.4 Disposition of patients

Summary of patient populations will be presented with counts (n) and percentages (%).

Study drug discontinuation will be summarized by reason for each treatment arm using the AT population. The premature discontinuation from the study will be also summarized by treatment arm and overall using the ITT population.

13.4 STATISTICAL METHODS

Continuous data will be summarized for each treatment group using the number of non-missing observations (N), mean, SD (standard deviation), median, minimum and maximum. In addition, 25%-percentile and 75%-percentile may be provided if needed. In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from baseline) by visit will be provided on observed cases, i.e. the inclusion of only subjects having non-missing assessments at a nominal visit. In addition, the tables summarizing the change from baseline will include only subjects having both a baseline and a post-baseline evaluation.

In general, categorical data will be summarized for each treatment group using counts (n) and percentages (%). The number of patients with missing data may be mentioned, but will not be included in the denominator for the calculation of percentages unless otherwise specified (in particular, see section 2.4.2 for handling of missing or non-evaluable data for efficacy response variables in Section 13.5.).

Time-to-event (or event-free survival) data will be analyzed using means of Kaplan-Meier method. Median time-to-event (or event-free survival) and its 95% confidence intervals by treatment arm will also be provided

13.4.1 Demographic and baseline characteristics

All patient demographic and baseline characteristics, medical history, and diagnoses will be summarized using descriptive statistics using the ITT population. Analyses for the all-treated population may be presented if the number of patients differs substantially from the ITT population.

13.4.2 Extent of study treatment exposure and compliance

Extent of study treatment exposure will be assessed in the AT population.

The summary of extent of exposure will include number of cycles administered, duration of dosing (weeks), cumulative dose (mg/kg for aflibercept/placebo, mg/m² for gemcitabine), dose intensity (mg/kg/week for aflibercept/placebo, mg/m²/week for gemcitabine) and relative dose intensity (%) by treatment group.

Dose delays, reductions, and interruption will be also summarized.

Concomitant medication and therapy while on study will be summarized by counts (n) and percentages (%). Medications of specific interest will be described in the SAP.

13.4.3 Analyses of efficacy variables

13.4.3.1 Analysis of primary efficacy variable(s)

The null hypothesis is that aflibercept + gemcitabine or placebo + gemcitabine have equal overall survival in this population. Overall survival will be compared between the two treatment groups using a log-rank test stratified by ECOG PS (0 *vs* 1 *vs* 2), curative surgery (pancreatectomy, yes *vs* no) and geographical region. The estimates of the hazard ratio and corresponding 95% confidence interval will be provided using a Cox proportional hazard model stratified by the baseline stratification factors. The median overall survival and its 95% confidence interval and survival curves will be presented by treatment arm using Kaplan-Meier estimates.

The final OS analysis will be conducted when 513 deaths have been observed. One interim analysis of OS for the purpose of futility and efficacy is planned when approximately 205 (40% of deaths) have occurred. Using a group sequential approach with an O'Brien Fleming α-spending function and an overall one-sided α level of 0.025, the one-sided α nominal significance level to be used at the final analysis is 0.0249 (see details on interim analysis in section 13.6).

- Non stratified logrank will be also performed as sensitivity analysis.

Additional exploratory analysis may be considered and will be detailed in the SAP. For example, the Cox proportional hazard model may be used to examine the effect of various baseline prognostic factors on OS (gender, age class, ECOG performance status, curative surgery, geographical region, clinical benefit components at baseline, CA19-9).

13.4.3.2 Analyses of secondary efficacy variables

Main secondary endpoints are PFS, clinical benefit (evaluated using time to symptom worsening and improvement in tumor related symptoms) and response rate. Analyses of secondary endpoints will be primarily based on the ITT population. Clinical benefit parameters will be assessed on the clinical benefit population. Response Rate will be also analyzed on the EP population.

