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Sponsor / Company: Sanofi Drug substance(s): AVE8062 (ombrabulin)	Study Identifiers: NCT01332656, EudraCT 2010-024631-16, UTN U1111-1118-5437 Study code: EFC10260
Title of the study: A Phase 2, multi-center, double-blind, placebo controlled, randomized study of ombrabulin in patients with platinum-sensitive recurrent ovarian cancer treated with carboplatin/paclitaxel (EFC10260/OPSALIN)	
Study center(s): 38 centers in 10 countries (Belgium, Czech Republic, France, Germany, Italy, Poland, Russia, Spain, Ukraine, and the United States)	
Study period: Date first patient enrolled: 13/May/2011 Date last patient completed: 09/Jul/2014	
Phase of development: 2	

Objectives:

Primary

- To demonstrate an improvement in progression-free survival (PFS) for ombrabulin versus placebo in patients with platinum-sensitive recurrent ovarian cancer treated with paclitaxel and carboplatin.

Secondary

- To compare the overall survival (OS) between the 2 treatment arms.
- To compare the objective response rate (ORR) between the 2 treatment arms.
- To evaluate the safety profile of ombrabulin versus placebo in patients treated with paclitaxel and carboplatin.
- To evaluate the pharmacokinetics (PK) of ombrabulin and its main metabolite RPR258063 using a population study approach.
- To evaluate potential predictive biomarkers on tumor samples as well as plasmatic biomarkers (including cancer antigen [CA]-125).
- To evaluate the potential interest of a computer-aided volumetric/densitometric tumor response assessment.

Methodology:

This was a multinational, randomized, double-blind, placebo-controlled Phase 2 study in patients with relapsed platinum-sensitive ovarian cancer. Patients were randomized to ombrabulin or placebo, combined with background chemotherapy (paclitaxel and carboplatin) in a ratio of 1:1.

Randomization was stratified according to the time to recurrence after platinum-containing regimen: 6 to 12 months or >12 months.

For both arms, treatment was to continue until disease progression or unacceptable toxicity or consent withdrawal. A minimum of 6 cycles of the combined therapies was encouraged to be administered to the patient, unless progression occurred before, or safety reasons induced the discontinuation of 1 or 2 drugs of the combination therapies. In case of absence of progression, it would be the Investigator's decision to continue or not the study treatment after 6 cycles according to his clinical practice. No therapy with ombrabulin alone was allowed, unless paclitaxel and carboplatin were discontinued for safety reasons.

This study was prematurely terminated due to the lack of study drug efficacy (interim analysis). Patients who had been assigned to the ombrabulin arm and experienced clinical benefit were offered to continue the ombrabulin in combination with the background chemotherapy (paclitaxel and carboplatin) per the Investigator's decision, and those patients were only followed for safety per protocol. Patients who had received the placebo in combination with the background chemotherapy were discontinued from the study, but could have continued their chemotherapy treatment outside of the study.
Number of patients: Planned: 150 Randomized: 154 Treated: 153 Evaluated: Efficacy: 154 Safety: 153 Pharmacokinetics: 108
Diagnosis and criteria for inclusion: Relapsed patients with histological and/or cytological diagnosis of epithelial ovarian carcinoma, fallopian tube cancer, or primary peritoneal carcinoma, who completed a maximum of 1 prior line of chemotherapy containing a platinum agent, documented as having sensitivity to platinum (that was defined by a relapse of more than 6 months after the last dose of platinum-based chemotherapy), and had measurable disease.
Study treatments Investigational medicinal product(s): ombrabulin hydrochloride Formulation: 50 mg/10 mL solution Route(s) of administration: intravenous (IV) Dose regimen: 35 mg/m^2, administered as a 30-minute IV infusion on Day 1 of each 21-day cycle
Investigational medicinal product(s): placebo Formulation: sterile sodium chloride (NaCl) 0.9% solution for injection 10 mL Route(s) of administration: IV infusion Dose regimen: administered over a 30-minute IV infusion every 3 weeks
Noninvestigational medicinal product(s): paclitaxel and carboplatin Formulation: refer to the manufacturer's product information Route(s) of administration: IV infusion Dose regimen: Day 2 of each 21-day cycle Paclitaxel 175 mg/m^2 administered as a 180-minute IV infusion followed by carboplatin area under curve (AUC) 5 or 6 administered as a 30-minute IV infusion, 24 hours after the end of ombrabulin infusion. Choice of carboplatin AUC 5 or 6 was at the Investigator's discretion; however, the choice was definite for all patients treated in the Investigator's site.
Duration of treatment: For both arms, treatment was to be continued until disease progression or unacceptable toxicity or consent withdrawal. A minimum of 6 cycles of the combined therapies was encouraged to be administered to the patient, unless progression occurred before or safety reasons induced the discontinuation of 1 or 2 drugs of the combination therapies. In case of absence of progression, it would be Investigator's decision to continue or not the study treatment after 6 cycles according to his clinical practice. No therapy with ombrabulin alone was allowed, unless paclitaxel and carboplatin were discontinued for safety reasons.

