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:** AVE8062 (ombrabulin)	**Study Identifiers:** NCT01193595, EudraCT 2009-017797-20 **Study code:** TCD11379
Title of the study: An open-label, non-randomized, dose escalation, safety and pharmacokinetic phase I study of ombrabulin (AVE8062) in combination with bevacizumab administered by intravenous infusion every 3 weeks in patients with advanced solid tumors (2013)	
Study center(s): 4 centers: France, Italy (2 centers), and the United Kingdom	
Study period: Date first patient enrolled: 01/Sep/2010 Cutoff date: 27/Feb/2013	
Phase of development: Phase 1	

Objectives:

Primary objectives:

To determine the maximum administered dose (MAD) and the maximum tolerated dose (MTD) of ombrabulin in combination with best tolerated dose of bevacizumab based on the incidence of related dose-limiting toxicities (DLTs).

Secondary objectives:

- To assess the overall safety profile of the combination.
- To characterize the pharmacokinetic (PK) profile of both ombrabulin and bevacizumab when given in combination.
- To evaluate preliminary evidence of antitumor activity of the combination using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for solid tumors or both the international workshop response criteria and the revised response criteria for non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) patients.
- To assess the pharmacodynamic (PD) effect using dynamic contrast-enhanced ultrasonography (DCE-US), measuring circulating biomarkers (circulating endothelial cells [CEC], circulating endothelial progenitor cells [CEP], matrix metalloproteinase 9 [MMP9], stromal cell-derived factor 1 [SDF-1], vascular endothelial growth factor [VEGF], soluble VEGF receptor 2 [sVEGFR2], granulocyte colony-stimulating factor [G-CSF], thrombomodulin, vascular endothelial [VE]-cadherin).
- To evaluate potential predictive biomarkers on tumor samples.

Methodology:

This was an open-label, nonrandomized, dose escalation, safety, PD, and PK study of ombrabulin given in combination with bevacizumab administered 24 hours after the end of ombrabulin infusion.

The combination was to be administered every 3 weeks to patients with advanced solid tumors according to the following schedule:

Day 1 T0: ombrabulin administered as a 30-minute intravenous (IV) infusion.

Day 2 T0: bevacizumab administered as a 30- to 90-minute IV (decreasing with cycles) infusion 24 hours after the end of ombrabulin infusion.

Cohorts of 3 patients were to be treated at each dose level. The decision to escalate to the following dose level was based on the number of patients experiencing drug-related DLTs during Cycle 1. Only drug-related DLTs were to be taken into account for the dose escalation decision. A Bayesian dose-escalation design was to be used to determine the dose level to be given to the next cohort of patients and finally estimate the MTD of the combination.

The MTD was defined as the well tolerated dose with maximum confidence that the risk of DLT associated with the dose lies in an interval ranging from 20% to 35% (ie, targeted interval). The dose escalation phase was to be stopped when 6 DLT evaluable patients had been treated at the same dose level and the dose escalation model recommended current dose level as the MTD after model updating. This defined, after data was analyzed and reviewed by the Study Committee, the MTD for the combination.

At the end of dose escalation, an expanded cohort of 10 patients was to be treated at a preliminary recommended Phase 2 dose (pRP2D) selected, based on the overall safety data and potential effectiveness, between the highest safely administered dose of bevacizumab 10 mg/kg and 15 mg/kg combination regimens, in order to confirm safety and potential antitumor activity.

Number of patients: Planned: 40-70 as per DLT occurrence

Treated: 39

Evaluated for DLT: 38

Number of patients evaluated:

Efficacy: 37

Pharmacodynamics: 39

Safety: 39

Pharmacokinetics: 38

Diagnosis and criteria for inclusion:

- Histologically or cytologically proven solid malignant tumor with the exception of squamous non-small-cell lung cancer (NSCLC).
- Advanced neoplastic disease (ie, metastatic or locally unresectable advanced disease); NHL and HL in progression after standard therapy and for which intensive therapy was not indicated could be included.

Study treatments

Investigational medicinal products:

Formulation:

Ombrabulin

Ombrabulin was supplied as a single dose vial containing a total of 27.5 mg of ombrabulin in a 5.5 mL aqueous solution at the concentration of 5 mg/mL. Excipients: water for injection and hydrochloric acid.

Bevacizumab

Bevacizumab was supplied as commercial formulation (Avastin®): bevacizumab is supplied as a single dose vial containing 100 mg of bevacizumab in a 4 mL solution or 400 mg of bevacizumab in a 16 mL solution (concentration of 25 mg/mL).

