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Sponsor / Company: Sanofi **Drug substance(s):** AVE0005 (aflibercept)	**Study Identifiers:** NCT01930552, U1111-1115-7286 **Study code:** TCD11470
Title of the study: A phase I study of the safety, tolerability, and pharmacokinetics of aflibercept in combination with FOLFIRI administered every 2 weeks in Chinese patients with advanced solid malignancies	
Study center(s): 2 clinical sites in China	
Study period: Date first patient enrolled: 26/Sep/2013 Date last patient completed: 17/Dec/2014 Cut-off Date for core part data analysis: 29/Sep/2014	
Phase of development: Phase 1	
Objectives: **Primary objective:** To assess the safety and pharmacokinetics (PK) of the dose of intravenously (IV) aflibercept used in western studies in combination with FOLFIRI given IV every 2 weeks in Chinese patients with solid tumors. **Secondary objectives:** • To make a preliminary assessment of antitumor effects of the combination of FOLFIRI plus aflibercept in patients with measurable disease (Response Evaluation Criteria for Solid Tumors [RECIST] 1.1), • To evaluate the immunogenicity of IV aflibercept.	
Methodology: This open-label study of aflibercept administered IV every 2 weeks in combination with FOLFIRI was designed to assess the safety and pharmacokinetics profile of the dose of aflibercept (4.0 mg/kg) in Chinese patients with solid tumors.	
Number of patients**:**	Planned: 20
	Randomized: 20
	Treated: 20
Evaluated:	
	Safety: 20
	Pharmacokinetics: 20
Diagnosis and criteria for inclusion: I 01. Histologically or cytologically confirmed solid malignancy that is metastatic or unresectable for which FOLFIRI treatment is appropriate. I 02. Patients must have received at least one prior line of treatment with any standard of care, who have failed the treatment, or who have not been eligible for standard of care for any reasons.	

Study treatments

Investigational medicinal product: aflibercept

Formulation: in 5 mM phosphate, 5 mM 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 10 mL vials filled with 8.4 mL content with a withdrawal content of 8.0 mL at a concentration of 25 mg/mL. The content of the vial must be diluted prior to infusion with 0.9% sodium chloride or 5% dextrose solution.

Route of administration: IV

Dose regimen: Aflibercept 4 mg/kg IV infusion for 1 hour, repeated every 2 weeks

Noninvestigational medicinal products: irinotecan, 5-FU, and leucovorin (FOLFIRI)

Formulation: Marketed formulations were used for irinotecan, 5-FU, and leucovorin

Route(s) of administration: IV

Dose regimen: Aflibercept administration was immediately followed by FOLFIRI: irinotecan 180 mg/m^2 IV infusion for 90 minutes, together with leucovorin 400mg/m^2 IV infusion for 2 hours on Day (D) 1, followed by 5-FU 400 mg/m^2 IV bolus then 2400 mg/m^2 continuous IV infusion for 46 hours starting on D1, repeated every 2 weeks

Duration of treatment: Patients were given aflibercept followed by FOLFIRI repeated every 2 weeks in the absence of study withdrawal criteria.

Duration of observation: From date of informed consent until last study treatment administration + 90 days.

Criteria for evaluation:

Efficacy: Tumor burden was assessed by CT or MRI scans. Tumor assessments were performed according to RECIST 1.1 criteria.

Safety: Safety was assessed through the collection of adverse events (AEs), laboratory data (hematology, chemistry, and urinalysis), and vital signs.

Immunogenicity: Presence of anti-aflibercept antibodies was assessed throughout the study before, during and after aflibercept treatment.

Pharmacokinetics: Concentration-time profiles to calculate following PK parameters:

- Aflibercept:
  - At Cycle 1:
    - Free aflibercept, maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), last concentration above lower limit of quantification (LLOQ) (C_{last}), time of Clast (t_{last}), area under the plasma concentration-time curve (AUC) up to last quantifiable time point (AUC_{last}), AUC extrapolated to infinity (AUC), AUC over the dosing interval (AUC0-14day), clearance (CL), volume of distribution at steady state (V_{ss}) and terminal elimination half- life ($t_{1/2z}$)
    - VEGF-bound aflibercept,: C_{max}, t_{max}, C_{last}, t_{last}, AUC_{last} and $AUC_{0\text{-}14\ day}$
  - Throughout the study:
    - Plasma concentration observed just before starting infusion on Day 1 of each odd-numbered cycle (C_{trough})
- Irinotecan: C_{max}, t_{max} , AUC, $t_{1/2z}$ for both irinotecan and SN-38 (active metabolite of irinotecan). Additionally, CL and V_{ss} for irinotecan only
- 5-FU: steady-state concentration (C_{ss}), clearance at steady-state (CL_{ss})

Pharmacokinetic sampling times and bioanalytical methods:

Aflibercept (Free and VEGF-bound aflibercept):

Cycle 1: prestart of aflibercept infusion, just before the end of infusion (EOI, 1 hour [h]), and 1h, 3h, 7h (Day 1), 23h, 29h (Day 2), 47h (D3) and 167 h (D8) after the end of aflibercept infusion.