Duration of observation: For each patient who signed the informed consent form, the study consisted of 21-day screening phase prior to randomization, start of study treatment administration within 3 calendar days of randomization, 21-day study treatment cycles, end of treatment (EOT) visit, and a follow-up phase every 9 weeks for 2 years, and every 6 months thereafter until documented disease progression or death, consent withdrawal, or study cutoff date. Subsequently, all patients were followed for survival update until death or study cutoff date, whichever came first.

All patients were followed for safety for a minimum of 30 days following the last administration of study drug.

Study drug-related adverse events (AEs) and all serious adverse events (SAEs) were followed until resolution/stabilization.

The end of the clinical study (cutoff) was planned to be reached when 90 PFS events were observed.

Criteria for evaluation:

Efficacy assessments: Tumor assessments were done according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria; the chest, abdominal, and pelvic computed tomography (CT) or magnetic resonance imaging (MRI) scans, and any other exams as clinically indicated, were performed at baseline, then every 9 weeks for 2 years, then every 6 months up to disease progression, using the same method that was used at baseline.

Overall survival was evaluated by collecting vital status information every 9 weeks for 2 years, and then every 6 months until death or study cutoff date, whichever came first.

Safety assessments: Safety assessments included reported AEs and other safety information, such as clinical laboratory data, vital signs, electrocardiograms (ECG), and cardiac examination. The observation of safety data included the pretreatment, on-treatment, and posttreatment periods.

A physical examination was included, but was not limited to the examination of major body systems. Height was recorded at baseline only, body weight was assessed every 3 weeks during the study treatment period, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) and vital signs were recorded prior to the start of each study drug treatment and at EOT. During the followup period, only ECOG PS was assessed every 9 weeks for 2 years and then every 6 months until disease progression, study cutoff, or death, whichever came first. Vital signs were recorded during the study treatment period; that is, prior to the start of each study drug treatment on Day 1 and Day 2 at each course.

Laboratory data (ie, hematology, blood chemistry, CA-125, coagulation test, urinalysis) were assessed at baseline, on Day 1 of each cycle, and at EOT. Liver tests were repeated on Day 2 and Day 8 of each cycle. Biochemistry assessments could have been repeated more often, if clinically indicated. In order to identify composite criteria for progression, CA-125 dosages were also performed at each followup. Pregnancy tests were only performed at baseline. Any clinically significant laboratory abnormalities were to have been reported as AEs.

The 12-lead ECG and left ventricular ejection fraction (LVEF) evaluations were assessed at baseline, every 3 cycles, EOT, the first followup visit, and thereafter only if clinically indicated.

Pharmacokinetic assessments: Blood samples for PK analysis were to have been obtained in at least 100 patients (50 in each treatment arm) on Day 1 Cycle 1 as follows: just before the end of infusion, between 5 to 20 minutes postinfusion, between 1 to 4 hours postinfusion, and 24 hours postinfusion.

Pharmacodynamic assessments: Paraffin-embedded tumor tissue blocks were collected from eligible and consenting patients.