Excipients: trehalose dihydrate, sodium phosphate, polysorbate 20, water for injections.

Route of administration: Ombrabulin and bevacizumab were administered by IV infusion every 3 weeks.

Dose regimen:

Ombrabulin: 8 Escalating doses from 8 to 50 mg/m^2 (8, 11.5, 15.5, 20, 25, 30, 35, and 50 mg/m^2).

Bevacizumab: 5 mg/kg in combination with 8 and 11.5 mg/m^2 of ombrabulin; 10 mg/kg in combination with 11.5 to 50 mg/m^2, and 15 mg/kg in combination with 25 to 50 mg/m^2. The dose of bevacizumab 15 mg/kg was added to the dose escalation steps after a protocol amendment.

Other intermediate dose levels could be tested for each treatment, after agreement between sponsor and Investigators (ie, bevacizumab between 5 and 10 mg/kg or other intermediate ombrabulin dose level).

On Day 1 of each cycle, the patients received ombrabulin as a 30-minute IV infusion and 24 hours following the completion of the ombrabulin infusion (Day 2), the patients received bevacizumab by IV infusion.

As per the Summary of Product Characteristics (SpC) of bevacizumab, the required IV administration was: first infusion over 90 minutes, second over 60 minutes, and later infusions over 30 minutes. However, for PK purposes, the first 2 infusions were to last 90 minutes, the third one 60 minutes, and the following ones 30 minutes.

Duration of treatment: The patients were to receive the treatments until disease progression, occurrence of an adverse event (AE or death) leading to treatment discontinuation, whichever comes first.

Duration of observation: The duration of the study for each patient was to include:

- An up to 28-day screening phase;
- 21-day study treatment cycles;
- An end of treatment visit (30 days after the last treatment infusion);
- Follow-up visits or patient contact every 30 days until further anticancer therapy, death, or progression for patients who discontinued treatment for safety reasons;
- An end of study visit.

The cutoff date (COD) for the global analysis of the study and for the issuing clinical report was defined as the date when the last treated patient had his 4th cycle course completed (30-day post-infusion = COD) or theoretical date if the last patient received less than 4 cycles, at a maximum. After this COD, patients were to receive the treatments until disease progression or occurrence of an AE (or death) leading to treatment discontinuation, whichever comes first; they were only to be followed for investigational product (IP) administration, further therapy, serious adverse events (SAEs), drug-related AEs, and AEs leading to study treatment discontinuation.

Criteria for evaluation:

Efficacy: The efficacy assessment was based on the objective tumor response as defined by the RECIST 1.1 for solid tumors or both the international workshop response criteria and the revised response criteria for NHL and HL patients in evaluable patients. These assessments were to be made at least every 2 cycles or less frequently if indicated; the Investigator determined the tumor response. Furthermore, a partial or complete response had to be confirmed on a second examination done at least 4 weeks apart, in order to be documented as a confirmed response to therapy (not mandatory in Phase 1 studies).

Safety: The safety assessment included: treatment-related AEs defined as DLTs at Cycle 1 (primary endpoint), treatment-emergent adverse events (TEAEs), SAEs, laboratory abnormalities, physical examination, vital signs, electrocardiogram (ECG) in all cycles, chest X-ray, echocardiography, and cardiac markers measurement every 2 cycles. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0 was to be used in this study to grade clinical and laboratory AEs. Safety profile was based on incidence, severity, and cumulative nature of TEAEs.

Pharmacodynamic assessments

DCE-US :

- Cycle 1: before infusion of ombrabulin, 24 hours after the end of ombrabulin infusion (Day 2, before bevacizumab infusion) and Day 8.
- Cycle 2: 24 hours after the end of ombrabulin infusion (Day 2, before bevacizumab infusion), Day 8 and Day 21.

- Even cycles: Day 21.

Circulating biomarkers measurement:

Plasma samples were to be collected at Cycle 1 for biomarkers analysis as follows:

- CEP & Plasmatic Proteins (MMP9, SDF-1, VEGF, sVEGFR2, G-CSF, and thrombomodulin): before ombrabulin infusion (Day 1), Day 1 at T4h after the end of ombrabulin infusion, Day 4, Day 8, Day 15 and Day 21.
- CEC: before ombrabulin infusion (Day 1), Day 1 at 6, 8 h, and 24 hours after the end of ombrabulin infusion (Day 2) and before bevacizumab infusion.
- VE-cadherin: before ombrabulin infusion (Day 1), Day 1 at 8 and 24 hours after the end of ombrabulin infusion (Day 2) and before bevacizumab infusion, Day 8, Day 15 and Day 21.

