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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** AVE0005 (aflibercept)	**Study Identifiers:** **Study code:** TCD6117
Title of the study: A Phase 1, dose-escalation, sequential-cohort study of the safety, tolerability, and pharmacokinetics of intravenous AVE0005A (VEGF Trap) in combination with intravenous oxaliplatin/5-fluorouracil/leucovorin administered every 2 weeks in subjects with advanced solid malignancies	
Study center(s): 3 study centers in United States	
Study period: Date first patient enrolled: 26/Apr/2005 Date last patient completed: 29/Apr/2008	
Phase of development: Phase 1	
Objectives: *Primary*: To determine dose-limiting toxicity (DLT) and recommended Phase 2 dose (RPTD) of aflibercept (AVE0005A/Vascular Endothelial Growth Factor [VEGF] Trap) administered intravenously (IV) in combination with oxaliplatin/5- fluorouracil/leucovorin (FOLFOX4) therapy in patients with advanced solid malignancies. *Secondary*: To assess the safety profile of IV aflibercept when administered in combination with FOLFOX4. To determine the pharmacokinetics (PK) of IV aflibercept, oxaliplatin, and 5-fluorouracil (5-FU) when administered in combination. To determine the immunogenicity of IV aflibercept. To make a preliminary assessment of antitumor effects of the combination of aflibercept plus FOLFOX4. To make a preliminary assessment of functional status in cancer patients treated with IV aflibercept plus FOLFOX4.	
Methodology: This study was designed as an open label, multicenter, dose escalation study with sequential cohorts of 3 to 6 safety evaluable patients with advanced solid malignancies, treated with successively higher doses of aflibercept plus standard doses of FOLFOX4, every 2 weeks, in the absence of withdrawal criteria.	
Number of patients**:**	Planned: 23 to 32 Enrolled: 37 Treated: 32
Evaluated:	Efficacy: 21 Safety: 32 Pharmacokinetics: 31
Diagnosis and criteria for inclusion: Adult patients with histologically or cytologically confirmed solid malignancy that was metastatic or unresectable, with adequate organ and bone marrow function and recovered from any previous therapy, and for whom standard curative measures do not exist, but for whom FOLFOX4 treatment was appropriate.	

Study treatments

Investigational medicinal product: Aflibercept

Route of administration: IV over at least 1 hour

Dose regimen: 2 mg/kg, 4 mg/kg, or 5 mg/kg

Duration of treatment: Patients were administered aflibercept immediately followed by FOLFOX4 every 2 weeks in the absence of study withdrawal criteria (patient request, Investigator decision, Sponsor request, Grade 3 or 4 toxicities as defined in the protocol, disease progression, withdrawal of consent, patient lost to follow-up, and concomitant treatment in violation of protocol parameters).

Duration of observation: From date of informed consent until last aflibercept dose + 60 days.

Combination therapy: FOLFOX4: oxaliplatin (Eloxatin™), 5-Fluorouracil, and leucovorin calcium

Dose: Commercial agent; per package insert

Administration: Oxaliplatin 85 mg/m^2 in 250-500 mL D5W IV over 2 hours on Day 1, together with leucovorin 200 mg/m^2 in D5W IV over 2 hours on Day 1, followed by 5-FU 400 mg/m^2 IV bolus over 2-4 minutes, then 600 mg/m^2 in 500 mL D5W IV continuous infusion over 22 hours on Day 1, followed by leucovorin 200 mg/m^2 IV over 2 hours on Day 2, followed by 5-FU 400 mg/m^2 IV bolus then 600 mg/m^2 IV continuous infusion over 22 hours on Day 2.

Criteria for evaluation:

Safety: Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, and laboratory safety tests (including complete blood counts, serum chemistries, and urinalyses) were obtained prior to drug administration and at designated intervals throughout the study. Type, frequency, severity, cycle, seriousness, and relatedness of study treatment-emergent adverse events (TEAEs) were assessed according to the Medical Dictionary for Regulatory Activities (MedDRA) version 11 or immediate previous version. Laboratory abnormalities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI-CTCAE v.3.0).

