These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** AVE0005	**Study Identifiers:** NCT01148615, UTN U1111-1116-5774 **Study code:** TCD11382
Title of the study: A Phase 1, dose-escalation study of the safety, tolerability, and PK of intravenous aflibercept in combination with intravenous Docetaxel administrated every 3 Weeks in Chinese patients with advanced solid malignancies (Study number: TCD11382)	
Study center(s): 1 center in China	
Study period: Date first patient enrolled: 08/Jul/2010 Date last patient completed: 30/Dec/2011	
Phase of development: Phase 1, dose escalation	
Objectives: **Primary objective:** To confirm the dose of aflibercept in western studies by assessing the dose-limiting toxicity (DLT) of intravenous (IV) aflibercept when administered in combination with docetaxel given IV every 3 weeks in Chinese patients with solid tumors. **Secondary objectives:** • To assess the safety profile of IV aflibercept when administered in combination with docetaxel. • To determine the pharmacokinetic (PK) of IV aflibercept and docetaxel when administered in combination. • To make a preliminary assessment of antitumor effects of the combination of docetaxel plus aflibercept in patients with evaluable disease. • To evaluate the immunogenicity of IV aflibercept. • To measure endogenous free vascular endothelial growth factor (VEGF)	
Methodology: This was an open-label, single center, dose-escalation study of aflbercept when administered in combination with docetaxel in patients with advanced solid malignancies to confirm the dose of aflibercept in western studies based on DLTs during Cycle 1. When a selected dose of IV aflibercept in combination with docetaxel was determined, the safety profile, PK, antitumor activity, and other characteristics of the selected dose of aflibercept were explored in an expansion cohort to find out a recommended dose of aflibercept for further clinical development. Sequential cohorts of 3-6 patients with advanced solid malignancies were treated with successively higher doses of aflibercept together with fixed doses of docetaxel (75 mg/m^2) every 3 weeks. Dose escalation was a joint decision between the Sponsor and the Investigator and was based on DLT observed during Cycle 1. Enrollment at the next higher dose level was not to be proceeded before at least 3 patients treated at the current dose level had received at least 1 cycle of study treatment and their safety had been evaluated.	
The selected aflibercept dose was confirmed by both Investigator and Sponsor based on the highest aflibercept dose at which no more than 1 of a maximum of 6 patients experienced DLT during Cycle 1. Another 10 patients as an expansion cohort were enrolled in addition to the current cohort to receive the selected dose of IV aflibercept in combination with fixed doses of docetaxel every 3 weeks. The safety profile, PK, preliminary antitumor effect and other characteristics of IV aflibercept at the selected dose were further explored.	

Number of patients**:**	Planned: 22
	Randomized: 20
	Treated: 20
Evaluated:	
	Efficacy: 20
	Safety: 20
	Pharmacokinetics: 20

Diagnosis and criteria for inclusion:

Patients ≥18 years with histologically or cytologically confirmed solid malignancy, metastatic or unresectable who failed standard treatment or ineligible for standard treatment for safety reasons and for whom docetaxel treatment was appropriate.

Study treatments

Investigational medicinal product(s): Aflibercept in combination with docetaxel.

Formulation: Aflibercept was formulated as a sterile liquid to a final concentration of 25 mg/mL aflibercept. Marketed formulation of docetaxel with a concentration of 40 mg/mL was used.

Route(s) of administration: Aflibercept was administered by IV infusion over a period of 1 hour (at an infusion concentration of 4 mg/mL). The volume of drug administered to each patient was based on each patient's weight. Aflibercept was immediately followed by docetaxel administration.

Dose regimen: Patients were administered aflibercept then docetaxel on Day 1 of every 3 weeks. The initial dose of 4.0 mg/kg aflibercept (in combination with 75 mg/m^2 docetaxel) was escalated to 6.0 mg/kg, which was determined by whether the 4.0 mg/kg dose level group met the dose-escalation criteria. In the expansion cohort, aflibercept was administered at the selected dose.

Duration of treatment: Patients were given aflibercept followed by combination chemotherapy every 3 weeks in the absence of a definitive treatment discontinuation criterion.

Duration of observation: From the date of informed consent until the last dose of aflibercept + 90 days follow-up.

Criteria for evaluation:

Efficacy: Tumor burden was assessed by head, chest, abdomen, and pelvis computerized tomography (CT) or magnetic resonance imaging (MRI) scans done at baseline. Chest, abdomen, and pelvis CT or MRI scans were done on Day 21 of every even-numbered cycle, whenever disease progression was suspected, to assess a tumor response (complete response [CR] or partial response [PR]) and at the end of study treatment. Tumor assessments and responses were performed according to response evaluation criteria in solid tumors (RECIST) 1.1 criteria. Free VEGF as a biomarker was measured.