Other Cycles after Cycle 1: pre-start of aflibercept infusion on D1 of Cycle 2 and every odd-numbered cycle; and then 30 and 90 days after the last administration of aflibercept.

Free and bound aflibercept were measured in plasma using a validated direct enzyme linked immunosorbant based assay (ELISA, Methods SOP PCL113 and SOP PCL2088, respectively). Concentrations of vascular endothelial growth factor (VEGF)-bound aflibercept were expressed as free aflibercept equivalent (ie, normalized to the amount of aflibercept present in the complex as adjusted bound aflibercept) before PK analysis. The corresponding lower limit of quantification (LLOQ) of free and VEGF-bound aflibercept were 15.6 ng/mL and 31.5 ng/mL, respectively.

Irinotecan and SN-38: prestart of aflibercept infusion, just before EOI (1.5h), 2h, 4h, and 23h poststart of irinotecan infusion during Cycle 1 only.

Concentrations of irinotecan and SN-38 were determined in plasma by a liquid chromatography with tandem mass spectrometry method (LC/MS-MS, Method PBRL-RD-1285). The LLOQ of irinotecan and SN-38 were 10.0 ng/mL and 1.00 ng/mL, respectively.

5-FU: prestart of aflibercept infusion, then 3h, 21h and 45h after IV bolus of 5-FU infusion during Cycle 1.

The plasma concentrations of 5-FU was determined by LC/MS-MS using a LLOQ of 5.00 ng/mL (Method Covance 8278-371).

Immunogenicity:

Samples for immunogenicity assessment were collected prestart of first aflibercept infusion, then on predose of each odd-numbered cycle and then 30 and 90 days after the last administration of aflibercept, and in specific circumstances when patient developed grade ≥2 systemic immunologic AE considered at least possibly related to the study drug, proteinuria >3.5 g/24h, or proteinuria of renal origin associated with hematuria.

The presence of anti-aflibercept antibodies was evaluated in serum using a nonquantitative assay, titer-based bridging immunoassay (Method SOP PCL2375).

Statistical methods:

The safety analysis and efficacy-related analysis were performed in all treated population, which included patients who took at least 1 dose (including partial dose) of study treatment (ie, aflibercept or FOLFIRI, regardless of correct/incorrect dose assignment) in this study. The safety analysis was descriptive on treatment emergent adverse events (TEAEs) and laboratory values. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE v.3.0).

PK parameters of free and VEGF-bound aflibercept, irinotecan and its active metabolite SN-38, and 5-FU were estimated using noncompartmental method and summarized with descriptive statistics (number of observations by treatment, arithmetic, and geometric means, standard deviation (SD), standard error of the mean (SE), coefficient of variation (CV), minimum, median, and maximum values).

RECIST 1.1-defined best overall response was determined for efficacy analysis.

Summary:

Population characteristics: A total of 20 Chinese patients were enrolled and treated in this study. Overall, 13 patients (65.0%) were male, the median age of all patients was 52 years (range: 26 to 70 years), and all patients had an eastern cooperative oncology group (ECOG) performance status of 1 at study entry. Prior treatment of the disease included: chemotherapy (20 patients, 100%), surgery (14 patients, 70.0%), radiotherapy (2 patients, 10.0%), and biologics (2 patients, 10%). The median number of prior anticancer regimens was 1.0 (range: 1 to 3). The vast majority of the patients had a colorectal cancer as the primary tumor site (15 patients, 75.0%).

Efficacy results: All of the 20 patients treated were evaluable for tumor response. Per RECIST 1.1, there were 6 confirmed partial responses (PR): 4 patients out of the 15 patients with colorectal cancer, 1 patient out of the 2 patients with esophagus cancer, and 1 patient out of the 2 patients with esophageal-gastric junction (EGJ) cancer.

Safety results: All patients have discontinued the study treatment at the time of the final database lock (23 January 2015): 12 patients discontinued due to disease progression, 7 patients due to patient's request, and 1 patient due to AE. Overall, 20 patients received a total of 193 cycles of study treatment (median number of cycles per patient: 9.0 cycles, range: 2 to 20 cycles). The total number of cycles with aflibercept was 170 cycles (median number of cycles per patient: 9.0 cycles, range: 2 to 19 cycles). Eighteen patients (90.0%) had cycle delays, mainly due to hematological toxicities (9 patients, 45.0%), asthenia (8 patients, 40.0%), gastrointestinal disorders (6 patients, 30.0%), proteinuria (4 patients, 20.0%), and hypertension (3 patients, 15.0%). Four patients (20.0%) required at least 1 dose reduction of aflibercept, while 5 (25.0%) and 6 (30.0%) patients required at least 1 dose reduction of irinotecan and 5-FU, respectively. The main reasons for dose reduction were gastrointestinal disorders (7 patients, 35.0%), protein urine present (6 patient, 30.0%), hypertension (3 patients, 15.0%), and hematological toxicities (3 patients, 15.0%).