Improvement in tumor related symptoms and response rate will be summarized by means of count (n) and percentage (%) and presented with 95% confidence intervals. PFS and TTSW will be analyzed by means of Kaplan-Meier method. Medians and its 95% confidence intervals by treatment arm will also be provided. Hazard ratios and 95% confidence interval will be calculated after adjustment for baseline stratification factors based on the Cox proportional hazard model.

The tests to be performed are Cochran-Mantel-Haenszel test (improvement in tumor related symptoms and objective response rate) and log-rank test stratified by ECOG performance status, curative surgery and geographical region (PFS, TTSW).

13.4.3.3 Type-I error rate control

The overall one-sided α significance level of Overall Survival is 0.025. Hypothesis testings of the main secondary efficacy variables will be carried out. In order to protect the overall type-I error level, a step-down procedure will be used in the analyses of efficacy variables according to the following sequential order:

- OS,
- PFS, if test on OS is statistically significant
- Time to symptom worsening, if test on PFS is statistically significant,
- Improvement in tumor related symptoms, if test on TTSW is statistically significant,
- Objective response rate, if test on improvement in tumor related symptoms is statistically significant.

At each step, the procedure will stop if the test at the current step does not meeting the pre-determined significance level. This procedure is applicable both at interim and final analysis of Overall Survival. All secondary endpoints among the step-down procedure will be tested at the 2-sided 5% level, whatever the stage of the statistical analysis (interim or final).

13.4.4 Analyses of safety data

Analysis of adverse events, vital signs, ECG, and laboratory data will be descriptive and conducted on the all treated population by treatment group. Summary of safety data will also be performed by cycle (where applicable). For each of the safety parameters, a baseline value will be defined as the last value or measurement taken up to the first dose in the study.

13.4.4.1 Adverse Events

TEAEs will be summarized with the number and percentage of patients with AEs, classified by MedDRA preferred term and intensity as graded by the NCI CTCAE version 3.0.

SAEs and treatment-emergent SAEs will be summarized using MedDRA classification up to the preferred term. SAEs will be also presented by worst NCI grade by patients.

TEAEs will be analyzed regardless of their relationship to the study drug. However, summaries will be done for specific subsets of AEs, such as those potentially related to study drug.

13.4.4.2 Laboratory safety data

Qualitative and quantitative results will be summarized for hematological toxicities. Qualitative data (worst NCI CTCAE grade) will be summarized by cycle and by patient.

Biochemistry and urinalysis will be analyzed using the worst NCI CTCAE grade, whenever applicable (laboratory normal ranges, otherwise) calculated from laboratory values. Specific attention will be given to incidence of proteinuria and impairment of renal function.

13.4.4.3 Vital signs

By visit descriptive analyses of vital signs will be provided for observed values and change from baseline.

13.4.5 Analyses of pharmacokinetic and pharmacodynamic variables

The PK analysis will include population pharmacokinetics of IV aflibercept with its associated interpatient variability. Concentrations of free aflibercept, VEGF:aflibercept complex, and the ratio free aflibercept to VEGF:aflibercept complex levels will be estimated. Levels of circulating endogenous VEGF will be assessed as well.

The population pharmacokinetics of free and bound aflibercept have been estimated from the Phase I studies in which intensive blood sampling protocols were used. The population estimates from this analysis provided a prior distribution from which individual Bayesian estimates of the pharmacokinetic parameters for each patient in this study will be derived.

13.4.6 Analyses of anti-aflibercept antibody measurements

Anti- aflibercept antibody levels will be categorized as negative and positive. A patient will be considered to have positive anti-body levels if antibodies were detected above the quantification limits.

13.5 DATA HANDLING CONVENTIONS

Some general rules of data handling conventions are listed below. Further details will be provided in the SAP.

Missing data: In general, no imputation is planned for missing data. The following approaches are default methods for missing data handling. Some exploratory analyses can be planned with different strategies for treating missing outcomes. The details will be provided in the SAP.