Safety:

- Selected dose as primary endpoint: The selected dose of aflibercept was defined as the dose at which 0 or 1of 3 to 6 patients experienced a DLT during the first cycle of the combination therapy. Once the selected dose was established with docetaxel at 75 mg/m², aflibercept was to be tested in an expansion cohort.
- Overall safety and tolerability profile: Safety and tolerability of this combination therapy were assessed through the collection of adverse events (AEs), laboratory data (hematology, chemistry, and urinalysis), vital signs, physical exam, Eastern Cooperative Oncology Group (ECOG) performance status, and assay for anti-aflibercept antibodies.

Pharmacokinetics: Individual PK parameters were assessed after the first administration of aflibercept and docetaxel:

- For free and VEGF-bound aflibercept

  Concentration before dosing (C_{trough}), maximum plasma concentration (C_{max}), area under concentration time curve ($AUC_{0\text{-}21}$ day and AUC_{last}) for both free and VEGF-bound aflibercept, AUC, Clearance (CL), volume of distribution at steady state (V_{ss}), terminal elimination half-life ($t_{1/2z}$) only for free aflibercept.
- For docetaxel

  C_{max}, AUC, CL, V_{ss}, and $t_{1/2z}$

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

- **Aflibercept (free and VEGF-bound):** Blood samples were taken during Cycle 1 at predose, end of infusion (EOI), 1, 3, 7, 23, 29, 47, 167, and 335 hours post EOI (ie, 0.0417, 0.0833, 0.167, 0.333, 1, 1.25, 2, 7 and 14 days) then at predose for subsequent cycles and Day 30 and Day 90 after last aflibercept dose. Free and VEGF-bound aflibercept were measured in plasma using an enzyme-linked immunosorbent based assay (ELISA). Concentrations of VEGF-bound aflibercept were to be normalized to the amount of aflibercept present in the complex (adjusted bound aflibercept) before PK analysis. The lower limit of quantification (LLOQ) was 0.0156 and 0.0315 µg/mL, respectively for free and VEGF-bound (adjusted) aflibercept.
- **Docetaxel:** Blood samples were taken during Cycle 1, at predose of aflibercept, 30 minutes after start of infusion (in 3 first patients only), at EOI then 10 minutes, 2, 5, 7 (in 3 first patients only) and, 24 hours post EOI. Concentrations were measured in plasma by a validated electrospray liquid chromatography mass spectrometry (LC-MS/MS) method with a LLOQ of 1.00 ng/mL.
- **Immunogenicity:** Blood samples were collected at each odd-numbered cycle prior dosing and 1 and 3 months post-end of treatment. The presence of anti-aflibercept antibodies was evaluated in serum using a non quantitative, titer-based bridging immunoassay.
- **Endogenous VEGF:** Endogenous VEGF was assessed in plasma from samples collected at Cycle 1 prior dosing and 3 months post-end of treatment using an ELISA with LLOQ of 15 pg/mL.

Statistical methods:

Safety: The primary safety analysis was defined as the frequency of DLTs at Cycle 1 to define the selected dose and was conducted based on DLT evaluable population. The safety profile of the selected dose of aflibercept in combination with docetaxel was evaluated in the treated population. Type, frequency, seriousness, and relatedness of treatment emergent adverse events (TEAEs), worst grade of laboratory parameters, and development of anti-aflibercept antibodies were presented descriptively by dose level. The national cancer institute (NCI) common terminology criteria for adverse events (CTCAE), version 3.0, were used to grade AEs and laboratory abnormalities.

Efficacy/antitumoral activity: The antitumor activity of the investigational product (IP) regimen was assessed through tumor response and evaluated with the RECIST 1.1 criteria performed. Endogenous free VEGF and tumor burden assessment were to be descriptively summarized by dose level for the treated population.

Pharmacokinetics: Pharmacokinetics parameters of free, VEGF-bound aflibercept and docetaxel were to be summarized with descriptive statistics. C_{max} and AUCs were assessed for dose proportionality and $t_{1/2z}$ and CL were assessed for dose effect with a linear mixed model.

Summary:

Population characteristics:

A total of 20 patients were enrolled, including 4 in the 4.0 mg/kg group and 16 in the 6.0 mg/kg group. One patient was excluded for DLT assessment because she received other anti-cancer therapies during Cycle 1. Therefore, the DLT evaluable population included 19 patients. All 20 patients included in the treated population for other safety and efficacy related evaluations.