For circulating biomarkers, 5 blood samples per patient at each time point (total of 25 samples) were to have been collected before the start, 6 hours, 24 hours, and 21 days after the ombrabulin/placebo infusion; and 4 hours after the end of the paclitaxel-carboplatin combination. The following biomarkers were measured using validated enzyme-linked immunosorbent assay (ELISA) methods: free vascular endothelial growth factor (VEGF) with limit of quantification of 15.0 pg/mL, matrix metallopeptidase 9 (MMP-9) with limit of quantification of 5.00 ng/mL, and stromal cell-derived factor 1-alpha (SDF1-alpha) with limit of quantification of 156 pg/mL. Granulocyte-colony stimulating factor (G-CSF) was measured using a validated sensitive Erenna® method with limit of quantification of 0.625 pg/mL.

Statistical methods:

Determination of sample size

The primary endpoint for the study was PFS. The median PFS for patients treated in the control arm (placebo + paclitaxel + carboplatin) was estimated to be 9.4 months based on previous studies. A 30% risk reduction (median PFS improvement from 9.4 months in the control arm to 13.4 months in the ombrabulin arm, corresponding to a hazard ratio of 0.70) was expected to be demonstrated, assuming that PFS times were exponentially distributed in both treatment arms. A total of 90 PFS events would be required to provide 80% power to detect a significant effect of ombrabulin on PFS using a one-sided log-rank test at a significance level of 20%. Based on an anticipated uniform accrual rate over a period of 10 months and a minimum 11-month followup period, a total of approximately 150 patients (75 patients per treatment arm) would need to be randomized in order to achieve the required number of events by the end of the minimum follow-up period. These calculations had been done using EAST 5.3.

The planned study cutoff date for the final PFS analysis was the date when the 90 required PFS events were observed.

Analysis populations

Intent-to-treat (ITT) population: defined as the all randomized population analyzed according to the treatment arm allocated by randomization.

Modified intent-to-treat (mITT) population: the subset of patients in the ITT population with measurable disease at baseline and who had at least 1 valid postbaseline tumor assessment before the initiation of further anticancer therapy.

Safety population: the randomized population who actually received at least 1 dose or part of a dose of study treatment (ombrabulin/placebo or paclitaxel or carboplatin) analyzed according to the treatment actually received.

The PK analyses were based on patients in the safety population who had an evaluable blood sample in the first cycle.

Primary efficacy endpoint

The primary efficacy endpoint was PFS defined as the time interval from the date of randomization to the date of the first documented event defining disease progression or death due to any cause.

Disease progression was defined as occurrence of one of the following events:

- Radiological tumor progression assessed on CT scan and/or MRI following the RECIST 1.1 criteria or
- A global deterioration of health status defined as symptomatic deterioration requiring treatment with an anticancer agent based on the Investigator's decision

CA-125 progression alone was not considered disease progression if not supported by radiological or clinical deterioration.

Secondary efficacy endpoints

Overall survival was defined as the time interval from the date of randomization to the date of death due to any cause.

Progression-free survival based on radiological progression as per RECIST 1.1 criteria (when applicable).

Objective response rate was defined as the proportion of patients with complete response (CR) or partial response (PR), defined by RECIST 1.1 criteria, regardless of confirmation.

Exploratory efficacy endpoints

Exploratory efficacy endpoints included tumor size change, volumetric response assessment, and CA-125.

Efficacy analyses

The primary analysis for PFS was based on the ITT population. Progression-free survival was compared between the 2 treatment arms using a log-rank asymptotic test stratified by the time to recurrence after platinum-containing regimen (6-12 months or >12 months) specified at the time of randomization (as per interactive voice response system [IVRS]), at a significant level of 0.20 (one-sided). Estimates of the hazard ratio (HR) and corresponding 60% and 95% confidence intervals (CI) were provided using

Cox proportional hazard model stratified by the same baseline stratification factor as the one used for the log-rank test. Survival curves were presented in each treatment arm using non-parametric Kaplan-Meier estimate, as well as PFS rates and associated 60% CI at 1, 3, 6, 9, 12, 15, and 18 months. The median PFS and associated 60% and 95% CI were computed using Greenwood's variance estimation.