Biopsies:

Potential predictive biomarkers of treatment outcome (thrombospondin-1, CD105, CD31 & CD34 and Fli-1) were to be assessed on biopsies performed before Cycle 1.

Potential predictive biomarkers of responsiveness to antiangiogenic drugs were to be assessed on biopsies performed before Cycle 1, during Cycle 1 and the last in case of progression disease on patients who had had a benefit from the treatment (at least stable disease as best overall response).

Pharmacokinetics

Following PK parameters of ombrabulin, its active metabolite RPR258063, and total bevacizumab in combination were to be determined using non-compartmental method first. Compartmental methods were to be also used when possible.

- Ombrabulin: C_{max}, AUC_{last}, AUC, CL, V_{ss}, and $t_{1/2}$
- RPR258063: t_{max}, C_{max}, AUC_{last}, AUC, $t_{1/2}$, and Metabolic ratio
- Bevacizumab: C_{max}, AUC_{last}, AUC, CL, V_{ss}, and $t_{1/2}$

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples for PK analyses of ombrabulin, RPR258063, and bevacizumab were to be obtained from all patients at Cycles1 & 2, and before infusion of bevacizumab at Cycle 3 for PK analyses of bevacizumab only.

Ombrabulin: A series of 1 mL blood samples were to be collected (ie, a total of 11 mL of blood per cycle)

- Cycle1 and Cycle 2, Day 1:
  - Immediately prior to the end of infusion;
  - Post infusion: 5, 10, 25 and 45 minutes; 1, 2, 4, 6, 8 hours.
- Cycle1 and Cycle 2, Day 2: One blood sample 24 hours post ombrabulin infusion and before bevacizumab infusion).

Bevacizumab: A series of 5 mL blood samples were to be collected (i.e. a total of 35 mL of blood at Cycle 1 and Cycle 2).

- Cycle1 and Cycle 2, Day 2:
  - Prior to the start of infusion;
  - Immediately prior to the end of bevacizumab infusion, 2 and 6 hours after the end of infusion.
- Cycle1 and Cycle 2, Days 4 , 8 and 15: One blood sample 48 hours, 6 and 13 days post bevacizumab infusion.
- Cycle 3: One blood sample before bevacizumab infusion.

The concentrations of ombrabulin and RPR258063 were measured by a validated Liquid Chromatography coupled with tandem Mass Spectrometry (LC/MS/MS) method [Limits of Quantifcation (LOQ) = 2 ng/mL for each analyte]. Bevacizumab concentration was measured by a validated enzyme-linked immunosorbent assay (ELISA) with a LOQ of 80 ng/mL.

Statistical methods:

Dose escalation design:

The primary objective of the trial was to find the MTD. The MTD was defined as the dose with maximum confidence that the risk of DLT associated to the dose lies in an interval ranging from 20% to 35% (ie, targeted interval).

The MTD of the combination was determined using a Bayesian dose-escalation design.

A Bayesian logistic 3-parameter model was to be used to guide the dose escalation.

Patients were to be treated sequentially at a given dose level by cohorts of 3 patients. After each cohort of 3 patients, the Bayesian model was to provide the posterior distribution of risk to have DLT for each dose level, based on the cumulative current data observed. The posterior distribution was to be used to identify the dose(s) with the highest probability to be in the targeted interval (ie, 20 to 35%). If the candidate doses were higher than the current dose level, the next dose level could be tested.

Statistical and graphical guidelines were to be provided regarding the dose to be given to the next cohort and the estimation of risk of DLT at each dose level. The dose given to the next cohort was thus to be chosen according to these guidelines and also taking into account the full clinical picture of patients previously treated. In particular, information regarding toxicities observed after Cycle 1 were not to be taken into account in the Bayesian model but could be used as supportive descriptive information to help decision-making on dose escalation.

After each cohort, 5 options were possible:

- Treat 3 patients at next planned higher dose level;
- Treat 3 patients at next higher optional dose level;
- Treat 3 additional patients at the same dose level;
- Treat 3 additional patients at a lower dose level;
- Stop the dose escalation and consider the current dose as the MTD.

The dose escalation was to be stopped when 2 consecutive cohorts of 3 patients had been treated at the same dose level and the dose escalation model recommended current/lower dose level as the MTD when the two cohorts were completed. In this way, the MTD for the combination was defined, after the data were analyzed and reviewed by the Study Committee.