Pharmacokinetic sampling times and bioanalytical methods: The PK analyses for aflibercept were performed on the safety evaluable population during Cycles 1 and 2 of therapy; PK samples for oxaliplatin and 5 FU were collected only in Cycle 1. Pharmacokinetic analysis of the data was carried out using non-compartmental analysis. Actual blood sampling times were used for PK analysis of free and bound aflibercept, oxaliplatin and 5-FU. Protocol-specified sampling times were used to prepare summary tables and graphs of mean plasma concentration as a function of time. For aflibercept, sampling was done pre-dose, and 1, 2, 4, 8, 24, 30, and 48 hours, and 7 days post-start of aflibercept infusion in Cycle 1 and Cycle 2, then pre-dose only on Day 1 of each cycle beyond Cycle 2, and again at the end of study treatment. For oxaliplatin, sampling was done pre-dose, 1, 3, 7, and 23 hours post-start of oxaliplatin infusion on Cycle 1 only. For 5-FU, samples were collected pre-dose, 2 and 21 hours post-start of 5-FU bolus #1, and pre-start of 5-FU bolus #2, then 1 and 21 hours post-start of 5-FU bolus #2 during Cycle 1 only. For VEGF, samples were collected for the assay of free endogenous VEGF at pre-dose on Day 1 of each odd-numbered cycle, upon study withdrawal, and 3 months after study treatment discontinuation.

Statistical methods:

The primary safety analysis was defined as the frequency of DLTs at Cycle 1 and 2 by dose level. Dose-limiting toxicities observed by dose levels were listed. All patients who received at least part of 1 dose of aflibercept are included in the safety analysis. Descriptive statistics are used to summarize patient characteristics, diagnoses, disposition, treatment administration and compliance, safety parameters, efficacy evaluations, anti-aflibercept antibodies, PK endpoints, and other biological parameters. The descriptive statistics include mean, standard deviation, median, minimum, and maximum values for continuous measures, and frequencies and percentages for categorical measures.

Summary:

Safety results: Overall, 32 patients received 237 cycles of aflibercept across the 3 doses levels: 2, 4, and 5 mg/kg. The average exposure (median) was 7.4 (6.5) cycles per patient across the 3 dose levels, with the highest number of 20 cycles administered at dose level 5 mg/kg in 1 patient. There was 1 DLT, febrile neutropenia, reported at the 5 mg/kg dose level. The most common non-biological TEAEs reported (≥30%) were fatigue, nausea, diarrhea, vomiting, anorexia, hypertension (50%), headache, constipation, mucosal inflammation, dysphonia (34%), epistaxis (34%), and abdominal pain. The most common Grade 3-4 non-biological TEAEs reported (≥10%) were hypertension and fatigue. Hypertension and proteinuria did not appear to be dose related. Hypertension was manageable with antihypertensive therapy. Proteinuria (Grade 2 or 3, based on laboratory values) was observed in 56% of the total patient population, and was often associated with hypertension but without any concomitant deterioration in renal function. Hematologic toxicity was commonly observed at all 3 aflibercept dose levels without a clear dose effect, taking into account the heavily pretreated nature of the patient population. Grade 3/4 serious adverse events (SAEs) possibly related to the combination study treatment regimen included events of gastrointestinal hemorrhage, epistaxis, hemorrhagic stroke, thrombocytopenia, hypertension, drug hypersensitivity, gastroesophageal reflux disease, hypotension, and reversible posterior leukoencephalopathy syndrome (RPLS). Two (2) patients experienced a fatal TEAE possibly related to the study drug: 1 hemorrhagic stroke (4 mg/kg) and 1 RPLS (5 mg/kg). One (1) patient had 1 isolated quantifiable anti-aflibercept antibody response value detected during therapy, without obvious clinical consequences.

Efficacy results: Sixteen (16) of 21 patients evaluable for efficacy had a partial response (2 PRs at 4 mg/kg and 2 PRs at 5 mg/kg) or stable disease (12 SD) based on Investigator-determined Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Five (5) patients derived a prolonged (≥24 weeks) clinical benefit (PR/SD) including 4 patients (2 with cholangiocarcinoma and 2 with pancreatic cancer) with confirmed PRs.

Pharmacokinetic results: Free aflibercept exposure increased approximately proportionally with dose in the dose range from 2 to 5 mg/kg. The concentration of bound trough aflibercept plateaued between 2 and 5 mg/kg, suggesting that free aflibercept was present in sufficient amount to bind all endogenous VEGF at these dose levels. Bound aflibercept steady-state was achieved approximately after the 3 first 14-day cycles. Target trough pharmacological exposure (free aflibercept/bound aflibercept ratio ≥1 in all patients) was reached at doses higher than 2.0 mg/kg IV given every 2 weeks. Free aflibercept levels remained in excess of bound aflibercept levels throughout the entire dosing interval at these doses. Oxaliplatin and 5-FU plasma concentrations were consistent with previously published values and were not markedly affected by co-administration of aflibercept.

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