- Categorical data at baseline will be summarized for each treatment group using counts (n) and percentages (%). The number of patients with missing data may be mentioned, but will not be included in the denominator for the calculation of percentages unless otherwise specified.
- Efficacy response variable: When a proportion is calculated for a binary variable (e.g. response rate), the denominator is based on the total number of patients in the analysis population used for the summary (ITT, AT, evaluable). There can be 3 observations: Yes, No, and Non-evaluable (or missing). For the patients with non-evaluable outcomes, the default rule is that the patients will be treated as “no events”.
- Continuous data: The analyses and summaries for variables with continuous scales will be based on observed data only. However, the number of patients with missing observations will be provided

- Time-to-event data: Missing outcomes due to different reasons will be handled using different censoring rules. The censoring rules are specified as part of the definition of the analysis variables.

- Analysis windows: For summaries about AE, exposure and tumor assessments, Cycles based on CRF data will be used. For certain other measurements such as Vital signs, a window defined around the date of treatment may be considered. Details will be provided in the SAP.

13.6 INTERIM ANALYSIS

The objective of the interim analysis is to provide a methodological rationale and decision rules to the members of the DMC to either recommend to continue the study as planned or to stop earlier the study because of already demonstrated efficacy given the pre-specified α-spending O'Brien Fleming boundaries or because of futility boundaries crossing. Further details will be provided in the DMC charter.

The interim analysis of OS is planned to stop for futility or overwhelming efficacy when approximately 205 OS events (40% information fraction) have occurred. The one-sided nominal significance level will be 0.0004 based on a O'Brien-Fleming α-spending function. If the p-value of the one-sided logrank test is <0.0004 at the time of interim analysis, considerations should be given to stop the trial for overwhelming efficacy of aflibercept + gemcitabine versus placebo + gemcitabine. Futility boundary, based on a Gamma(-4) β-spending function, will be crossed if the hazard ratio is ≥ 1.05 in favor of the gemcitabine plus placebo arm.

13.7 CLINICAL STUDY REPORT ANALYSES

The clinical study report will be issued with all data collected up to the end of the cycle ongoing on 11 September 2009. The patients continuing to receive study treatment will be identified and will continue to provide limited safety data for result reporting. The limited data collection (ie, at least serious adverse events, and reason for end of treatment) will ultimately be added to the clinical study report following the termination of these patients from the study. This re-exposure data from these patients will be added as an addendum to the clinical study report in the form of at least updated patient listings and updated patient narrative.

14 ETHICAL AND REGULATORY STANDARDS

14.1 ETHICAL PRINCIPLES

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for Good Clinical Practice (GCP).

14.2 LAWS AND REGULATIONS

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country(ies) in which the Clinical Trial is performed, as well as any applicable guidelines.

14.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the Patient of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the IRB/IEC. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the Clinical Trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/IEC for approval/favorable opinion.

14.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator’s Brochure, Investigator’s CV, etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational Product will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigators undertake to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the Case Report Form [CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems. These monitoring visits, will include but not be limited to review of the following aspects : patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AE documentation, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. The Informed Consent Form will include a statement by which

the patient allows the Sponsor's duly authorized personnel, the IRB/IEC, and the regulatory authorities to have direct access to original medical records which support the data on the Case Report Forms (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation.

In this study an electronic CRF will be used to collect part of the requested information for all enrolled patients. All CRFs should be completed in their entirety to ensure accurate interpretation of data.

The computerized handling of the data by the Sponsor after receipt of the CRFs may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned.

A separate manual will describe in detail the procedures for using the electronic CRF. The sponsor is responsible for ensuring that appropriate material is available at the investigative sites for completion of the electronic CRFs or for providing this material, if needed.