Sample size:

The sample size depended on the toxicity of the combination and was to be in the range of approximately 40 to 70 patients in the event of completion of the full planed dose levels (bevacizumab 5 mg/kg).

Analysis population:

The safety population was the all treated population defined as the subset of all registered patients exposed to ombrabulin or bevacizumab, regardless of the amount of treatment administered.

Activity/efficacy population was defined as all registered patients who had received at least two cycles of ombrabulin and bevacizumab, and provided a baseline and at least one post-baseline assessment for the efficacy variable of interest. Patients with an early progression as per RECIST 1.1 were also to be included in this set.

Statistical analysis

The primary safety analysis was to assess DLT for Cycle 1. The secondary safety analysis was to summarize treatment-emergent adverse events (TEAEs) and post-TEAE by actual dose level in the all treated patient population. Adverse events were to be summarized with respect to frequency, incidence, intensity/severity (as graded by the NCI CTCAE, version 4.0), relationship to the study treatment, and cumulative nature. All adverse events were to be coded using the MedDRA system. Serious TEAE, post-TEAE and deaths were to be tabulated.

PK parameters were to be summarized with descriptive statistics. Statistical modeling was to be used to assess dose proportionality of C_{max} and AUC and dose effect.

Anti-tumor activity as assessed by the best overall response using RECIST 1.1 or both the international workshop response criteria and the revised response criteria were to be descriptively presented by actual dose level in the activity/efficacy population.

Summary:

A total of 39 patients were registered and treated in this study. The patients received escalating doses of ombrabulin (from 11.5 to 50 mg/m^2) in combination with bevacizumab (from 5 to 15 mg/kg) every three weeks. One patient experienced Grade 2 serious tumor hemorrhage after receiving Cycle 1 of ombrabulin 15.5 mg/m^2, leading to study drug discontinuation before bevacizumab was ever administered.

At the cutoff date, 36 patients had discontinued the study treatment (92.3%): 29 patients (74.4%) for disease progression and 7 patients (17.9%) because of TEAEs (ileal perforation, intestinal perforation, tumor hemorrhage, lacunar infarction, atrial fibrillation, acute myocardial infarction, and pulmonary embolism). Three patients were still on treatment.

The patients were mainly female (74.4%) and were all Caucasian. The median age was 51.0 (from 25 to 75) years. Seven patients (17.9%) were elderly (equal or greater than 65 years). All patients had an ECOG performance status of 0 or 1.

The most frequent primary tumor sites at baseline were ovaries (41.0%) and colon (10.3%). The most common initial pathology cell type was adenocarcinoma (69.2%). The median time from diagnosis to first study treatment infusion was about 35.5 months (ranging from 5.9 months to 26 years). Median time from progression/relapse to first infusion was 1.87 months (from 0.5 to 13.5 months).

Among the 38 patients with solid tumors, the disease was metastatic in 30 patients (78.9%), locally advanced in 5 patients (13.2%), and loco-regional in 3 patients (7.9%) at baseline. Thirty-two patients (82.1%) had at least 2 organs involved, including 8 patients (20.5%) with at least 4 organs involved. All patients had measurable disease at baseline. The most frequent organs with lesions (where a patient could have multiple lesions in different organs) were peritoneum (56.4%), liver (43.6%), lungs (38.5%), and lymph nodes (33.3%).

All patients had received prior chemotherapy before entering the study. Other prior anti-cancer therapies were surgery (89.7%), radiotherapy (30.8%) and hormonotherapy (10.3%).

Safety results:

Regardless of the dose group, the patients received between 1 and 21 cycles of treatment (between 2 and 21 cycles for bevacizumab) for 3 to 67 weeks.

The patients treated with ombrabulin (8 or 11.5 mg/m^2) in combination with bevacizumab 5 mg/kg received between 2 and 14 cycles of study treatment.

The patients treated with ombrabulin (from 11.5 to 50 mg/m^2) in combination with bevacizumab 10 mg/kg received from 1 to 21 cycles of study treatment and those treated with ombrabulin (from 35 to 50 mg/m^2) in combination with bevacizumab 15 mg/kg received between 2 and 10 cycles of treatment. However, at the cutoff date, 3 patients were still on treatment: 2 patients at ombrabulin 50 mg/m², the first one with bevacizumab 10 and the second with 15 mg/kg dose levels; and 1 patient at ombrabulin 42 mg/m².

Regardless of the doses of ombrabulin and bevacizumab, the relative dose intensity ranged from 0.8 to 1.1.