The OS analysis was based on the ITT population. The estimates of the HR and corresponding 60% and 95% CI were provided using Cox proportional hazard model stratified by the time to recurrence after platinum-containing regimen (as per IVRS). Survival curves were presented in each treatment arm using non-parametric Kaplan-Meier estimate, as well as survival rates and associated 60% CI at 1, 3, 6, 9, 12, 15, 18, and 24 months. The median of survival and its 60% and 95% CI were provided.

The analysis for ORR was summarized by treatment arm based on the mITT population and by stratification factor (time to recurrence after platinum-containing regimen as per IVRS) by means of count (n) and percentage (%) and presented with 60% and 95% exact binomial CI (Clopper-Pearson).

Safety endpoints

Safety profile of the study treatment in terms of AEs/SAEs and laboratory parameters:

- Type according to the Medical Dictionary for Regulatory Activities (MedDRA), frequency, and severity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03, seriousness, and relatedness of study treatment emergent adverse events (TEAEs) was assessed.
- Laboratory abnormalities (hematology, blood chemistry, and urinalysis) were assessed according to the NCI-CTCAE version 4.03.

The observation of safety data was divided into 3 periods:

- The pretreatment period: from signed informed consent to first study treatment intake
- The on-treatment period: from first study treatment intake to 30 days after the last study treatment intake
- The posttreatment period was defined as the period of time starting the day after the end of the on-treatment period

Safety analyses

All safety analyses were based on the safety population and included descriptive statistics. The primary focus of AE reporting was TEAEs.

Pharmacokinetic endpoints

A limited sampling strategy with 4 samples was implemented to assess the PK of ombrabulin and its main metabolite.

Pharmacodynamic endpoints

Analyses of potential biomarkers on tumor and blood samples were planned.

Interim analysis

An interim analysis was planned when approximately 54 PFS events (60% of the targeted PFS events) had occurred. The purpose of this interim analysis was to investigate whether the transition from Phase 2 into Phase 3 could be done at this early stage. The unblinding of the interim analysis was performed by an external independent statistician.

Summary:

Interim analysis: The planned interim analysis occurred at a cutoff date of 26 October 2012 when 57 PFS events were observed. Since the results of this analysis did not show an efficacious advantage of adding ombrabulin to carboplatin and paclitaxel in patients with platinum-sensitive recurrent ovarian cancer, the study was prematurely discontinued. Therefore, the efficacy results presented in this synoptic report are considered to be final.

Population characteristics: A total of 154 patients with platinum-sensitive recurrent ovarian cancer (77 per arm) were randomized to receive placebo or ombrabulin in combination with paclitaxel and carboplatin therapy and were included in the ITT population. The mITT population consisted of 147 patients (1 patient in the placebo arm and 6 patients in the ombrabulin arm had no measurable disease at baseline or no valid postbaseline tumor assessment before initiation of further anticancer therapy). The safety population included 76 patients in the placebo arm and 77 patients in the ombrabulin arm. The difference in the number of patients in the ITT and safety populations was due to 1 patient who was randomized and not treated.

Randomization was done centrally using an IVRS, and patients were stratified according to the time to recurrence after platinum-containing regimen: 6 to 12 months or >12 months. The time to recurrence after platinum-containing regimen in the study was the same for both treatment arms (6 to 12 months: 36 patients [46.8%] in each arm; >12 months: 41 patients [53.2%] in each arm).