Nine and 5 patients discontinued the study treatment because of AE and disease progression, respectively. Other 6 patients discontinued the treatment for “other reasons”, which was specified in the case report form (CRF) as “study treatment completion” since further study treatment continuation would be detrimental to the patient’s well being at the discretion of the Investigators.

There were 3 females and 17 males, with a median age of 45.5 years (range: 22 to 63) and an ECOG performance status of 0 or 1. Nine patients had history of thrombovascular and/or cardiovascular events and their risk factors, including 3 patients with hypertension and 5 patients being a smoker. The primary tumor sites were in either nasopharynx or lung. All patients had metastatic malignancy, except for 1 with locally advanced tumor. The median time between the first cancer diagnosis and the patients’ first treatment infusion was around 28 months. All patients had a measurable tumor at baseline with ≤3 organs involved in 70% of patients. The three most frequently involved organs were lymph nodes (95%), lungs (75%), and liver (50%). All patients had prior chemotherapy, of which 75% patient had prior radiotherapy. No patient had received surgical resection prior to study entry. The median number of anticancer regimens was 2.0 (range: 1 to 8). The median time between previous anti-cancer therapy and initiation of the study drug was 1.93 months. Four patients were on medication grouped under “antihypertensive medication” prior to entering the study, including 3 receiving Nifedipine. A total of 18 patients were receiving medication grouped under “antibiotics” and all of them had Corticosteroid nos. During the study treatment, 4 patients received antihypertensive medication and 19 patients took medications grouped under “antibiotics”. All 20 patients received hematopoietic growth factors, including granulocyte-colony stimulating factor (G-CSF) in 19 patients.

Efficacy results:

A total of 16 out of 20 patients were evaluable for best overall response, including all patients at the 4.0 mg/kg group and 12 patients at the 6.0 mg/kg group. Two PR and 1 stable disease were observed in the 4.0 mg/kg dose level, whereas 9 PR and 2 stable diseases were observed in the other dose level.

Mean endogenous free VEGF baseline concentrations were 33.26 pg/mL. At the follow-up visit, 90 days after last treatment, mean endogenous free VEGF plasma levels were around 2-fold higher (58.75 pg/mL).

Safety results:

Overall, a total of 20 patients were treated with aflibercept (4.0- 6.0 mg/kg) with docetaxel 75 mg/m^2 in this study. The DLT evaluable population included 19 patients. There were 3 females and 17 males with a median age of 45.5 years (range: 22-63), and an ECOG performance status of 0 or 1. The primary tumor sites were in nasopharyngeal region (16 patients, 80%) and lung (4 patients, 20%). The median number of prior anticancer regimens was 2.0 (range: 1-8). All patients had prior chemotherapy, and 9 patients (45%) had received molecular targeting agents previously.

Patients at aflibercept 4.0 mg/kg and 6.0 mg/kg dose level received total 14 and 45 cycles, respectively. The median number of cycles administered per patient was 3.5 at the both 4.0 mg/kg and 6.0 mg/kg dose levels. There was no dose reduction for either aflibercept or docetaxel in the study. Treatment cycle delays (>2 days) occurred in 1 of 4 (25%) patients at the 4.0 mg/kg dose level and in 4 of 16 (25%) patients at the 6.0 mg/kg dose level. The median relative dose intensity (RDI) of aflibercept per patient was 0.98 at the 4.0 mg/kg dose level and 1.00 at the 6.0 mg/kg dose level.

There was no DLT at the 4.0 mg/kg dose level and 1 DLT (neutropenic infection) at 6.0 mg/kg dose level in the first cycle.

All patients experienced at least 1 TEAE and related TEAE. One patient (25%) at the 4.0 mg/kg dose level and 14 patients (87.5%) at the 6.0 mg/kg dose level experienced ≥Grade 3 related TEAEs.

The frequently reported TEAE (all grade) at the 4.0 mg/kg dose level were stomatitis (75%), hypertension, dysphonia, cough, neck pain, and weight decreased (50% for each term). The frequently reported TEAEs (all grade) at the 6.0 mg/kg dose level were oropharyngeal pain (75%), stomatitis (68.8%), alopecia (56.3%), dysphonia (43.8%), insomnia (37.5%), neutropenic infection (31.3%), hypertension, cough, epistaxis, and pharyngeal inflammation (25% for each term).

The frequently reported ≥Grade 3 TEAEs at the 4.0 mg/kg dose level were febrile neutropenia, hypoacusis, stomatitis (25% for each term), and at the 6.0 mg/kg dose level were oropharyngeal pain (37.5%), neutropenic infection (31.3%), stomatitis (31.3%) and neutropenia (12.5%).