The dose escalation was stopped after administration of the highest dose of ombrabulin (50 mg/m^2) in combination with bevacizumab 15 mg/kg in agreement with the investigators and the Sponsor. This decision was based on the ombrabulin single agent RD established at 50 mg/m^2 in a previous Phase 1 study (TCD6297) and on the highest RD of bevacizumab for approved indications.

No DLTs were reported during Cycle 1 of the study and the MTD was not reached as per protocol criteria.

No expansion cohort was constituted since the ombrabulin development program has been discontinued after the results have shown no clinical benefit of ombrabulin combined with chemotherapy in the Phase 2 studies in first line NSCLC and second line platinum sensitive ovarian cancer indications as well as in the Phase 3 study in advanced soft tissue sarcoma indication.

Regardless of the dose received, all patients experienced at least 1 TEAE including 34 patients (87.2%) with at least 1 related TEAE. Nineteen patients (48.7%) experienced at least one serious TEAE, including 6 patients with SAE considered IP-related.

Seven patients (17.9%) discontinued the treatment because of TEAEs including 5 patients with related TEAE (ileal perforation, intestinal perforation, atrial fibrillation, acute myocardial infarction, tumour haemorrhage and pulmonary embolism). Among these 5 patients, 4 patients had received ombrabulin dose levels ≥ 35 mg/m^2 and bevacizumab dose levels ≥ 10 mg/kg.

Two patients died of disease progression within 30 days after the last infusion: 1 patient treated with ombrabulin 11.5 mg/m^2 and bevacizumab 5 mg/kg, and another one treated with ombrabulin 35 mg/m^2 and bevacizumab 15 mg/kg. One patient treated with ombrabulin 25 mg/m^2 and bevacizumab 10 mg/kg experienced Grade 4 duodenal perforation. The patient died because of disease progression 35 days after the last infusion of ombrabulin.

The most common TEAEs across all ombrabulin treatment groups were: asthenia (46.2%), diarrhea (43.6%), nausea and headache (41.0% for each), fatigue (38.5%), hypertension (33.3%), abdominal pain, dyspnoea, and vomiting (30.8% for each).

The most common TEAEs related to IP across all ombrabulin treatment groups were: diarrhea and nausea (33.3% for each), hypertension, vomiting, and asthenia (23.1% for each), and abdominal pain and epistaxis (20.5% for each).

The most common grade 3-4 TEAEs reported were hypertension (20.5%) and disease progression (10.3%).

Seven patients (17.9%) had dose delayed because of TEAEs and 3 of them had received ombrabulin dose levels ≥ 35 mg/m^2 and bevacizumab dose levels ≥ 10 mg/kg. One patient who received ombrabulin 35 mg/m^2 with bevacizumab 15 mg/kg had bevacizumab dose reduction because of TEAE (weight decreased).

Six patients (15.4%) experienced cardiac disorders including the 3 following patients with cardiac disorders considered related to IP: 1 patient with medical history of ongoing myocardial infarction experienced serious Grade 4 acute myocardial infarction, which led to permanent treatment discontinuation (recovered), 1 patient without cardiovascular medical history experienced non-serious Grade 1 arrhythmia (recovered) and 1 patient with possible atrial hypertrophy at baseline experienced serious Grade 2 atrial fibrillation (recovered) which led to permanent treatment discontinuation.

Regarding cardiac markers, 7 patients had troponin I values higher than ULN. One of them (troponin I values of 2.01 and 1.2 µg/L at Day 1 of Cycle 4, ULN > 0.04 µg/L) who received ombrabulin 50 mg/m^2 with bevacizumab 10 mg/kg experienced concomitant serious Grade 4 acute myocardial infarction considered related to IP at Cycle 4 and leading to permanent discontinuation (see narrative for details). He recovered after corrective treatment. No other cardiac TEAE concomitant to troponin I elevation was observed.

Vascular disorders were reported in 20 patients (51.3%). Among them, 13 patients experienced hypertension (none reported as SAE). Five of these patients had medical history of hypertension. Hypertension resolved in 8 patients and one patient was recovering. In all 8 cases, resolution occurred with administration of corrective treatment. The hypertension was considered related to IP in 9 patients and rated Grade 3 or 4 in 7 of them.

Regarding laboratory abnormalities: the most frequent hematological abnormalities observed included anemia (87.2% versus 56.4% at baseline), lymphopenia (51.3% versus 30.8%), and leukopenia (38.5% versus 15.4%).

Four patients had Grade 3 lymphopenia. Three of them who had Grade 2 lymphopenia at baseline did not recover. Grade 3 and Grade 4 neutropenia were also reported in 1 patient each and both recovered and 1 patient had Grade 3 anemia that did not resolve.