15.5 USE OF COMPUTERIZED SYSTEMS

Procedures shall be employed and controls designed to ensure the confidentiality of electronic records. Such procedures and controls shall include validation of systems to ensure accuracy and reliability, ability to generate accurate and complete copies of records, protection of records to enable retrieval, use of secure, computer-generated, time-stamped entries, use of operational system checks, use of device checks to determine validity of source data input, determination that person who develop, maintain, or use such systems have adequate education and training, the establishment and adherence of written policies to deter record falsification, the use of appropriate controls over systems documentation including the distribution of or use of documentation for system operation and maintenance, and revision and change control procedures which document time-sequenced development and modifications of systems documentation.

16 ADMINISTRATIVE RULES

16.1 CURRICULUM VITAE

An updated copy of the curriculum vitae limited to the experience, qualification and training of each Investigator and Sub-Investigator will be provided to the Sponsor prior to the beginning of the Clinical Trial.

16.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

It is recommended that the Investigator retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the Clinical Trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

17 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential. The Investigator and any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this Clinical Trial Protocol and other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.

18 PROPERTY RIGHTS

All information, documents and Investigational Product provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the Clinical Trial.

As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

19 DATA PROTECTION

- The patient's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

20 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy which covers the liability of the Investigator. This insurance policy is in accordance with local laws and requirements.

An insurance certificate will be provided to the Investigator in countries requiring this document.

The insurance of the Sponsor does not relieve the Investigator and the collaborators of any obligation to maintain their own liability insurance policy as required by applicable law.

21 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

22 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

22.1 DECIDED BY THE SPONSOR IN THE FOLLOWING CASES:

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all Investigational Product, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice;
- If the total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

22.2 DECIDED BY THE INVESTIGATOR

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate IRB/IEC and Health Authorities should be informed according to applicable regulatory requirements.

23 CLINICAL TRIAL RESULTS

- The Sponsor will be responsible for preparing a Clinical Study Report and to provide a summary of study results to Investigator;
- When the data from all investigational sites have been fully analyzed by the Sponsor, the latter will communicate the results of the Clinical Trial to the Investigator(s).

24 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the Study and/or results of the Study the sponsor's prior written consent, being understood that the sponsor will not unreasonably withhold its approval.

If the Study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol. However, if no multicenter publication has occurred within twelve (12) months of the completion of this Study at all sites, the investigator shall have the right to publish or present independently the results of this Study patient to the review procedure set forth herein.

The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the Study for review and comment at least thirty (30) days in advance of any presentation or submission for publication. In addition, if requested by the sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed ninety (90) days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

If the study is conducted with the support of a Steering Committee, the latter may define specific rules for publication.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

For the main publication, authors ranking will be based on the number of eligible patients included by centers (only 1 author per center) and the principal investigator will be at least the last author.

25 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to Clinical Trial Patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this Clinical Trial Protocol.

Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.

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27 APPENDICES

Appendix A Cockroft-Gault Formula

Cockroft-Gault Formula [39]

$$\text{Creatinine Clearance} = \frac{(140 - \text{Age [yrs]}) \times \text{Body Mass (kg)}}{\text{Plasma Creatinine (mg/dL)} \times 72} \times \text{Gender Correction Factor}$$
$$(\text{male}: 1.00;\ \text{female}: 0.85)$$

Appendix B ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix C Response evaluation criteria in solid tumors (RECIST) quick reference (41)

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of the 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
Stable disease (SD)	Neither sufficient shrinkage to quality for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response / Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions[1]

[1] Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician. Should prevail and the progression status should be confirmed later on by the review panel (or study chairmen).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for

response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these

subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

- The 95% confidence intervals should be provided.

Appendix D National Cancer Institute Common Terminology Criteria for Adverse Events

- Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

- When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

- The evaluator must attempt to discriminate between disease / treatment and related signs / symptoms.

- An accurate baseline prior to therapy is essential.

See [40] Common Terminology Criteria for Adverse Events (CTCAE) v3.0 March 31, 2003, Publish Date: August 9, 2006 (http://ctep.info.nih.gov/reporting/ctc_v30.html).