Serious TEAEs were reported in 1 of the 4 patients (25%) at the 4.0 mg/kg dose level and 7 of 16 (43.8%) at the 6.0 mg/kg dose level.

Four deaths (100%) were reported at the 4.0 mg/kg dose level, due to disease progression. Five deaths (31.3%) were reported at the 6.0 mg/kg dose (4 patients due to disease progression, 1 patient possibly related to a serious adverse event (SAE) of sudden hematemesis). One of 4 deaths due to disease progression occurred within 30 days of the last administration of aflibercept.

The most frequent TEAEs leading to cycle delays were vision blurred (25%) at the 4.0 mg/kg dose level and oropharyngeal pain and stomatitis (12.5%, each, all grades) at the 6.0 mg/kg dose level.

Hematological toxicities by laboratory test were observed at both dose levels (4.0 mg/kg and 6.0 mg/kg). The incidence of grade 3/4 neutropenia was 3 of 4 patients (75%) at the 4.0 mg/kg dose level and 14 of 16 patients (87.5%) at the 6.0 mg/kg dose level.

With regards to liver, renal and metabolic abnormalities, grade 3 hyponatremia was observed in 1 patient (25%) at the 4.0 mg/kg dose level. At the 6.0 mg/kg dose level, grade 3/4 laboratory abnormalities were hyponatremia (grade 4) in 1 patient and hypophosphatemia (grade 3) in 1 patient (6.3% each).

Regarding proteinuria, no patients developed proteinuria at the 4.0 mg/kg dose level. At the 6.0 mg/kg dose level, 2 patients had grade 1 proteinuria while 1 patient had grade 2 proteinuria.

All patients evaluable for immunogenicity (N=18) showed a negative response in the anti aflibercept antibodies assay after treatment.

Pharmacokinetic results:

Aflibercept:

Pharmacokinetic parameters of free and VEGF-bound aflibercept obtained after 1 dose of aflibercept (cycle 1) are summarized in the Table below:

Aflibercept PK parameters at Cycle 1

Mean ± SD (Geometric Mean) [CV%]	Free aflibercept		VEGF-bound aflibercept	
Aflibercept dose	**4.0 mg/kg**	**6.0 mg/kg**	**4.0 mg/kg**	**6.0 mg/kg**
N	4	16	3 [b]	15 [c]
C_{max} (µg/mL)	52.3 ± 7.40 (51.9) [14]	92.8 ± 17.7 (91.1) [19]	2.41 ± 0.447 (2.38) [19]	2.29 ± 0.587 (2.22) [26]
t_{max} [a] (day)	0.15 (0.06 - 0.19)	0.06 (0.06 - 0.19)	20.87 (14.02 - 21.79)	21.02 (14.02 - 31.93)
$AUC_{0\text{-}21\ day}$ (µg•day/mL)	182 ± 40.6 [b] (179) [22]	309 ± 63.5 [c] (301) [21]	31.1 ± 7.41 (30.5) [24]	28.2 ± 4.76 (27.9) [17]
$t_{1/2z}$ (day)	4.65 ± 0.899 [b] (4.59) [19]	5.32 ± 1.02 [c] (5.24) [19]	-	-
CL (L/day)	1.44 ± 0.255 [b] (1.42) [18]	1.17 ± 0.305 [c] (1.13) [26]	-	-
V_{ss} (L)	7.98 ± 1.45 [b] (7.90) [18]	6.39 ± 1.17 [c] (6.29) [18]	-	-

[a] Median (Min - Max)

[b] N=3 (Patient N°156001003 excluded from statistical analysis)

[c] N=15 (Patient N°156001007 excluded from statistical analysis)

Following administration of aflibercept at 4.0 and 6.0 mg/kg in combination with docetaxel at 75 mg/m², free aflibercept PK was characterized by a long $t_{1/2z}$ (4.9 days) and a low clearance (1.27 L/day) estimated across doses, and a low volume of distribution at steady-state (~ 7 L). Exposure to free aflibercept increased in a dose proportional manner while VEGF-bound aflibercept exposure remained similar. For a 1.5-fold increased in dose, free aflibercept C_{max} and AUC increased by around 1.7-fold. Steady state conditions were not reached at the end of the third cycle of treatment neither for free or VEGF-bound aflibercept.

Docetaxel:

When administered at 75 mg/m², docetaxel mean clearance value observed in the current study was 19.7 L/h/m².

Issue date: 15-Oct-2014