Grade 2 anemia was reported as TEAE in 1 patient who received ombrabulin 35 mg/m^2 with bevacizumab 10 mg/kg (recovered). This anemia was already present at baseline. No other laboratory hematological abnormalities were reported as TEAE.

One patient with liver cancer had Grade 3 ALT increased (231 IU/L versus 20 IU/L, Grade 0 at baseline) and Grade 1 hyperbilirubinemia (20 µmol/L) at Cycle 4 concomitant with serious biliary tract infections. Both ALT increased and hyperbilirubinemia resolved. No other Grade 3 or 4 laboratory liver or renal abnormalities were reported. Four other patients with ovarian (2 patients), thyroid and lymph nodes cancer had Grade 1 hyperbilirubinemia that resolved.

One patient who received ombrabulin 50 mg/m2 with bevacizumab 10 mg/kg experienced urinary creatinine protein ratio increased (1.24) reported as TEAE at Cycle 5 and considered as related to IP. Spontaneous recovery was observed. No other liver or renal laboratory abnormalities were reported as TEAE.

Grade ≥3 abnormal electrolytes values were reported: 4 patients had Grade 3 hyponatremia, 2 patients had Grade 4 hypercalcemia, 1 patient had Grade 3 hypoalbuminemia and 1 patient had Grade 3 hyperkalaemia. Grade 1 hypokalaemia (3.1 mmol/L) was reported as an AE in 1 patient at baseline and resolved before Cycle 1 administration. No electrolytes abnormalities were reported as TEAE.

Three patients experienced serious gastrointestinal perforation:

- one patient with ovarian cancer and peritoneal carcinosis treated with ombrabulin 11.5 mg/m^2 and bevacizumab 10 mg/kg experienced Grade 4 ileal perforation considered related to IP and leading to study treatment discontinuation,
- a second patient with bladder cancer treated with ombrabulin 25 mg/m^2 and bevacizumab 10 mg/kg experienced Grade 4 duodenal perforation with fatal outcome considered not related to IP but possibly related to chronic use of NSAIDs,
- a third patient with ovarian cancer with peritoneal disease and para-aortic lymph nodes and treated with ombrabulin 35 mg/m^2 and bevacizumab 15 mg/kg experienced Grade 4 intestinal perforation considered related to IP and leading to study treatment discontinuation.

No LVEF abnormality was reported. Four patients had creatinine kinase MB higher than ULN. None of them were reported as TEAE.

Efficacy results: Among the 37 patients evaluable for anti-tumor activity assessment, 2 patients (5.4%) had partial response, 23 (62.2%) had stable disease and 10 (27.0%) had progressive disease. No complete response was observed and 2 patients with non-target lesions had non CR/non PD. Overall, time to progression (TTP) ranged from 1.2 to 15.2 months.

Partial responses were observed in 2 patients with ovarian cancer. These two patients received 12 and 21 cycles of ombrabulin 20 and 25 mg/m² in combination with bevacizumab 10 mg/kg and had TTP of 8.4 and 15.2 months, respectively.

Twenty-three patients had SD with TTP ranging from 1.2 to 10.0 months including 2 patients with TTP longer than 6 months (1 patient with lung cancer treated with ombrabulin 8 mg/m2 and bevacizumab 5 mg/kg with TTP of 9.5 months and another patient with thyroid cancer treated with ombrabulin 50 mg/m2 and bevacizumab 10 mg/kg with TTP of 10.0 months).

Pharmacokinetic results:

Blood samples were collected and assayed for PK purpose but PK analysis was not performed.

Pharmacodynamic results:

Because of the discontinuation of the global ombrabulin project including clinical development, the biopsies and the blood samples collected for VE-cadherin and plasmatic proteins assessments were not assayed. The DCE-US results were not reported.

Therefore, the circulating biomarkers CEC and CEP were measured however the potential predictive biomarkers of treatment outcome and the potential predictive biomarkers of responsiveness to antiangiogenic drugs were not assessed in this study.

Issue date: 05-Oct-2015

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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):** AVE8062 (ombrabulin)	**Study Identifiers:** NCT01193595, EudraCT 2009-017797-20 **Study code:** TCD11379
Title of the study: An open-label, non-randomized, dose escalation, safety and pharmacokinetic phase I study of ombrabulin (AVE8062) in combination with bevacizumab administered by intravenous infusion every 3 weeks in patients with advanced solid tumors (2015)	
Study center(s): 4 centers: France, Italy (2 centers), and the United Kingdom	
Study period: Date first patient enrolled: 01/Sep/2010 Date last patient completed: 27/Oct/2014	
Phase of development: Phase 1	

Objectives:

Primary objectives:

To determine the maximum administered dose (MAD) and the maximum tolerated dose (MTD) of ombrabulin in combination with best tolerated dose of bevacizumab based on the incidence of related dose-limiting toxicities (DLTs).