Appendix E Visual Analog Scale

AVE0005 EFC10547	Country No. _____	Center No. _____	Subject No. _____	Visit ____

TO BE COMPLETED BY PATIENT

Clinical Evaluation of Pain Severity

Instructions: If you have had no pain during the past 24-hours, you may circle the words "No Pain" or make an "**X**" at the very left end of the scale. If your average pain during the past 24-hours has been Worst Possible Pain, you may circle the words "Worst Possible Pain" or make an "**X**" at the very right end of the scale. If your average pain has been between these two extremes, make an "**X**" on the line somewhere between the two ends, indicating the average severity of your pain during the past 24-hours.
Place an "**X**" on the line that shows what your pain was like, on average, over the past 24-hours.

Date: ____/____/____
(day/month/year)

No Pain ——————————————— Worst Possible Pain ---------- mm

Date: ____/____/____
(day/month/year)

No Pain ——————————————— Worst Possible Pain ---------- mm

Date: ____/____/____
(day/month/year)

No Pain ——————————————— Worst Possible Pain ---------- mm

Date: ____/____/____
(day/month/year)

No Pain ——————————————— Worst Possible Pain ---------- mm

Date: ____/____/____
(day/month/year)

No Pain ——————————————— Worst Possible Pain ---------- mm

Date: ____/____/____
(day/month/year)

No Pain ——————————————— Worst Possible Pain ---------- mm

Date: ____/____/____
(day/month/year)

No Pain ———————————————— Worst Possible Pain --------------------- mm

Date: ____/____/____
(day/month/year)

No Pain ———————————————— Worst Possible Pain --------------------- mm

Date: ____/____/____
(day/month/year)

No Pain ———————————————— Worst Possible Pain --------------------- mm

Date: ____/____/____
(day/month/year)

No Pain ———————————————— Worst Possible Pain --------------------- mm

Date: ____/____/____
(day/month/year)

No Pain ———————————————— Worst Possible Pain --------------------- mm

Date: ____/____/____
(day/month/year)

No Pain ———————————————— Worst Possible Pain --------------------- mm

Date: ____/____/____
(day/month/year)

No Pain ———————————————— Worst Possible Pain --------------------- mm

Date: ____/____/____
(day/month/year)

No Pain ———————————————— Worst Possible Pain --------------------- mm

Date: ____/____/____
(day/month/year)

Date of Day 1 Cycle N: _____/_____/_____
(day/month/year)

Drug Name, Strength and Route	Day 1 Dose	Day 2 Dose	Day 3 Dose	Day 4 Dose	Day 5 Dose	Day 6 Dose	Day 7 Dose	Day 8 Dose	Day 9 Dose	Day 10 Dose	Day 11 Dose	Day 12 Dose	Day 13 Dose	Day 14 Dose	Day 15 Dose	Day 16 Dose	Day 17 Dose	Day 18 Dose	Day 19 Dose	Day 20 Dose	Day 21 Dose	Day 22 Dose	Day 23 Dose	Day 24 Dose	Day 25 Dose	Day 26 Dose	Day 27 Dose	Day 28 Dose
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PAIN MEDICATION

Patient Initials _____

Day of Week _____ Date _____/_____/_____|
(day) (month) (year)

Please list the type of pain relief (analgesic) medication taken over the last 24 hours and the amount. **Only information about pain medication is needed.** Please do not include medication for other conditions (e.g. heart problems).

This section to be completed by site personnel				This column is to be completed by the patient ↓
Drug / Therapy (Brand or Generic Name)	Dose	Unit	Route	Number of Doses / 24 hours

PAINMED1 - 09-JUN-2004

Appendix F Morphinic Equivalent

Analgesic use will be recorded in a diary. The Sponsor or Sponsor's designate will convert the analgesic dose to the analgesic score (AS) utilizing the following table.