All 20 patients experienced at least 1 TEAE while on study treatment. The most commonly reported all grade TEAEs were decreased appetite (18 patients, 90.0%), nausea (17 patients, 85.0%), vomiting (14 patients, 70.0%), hypertension (14 patients, 70.0%), leukopenia (11 patients, 55.0%), neutropenia (10 patients, 50.0%), asthenia (9 patients, 45.0%), diarrhea (9 patients, 45.0%), abdominal pain (8 patients, 40.0%), stomatitis (8 patients, 40.0%) , protein urine present (7 patients, 35.0%), and epistaxis (7 patients, 35.0%).

The most commonly reported Grade 3/4 TEAEs were neutropenia (7 patients, 35.0%), leukopenia (3 patients, 15.0%), febrile neutropenia (3 patients, 15.0%), hypertension (6 patients, 30.0%), protein urine present (4 patients, 20.0%), stomatitis (4 patients, 20.0%), and diarrhea (3 patients, 15.0%).

Hypertension (14 patients, 70.0%), hemorrhage events (7 patients, 35.0%), impaired wound healing (2 patients, 10.0%), and venous thrombosis (1 patient, 5.0%) were reported as TEAEs of special interest in this study.

Of note, laboratory abnormalities were only reported as AEs when they were considered clinically significant by the Investigator; therefore, the laboratory data is the primary source of data for a comprehensive and objective evaluation of the incidence of laboratory abnormalities (see below).

No death during study period was observed. Three patients each experienced a serious TEAE of venous thrombosis limb, hemorrhoids, and anastomotic stenosis, respectively; the events of venous thrombosis limb and hemorrhoids were considered to be possibly related to the study treatment. One patient discontinued the study treatment due to a TEAE of anastomotic stenosis, which was serious and considered as unrelated to the study treatment by the Investigator.

The most common laboratory abnormality was hematologic toxicity. Neutropenia was reported in 15 patients (75.0%), and 11 patients (55.0%) experienced a Grade 3 or 4 neutropenia. Anemia and thrombocytopenia were reported in 13 patients (65.0%) and 10 patients (50.0%), respectively, and most of the abnormalities were Grade <3. Liver and renal function test abnormalities were observed in few patients, and all were Grade 1. Proteinuria based on laboratory measurements was observed in 13 patients (65.0%), and 4 patients (20.0%) experienced a Grade 3 proteinuria.

No unexpected significant changes in vital signs, ECG, and physical findings were observed.

Immunogenicity results: No anti-aflibercept antibodies were detected in any of the patients evaluable for immunogenicity assessment (19 out of the 20 treated).

Pharmacokinetic results:

Aflibercept

Mean (CV %) PK parameters of free and VEGF-bound aflibercept obtained at Cycle 1 are summarized in the table below:

Aflibercept 4 mg/kg (N=20)

Free aflibercept

t_{max} [a]	C_{max}	$AUC_{0\text{-}14\ day}$	AUC	CL	CL/Weight	V_{ss}	V_{ss}/Weight	$t_{1/2z}$
(day)	(µg/mL)	(µg.day/mL)	(µg.day/mL)	(L/day)	(L/day/kg)	(L)	(L/kg)	(day)
0.04	64.8	249	291[b]	0.915[b]	0.0143[b]	5.87[b]	0.0915[b]	4.97[b]
(0.04-0.17)	(26)	(18)	(19)	(27)	(21)	(31)	(25)	(13)

VEGF-bound aflibercept

t_{max} [a] (day)	C_{max} (µg/mL)	$AUC_{0\text{-}14\ day}$ (µg.day/mL)	t_{last} [a] (day)	AUC_{last} (µg.day/mL)
14.01c	2.78c	19.8c	14.01c	20.8c
(12.88-15.94)	(22)	(31)	(12.88-15.94)	(28)

[a] Median (Min-Max), [b] N=19, [c] N=18, [d] N=13

Following a first administration of aflibercept (4 mg/kg), median t_{max} was observed at the end of infusion (median t_{max}=1h) for free aflibercept while VEGF-bound aflibercept concentrations increased regularly over first cycle and reached a C_{max} at the end of Cycle 1 (median t_{max}=14 days).
Free aflibercept was eliminated with a clearance of 0.9 L/day and a terminal half-life of 5 days. Volume of distribution was around 6 L. Variability on both free and VEGF-bound aflibercept PK parameters was low to moderate (13% to 31%).

Concomitant drugs:
Irinotecan: Following a first administration of irinotecan (180 mg/m^2), mean (CV %) of C_{max} and AUC of irinotecan was 2160 ng/mL (25%) and 15200 ngh/mL (20%), respectively. Irinotecan was eliminated with a clearance of 11.8 L/h/m² (31%) and a terminal half-life of about 5h. SN-38 showed lower exposure with a C_{max} and AUC_{last} of 35.8 ng/mL (48%) and 265 ngh/mL (36%), respectively, corresponding to around 3% of the parent drug exposure (on a molar basis).

5-FU: During IV infusion of 5-FU at 2400 mg/m², mean (CV%) steady state clearance was 79.4 L/h/m² (44%).

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