Secondary objectives:

- To assess the overall safety profile of the combination.
- To characterize the pharmacokinetic (PK) profile of both ombrabulin and bevacizumab when given in combination.
- To evaluate preliminary evidence of antitumor activity of the combination using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for solid tumors or both the international workshop response criteria and the revised response criteria for non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) patients.
- To assess the pharmacodynamic (PD) effect using dynamic contrast-enhanced ultrasonography (DCE-US), measuring circulating biomarkers (circulating endothelial cells [CEC], circulating endothelial progenitor cells [CEP], matrix metalloproteinase 9 [MMP9], stromal cell-derived factor 1 [SDF-1], vascular endothelial growth factor [VEGF], soluble VEGF receptor 2 [sVEGFR2], granulocyte colony-stimulating factor [G-CSF], thrombomodulin, vascular endothelial [VE]-cadherin).
- To evaluate potential predictive biomarkers on tumor samples.

Methodology:

This was an open-label, nonrandomized, dose escalation, safety, PD, and PK study of ombrabulin given in combination with bevacizumab administered 24 hours after the end of ombrabulin infusion.

The combination was to be administered every 3 weeks to patients with advanced solid tumors according to the following schedule:

Day 1 T0: ombrabulin administered as a 30-minute intravenous (IV) infusion.

Day 2 T0: bevacizumab administered as a 30- to 90-minute IV (decreasing with cycles) infusion 24 hours after the end of ombrabulin infusion.

Cohorts of 3 patients were to be treated at each dose level. The decision to escalate to the following dose level was based on the number of patients experiencing drug-related DLTs during Cycle 1. Only drug-related DLTs were to be taken into account for the dose escalation decision. A Bayesian dose-escalation design was to be used to determine the dose level to be given to the next cohort of patients and finally estimate the MTD of the combination.

The MTD was defined as the well tolerated dose with maximum confidence that the risk of DLT associated with the dose lies in an interval ranging from 20% to 35% (ie, targeted interval). The dose escalation phase was to be stopped when 6 DLT evaluable patients had been treated at the same dose level and the dose escalation model recommended current dose level as the MTD after model updating. This defined, after data was analyzed and reviewed by the Study Committee, the MTD for the combination.

At the end of dose escalation, an expanded cohort of 10 patients was to be treated at a preliminary recommended Phase 2 dose (pRP2D) selected, based on the overall safety data and potential effectiveness, between the highest safely administered dose of bevacizumab 10 mg/kg and 15 mg/kg combination regimens, in order to confirm safety and potential antitumor activity.

The initial CSR, dated 30 July 2013, contained safety, efficacy, PK, and pharmacodynamic data for 39 patients through 27 February 2013 (data cutoff date). This study and the ombrabulin program were terminated due to a lack of efficacy.

A total of 3 patients continued to receive study treatment after the data cutoff date until study discontinuation. The Sponsor continued to gather key safety information (ie, study treatment administration, study treatment related AEs, any SAEs regardless of the relationship to study treatment, deaths, AEs leading to discontinuation of the study treatment, and clinical laboratory data) for these 3 patients until the last patient's discontinuation from the study. This follow-up report to the initial CSR presents the updated key safety data from the 3 patients.

Number of patients: Planned: 40-70 as per DLT occurrence

Treated: 39

Number of patients evaluated:

Efficacy: 37

Safety: 39

Diagnosis and criteria for inclusion:

- Histologically or cytologically proven solid malignant tumor with the exception of squamous non-small-cell lung cancer (NSCLC).
- Advanced neoplastic disease (ie, metastatic or locally unresectable advanced disease); NHL and HL in progression after standard therapy and for which intensive therapy was not indicated could be included.

Study treatments

Investigational medicinal product(s):

Formulation:

Ombrabulin

Ombrabulin was supplied as a single dose vial containing a total of 27.5 mg of ombrabulin in a 5.5 mL aqueous solution at the concentration of 5 mg/mL. Excipients: water for injection and hydrochloric acid

Bevacizumab

Bevacizumab was supplied as commercial formulation (Avastin®): bevacizumab is supplied as a single dose vial containing 100 mg of bevacizumab in a 4 mL solution or 400 mg of bevacizumab in a 16 mL solution (concentration of 25 mg/mL).