Preferred Term Decode	Route	Conversion Factor
Acetylsalicylic Acid	Oral	0.008
Acetylsalicylic Acid	Rectal	0.008
Indomethacin	Oral	0.07
Indomethacin	Rectal	0.07
Phenylbutazone	Oral	0.02
Phenylbutazone	Rectal	0.02
Codeine	Sublingual	0.08
Codeine	Intramuscular	0.08
Codeine	Intravenous	0.08
Codeine	Oral	0.05
Codeine	Rectal	0.05
Codeine	Subcutaneous	0.08
Pethidine	Sublingual	0.1
Pethidine	Intramuscular	0.1
Pethidine	Intravenous	0.1
Pethidine	Oral	0.033
Pethidine	Rectal	0.033
Pethidine	Subcutaneous	0.1
Dextropropoxyphene	Oral	0.066
Dextropropoxyphene	Rectal	0.066
Paracetamol	Oral	0.008
Paracetamol	Rectal	0.008
Salicylic Acid	Oral	0.008
Salicylic Acid	Rectal	0.008
Morphine	Sublingual	1
Morphine	Intramuscular	1
Morphine	Intravenous	1
Morphine	Oral	0.33
Morphine	Rectal	0.33

Preferred Term Decode	Route	Conversion Factor
Morphine	Subcutaneous	1
Metamizole Sodium	Oral	0.005
Metamizole Sodium	Rectal	0.005
Mefenamic Acid	Oral	0.01
Mefenamic Acid	Rectal	0.01
Oxycodone	Sublingual	0.67
Oxycodone	Intramuscular	0.67
Oxycodone	Intravenous	0.67
Oxycodone	Oral	0.33
Oxycodone	Rectal	0.33
Oxycodone	Subcutaneous	0.67
Aminophenazone	Oral	0.005
Aminophenazone	Rectal	0.005
Pentazocine	Sublingual	0.33
Pentazocine	Intramuscular	0.33
Pentazocine	Intravenous	0.33
Pentazocine	Oral	0.11
Pentazocine	Rectal	0.11
Pentazocine	Subcutaneous	0.33
Oxyphenbutazone	Oral	0.02
Oxyphenbutazone	Rectal	0.02
Hydrocodone	Oral	0.33
Hydrocodone	Rectal	0.33
Levorphanol	Sublingual	5
Levorphanol	Intramuscular	5
Levorphanol	Intravenous	5
Levorphanol	Oral	2.5
Levorphanol	Rectal	2.5
Levorphanol	Subcutaneous	5
Methadone	Sublingual	1
Methadone	Intramuscular	1
Methadone	Intravenous	1
Methadone	Oral	0.5
Methadone	Rectal	0.5
Methadone	Subcutaneous	1

Preferred Term Decode	Route	Conversion Factor
Salsalate	Oral	0.007
Salsalate	Rectal	0.007
Hydromorphone	Sublingual	7
Hydromorphone	Intramuscular	7
Hydromorphone	Intravenous	7
Hydromorphone	Oral	1.33
Hydromorphone	Rectal	1.33
Hydromorphone	Subcutaneous	7
Ibuprofen	Oral	0.006
Ibuprofen	Rectal	0.006
Panadeine Co	Sublingual	0.08
Panadeine Co	Intramuscular	0.08
Panadeine Co	Intravenous	0.08
Panadeine Co	Oral	0.05
Panadeine Co	Rectal	0.05
Panadeine Co	Subcutaneous	0.08
Fentanyl	Sublingual	50
Fentanyl	Intramuscular	50
Fentanyl	Intravenous	50
Fentanyl	Oral	50
Fentanyl	Rectal	50
Fentanyl	Subcutaneous	50
Fentanyl	Topical	50
Fentanyl	Transdermal	50
Oxymorphone	Sublingual	10
Oxymorphone	Intramuscular	10
Oxymorphone	Intravenous	10
Oxymorphone	Oral	2
Oxymorphone	Rectal	2
Oxymorphone	Subcutaneous	10
Naproxen	Oral	0.01
Naproxen	Rectal	0.01
Ketoprofen	Oral	0.05
Ketoprofen	Rectal	0.05
Diclofenac	Oral	0.1

Preferred Term Decode	Route	Conversion Factor
Diclofenac	Rectal	0.1
Tolmetin	Oral	0.008
Tolmetin	Rectal	0.008
Mepergan	Oral	0.1
Mepergan	Rectal	0.1
Fenoprofen	Oral	0.01
Fenoprofen	Rectal	0.01
Sulindac	Oral	0.25
Sulindac	Rectal	0.25
Flurbiprofen	Oral	0.05
Flurbiprofen	Rectal	0.05
Buprenorphine	Sublingual	33
Buprenorphine	Intramuscular	33
Buprenorphine	Intravenous	33
Buprenorphine	Subcutaneous	33
Diflunisal	Oral	0.01
Diflunisal	Rectal	0.01
Butorphanol	Sublingual	5
Butorphanol	Intramuscular	5
Butorphanol	Intravenous	5
Butorphanol	Subcutaneous	5
Piroxicam	Oral	0.5
Piroxicam	Rectal	0.5
Meclofenamic Acid	Oral	0.05
Meclofenamic Acid	Rectal	0.05
Nalbuphine	Sublingual	1
Nalbuphine	Intramuscular	1
Nalbuphine	Intravenous	1
Nalbuphine	Subcutaneous	1
Tramadol	Oral	0.2
Tramadol	Rectal	0.2
Etodolac	Oral	0.01
Etodolac	Rectal	0.01
Alfentanil	Sublingual	3
Alfentanil	Intramuscular	3

Preferred Term Decode	Route	Conversion Factor
Alfentanil	Intravenous	3
Alfentanil	Subcutaneous	3
Nabumetone	Oral	0.01
Nabumetone	Rectal	0.01
Oxycocet	Oral	0.33
Oxycocet	Rectal	0.33
Oxaprozin	Oral	0.008
Oxaprozin	Rectal	0.008
Ketorolac	Sublingual	0.25
Ketorolac	Intramuscular	0.25
Ketorolac	Intravenous	0.25
Ketorolac	Oral	0.25
Ketorolac	Rectal	0.25
Ketorolac	Subcutaneous	0.25
Tylenol PM	Oral	0.008
Tylenol PM	Rectal	0.008
Choline Magnesium Trisalicylate	Oral	0.007
Choline Magnesium Trisalicylate	Rectal	0.007
Hydrocodone Compound	Oral	0.33
Hydrocodone Compound	Rectal	0.33
Celecoxib	Oral	0.025
Celecoxib	Rectal	0.025
Rofecoxib	Oral	0.4
Rofecoxib	Rectal	0.4

Appendix G Specialized blood sample collection, handling and shipping

Recommended methods for pharmacokinetic, the assay of free endogenous VEGF and anti-aflibercept antibody blood sample collection and handling

Since study treatment is administered intravenously, blood samples for pharmacokinetic analysis should not be collected from the arm where study treatment is infused, or from a central line used for study treatment administration. For samples collected through a catheter, 1 mL of blood should be withdrawn and discarded at each sampling time to ensure that the solution used to maintain catheter patency does not dilute the blood sample.

It is extremely important to collect all blood samples as close to the protocol-specified times as possible. The reasons for any missed or lost blood samples should be documented. Both the scheduled and actual dates/times of blood collection should appear on the blood collection record at the study site. The times of aflibercept administration should also be precisely recorded.

Blood collection for aflibercept pharmacokinetic analysis in CTAD plasma

At the protocol-specified intervals indicated in Sections 9.3, "CTAD" vacutainer tubes (containing 1 mL of citrate buffer, sodium citrate, and 4.2 mg of citric acid) will be used to collect 4 mL of whole blood from patients for plasma preparation for the determination of circulating free aflibercept and VEGF: aflibercept complex levels for pharmacokinetic analysis.