Excipients: trehalose dihydrate, sodium phosphate, polysorbate 20, water for injections

Route(s) of administration: Ombrabulin and bevacizumab were administered by IV infusion every 3 weeks.

Dose regimen:

Ombrabulin: 8 Escalating doses from 8 to 50 mg/m^2 (8, 11.5, 15.5, 20, 25, 30, 35, and 50 mg/m^2)

Bevacizumab: 5 mg/kg in combination with 8 and 11.5 mg/m^2 of ombrabulin; 10 mg/kg in combination with 11.5 to 50 mg/m^2, and 15 mg/kg in combination with 25 to 50 mg/m^2. The dose of bevacizumab 15 mg/kg was added to the dose escalation steps after a protocol amendment.

Other intermediate dose levels could be tested for each treatment, after agreement between sponsor and Investigators (ie, bevacizumab between 5 and10 mg/kg or other intermediate ombrabulin dose level).

On Day 1 of each cycle, the patients received ombrabulin as a 30-minute IV infusion and 24 hours following the completion of the ombrabulin infusion (Day 2), the patients received bevacizumab by IV infusion.

As per the Summary of Product Characteristics (SpC) of bevacizumab, the required IV administration was: first infusion over 90 minutes, second over 60 minutes, and later infusions over 30 minutes. However, for PK purposes, the first 2 infusions were to last 90 minutes, the third one 60 minutes, and the following ones 30 minutes.

Duration of treatment: The patients were to receive the treatments until disease progression, occurrence of an adverse event (AE, or death) leading to treatment discontinuation, whichever comes first.

Duration of observation: The duration of the study for each patient was to include:

- An up to 28-day screening phase;
- 21-day study treatment cycles;
- An end of treatment visit (30 days after the last treatment infusion);
- Follow-up visits or patient contact every 30 days until further anticancer therapy, death, or progression for patients who discontinued treatment for safety reasons;
- An end of study visit.

The cutoff date (COD) for the global analysis of the study and for the issuing clinical report was defined as the date when the last treated patient had his fourth cycle course completed (30-day post-infusion=COD) or theoretical date if the last patient received less than 4 cycles, at a maximum. After this COD, patients were to receive the treatments until disease progression or occurrence of an AE (or death) leading to treatment discontinuation, whichever comes first; they were only to be followed for investigational product (IP) administration, further therapy, serious adverse events (SAEs), drug-related AEs, and AEs leading to study treatment discontinuation.

Criteria for evaluation:

Efficacy: The efficacy assessment was based on the objective tumor response as defined by the RECIST 1.1 for solid tumors or both the international workshop response criteria and the revised response criteria for NHL and HL patients in evaluable patients. These assessments were to be made at least every 2 cycles or less frequently if indicated; the Investigator determined the tumor response. Furthermore, a partial or complete response had to be confirmed on a second examination done at least 4 weeks apart, in order to be documented as a confirmed response to therapy (not mandatory in Phase 1 studies).

Safety: The safety assessment included: treatment-related AEs defined as DLTs at Cycle 1 (primary endpoint), treatment-emergent adverse events (TEAEs), SAEs, laboratory abnormalities, physical examination, vital signs, electrocardiogram (ECG) in all cycles, chest X-ray, echocardiography, and cardiac markers measurement every 2 cycles. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0 was to be used in this study to grade clinical and laboratory AEs. Safety profile was based on incidence, severity, and cumulative nature of TEAEs.

Summary:

Population characteristics: At the time of the data cutoff date of the initial report (27 February 2013), 36 patients had discontinued the study treatment, and 3 patients were still on treatment as follows: 2 patients at ombrabulin 50 mg/m², the first one with bevacizumab 10 mg/kg and the second with bevacizumab 15 mg/kg; and 1 patient at the ombrabulin 42 mg/m² and bevacizumab 15 mg/kg dose level.

Disease progression (31 patients, 79.5%) and AEs (8 patients, 20.5%) were the most frequent reasons for study treatment discontinuation; of those patients, 2 had discontinued due to disease progression, and 1 had discontinued due to an AE post the data cutoff date of the initial report.

Efficacy results: As reported in the initial CSR, per RECIST 1.1 criteria, 2 patients with ovarian cancer had PR, and no CR was observed.

Safety results: The updated summaries of TEAE and clinical laboratory data did not change the previous conclusions reported in the initial CSR.

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