Because platelet lysis can release VEGF into the serum and possibly affect aflibercept measurements, it is important to carefully follow the steps outlined below:

1. Draw blood slowly, using the largest-bore catheter that is feasible for the patient and transfer blood to a CTAD vacutainer tube (B-D Hemogard, sedimentation rate determination 4.5 mL tubes), being careful to minimize agitation of the sample.
2. gently mix tube by inverting 4 times.
3. Centrifuge at 2000 x g for 15 minutes at room temperature within 1 hour of blood draw.
4. Within 30 minutes after centrifugation, draw off plasma very slowly with transfer pipette to within 0.5 cm of the buffy coat, taking great care not to disturb the buffy coat (any contamination may invalidate the assay).
5. Pipette the plasma specimen into two separate plastic cryovials.
6. Complete corresponding lines for each blood draw on the shipping log. Include patient identification number, initials, and date of specimen collection.
7. All specimens must be stored frozen at -20°C (or colder) in a freezer that is not frost-free until shipped to Regeneron.
8. The Regeneron Specimen Log Sheets must be completed and included along with all shipments to Regeneron.

9. Only the primary samples of each patient should be sent with the first shipment to ensure that duplicates are available at the site for backup in case of damage during shipment.
10. On the day specimens will be shipped, please notify Regeneron to expect arrival.

Sufficient dry ice is to be included for samples to remain frozen for at least 48 hours (recommend at least 14 lbs. of dry ice).

For free aflibercept and VEGF: aflibercept complex assays, the transport of plasma samples from the clinical site to Regeneron Pharmaceuticals, Inc. will take place in containers of solid CO2 and be coordinated with:

Blood collection for Anti- Aflibercept Antibody analysis

At the protocol-specified intervals indicated in Sections 9.3, red-top vacutainer tubes without clot activator will be used to collect 4 mL of whole blood from patients for serum preparation for the analysis of anti-aflibercept antibodies formation. The following procedures should be followed:

1. Complete the pre-printed labels with Investigator's name, patient identification numbers, initials and date of specimen collection.
2. Allow serum to clot for 30 minutes. Spin at 2000 x g for 15 minutes to separate clot from serum.
3. Pipette the serum specimen into two separate plastic cryovials (supplied by Regeneron Pharmaceuticals, Inc.).
4. Complete corresponding lines for each blood draw on the shipping log. Include: patient identification number, initials, date of specimen collection.
5. All specimens must be stored frozen at -20°C (or colder) until shipped to the laboratory designated by Regeneron Pharmaceuticals, Inc.
6. The Specimen Log Sheet must be completed and included along with all shipments.
7. Only the primary samples of each patient should be sent with the first shipment. This is to ensure that in case of damage during shipment there are duplicates at the site for backup.
8. On the day you will be shipping specimens, please notify [redacted] or designee at Regeneron to expect arrival of the package.

Sufficient dry ice is to be included for samples to remain frozen for at least 48 hours (recommend 14 lbs. of dry ice).

For the analysis of anti-aflibercept antibodies, the transport of serum samples from the clinical site to Regeneron Pharmaceuticals, Inc. will take place in containers of solid CO2 and be coordinated with:

[redacted]

Blood collection for the assay of free endogenous VEGF

Blood samples (4 ml) will be collected in **CPD (or ACD) tubes** and centrifuged at +4°C, at 2000 g for 20 minutes. The plasma will be transferred into two polypropylene screw caps tubes (500 µL in each tube as a minimum) and frozen immediately at -20°C in the upright position within 1 hour after the puncture.
All specimens must be stored frozen at -20°C until shipped to sanofi-aventis
The Specimen Log Sheet must be completed and included along with all shipments.
One week before specimen shipment, please notify [redacted] to expect arrival of the package.

The plasma free VEGF concentrations will be determined at sanofi-aventis, GMPK Alfortville under the responsibility of [redacted] at the following address:

[redacted]

Appendix H New York Heart Association Classification

Functional Class	Description
0	No cardiac disease or limitations
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea or palpitation.
II	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina.
III	Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.