Five patients (6.5%) in the placebo arm and 7 patients (9.1%) in the ombrabulin arm had randomization and/or drug allocation irregularities. The most common irregularity was stratification error (placebo: 5 patients [6.5%]; ombrabulin: 4 patients [5.2%]). Of the 5 patients in the placebo arm, 4 were stratified as 6 to 12 months instead of >12 months and 1 patient as >12 months instead of 6 to 12 months. Of the 4 patients in the ombrabulin arm, 1 was stratified as 6 to 12 months instead of >12 months and 3 patients as >12 months instead of 6 to 12 months. Two patients randomized to the ombrabulin arm had erroneous kit dispensation (1 patient received placebo for 1 cycle among 41, and the other patient received a kit of ombrabulin which was not the allocated one). There was 1 patient whose kit was not available at Cycle 4 in the ombrabulin arm.

Patient demographics were well balanced between the 2 treatment arms with a similar balance of age, race, ethnicity, weight, and body surface area. Median age was 56.0 years (range: 34 to 79 years).

Overall, 99 patients (64.3%) had the histological subtype of serous adenocarcinoma, 35 patients (22.7%) for adenocarcinoma, 8 patients (5.2%) for endometrioid adenocarcinoma, 6 patients (3.9%) for mucinous adenocarcinoma, and 5 patients (3.2%) for clear cell adenocarcinoma. The most common primary site at initial diagnosis was ovary (143 patients [92.9%]). Median time from first diagnosis to randomization for patients was 20.35 months (range: 7.2 to 245.7 months). The distribution of ECOG PS was generally well balanced between treatment arms.

The main reasons for early treatment discontinuation were AE (placebo: 16 patients [20.8%]; ombrabulin: 15 patients [19.5%]) and disease progression (placebo: 10 patients [13.0%]; ombrabulin: 15 patients [19.5%]). Most of the patients who discontinued for other reason stopped after 6 cycles as per hospital guidelines.

Efficacy: The analysis for all the efficacy endpoints was done at the time of the interim analysis and based on a cutoff date of 26 October 2012. This interim analysis is considered to be the final analysis for the efficacy endpoints.

Primary efficacy

The primary efficacy analysis for PFS was based on ITT population, which included 154 patients (77 per arm).

The primary analysis was performed when 57 PFS events were observed, including 27 events in the placebo arm and 30 events in the ombrabulin arm. There was no significant difference in PFS between the placebo and the ombrabulin arms. Median PFS was 10.41 months (95% CI: 8.246 to 10.612 months) in the placebo arm and 8.84 months (95% CI: 7.918 to 10.218 months) in the ombrabulin arm corresponding to a 47-day difference and a stratified HR of 1.317 (95% CI: 0.777 to 2.231 months). No significant interaction between treatment arm and time to recurrence after platinum-containing regimen (as per IVRS) was observed.

The sensitivity and subgroup analyses for the primary endpoint were planned but not analyzed due to early study termination.

Secondary efficacy

The OS analysis was based only on the ITT population and ORR analysis was based on the mITT population, which included 147 patients (76 patients in the placebo arm and 71 patients in the ombrabulin arm).

Overall survival was based on a total of 8 deaths at the time of the data cutoff: 3 (3.9%) in the placebo arm and 5 (6.5%) in the ombrabulin arm. Median OS was not calculated based on the small number of death events.

The ORR was similar in both arms: 75.0% of patients (95% CI: 63.7% to 84.2%) in the placebo arm and 74.6% of patients (95% CI: 62.9% to 84.2%) in the ombrabulin arm; most patients had PR in both arms (46 patients [60.5%] in the placebo arm

and 45 patients [63.4%] in the ombrabulin arm) and CR was reported in 11 patients [14.5%] and 8 patients [11.3%] in the placebo and ombrabulin arms, respectively. Stable disease was confirmed as a best response for 16 patients [21.1%] and 14 patients [19.7%] in the placebo and ombrabulin arms, respectively.

The analysis for secondary endpoint, PFS based on RECIST 1.1 criteria, was planned but not analyzed due to early study termination.

Exploratory efficacy

The analyses for exploratory efficacy endpoints were planned but not analyzed due to early study termination.

Safety:

Exposure

The median number of weeks on treatment was 19.6 (range: 3 to 57 weeks) for patients in the placebo arm and 20.9 (range: 3 to 125 weeks) for patients in the ombrabulin arm with a median number of cycles was 6.0 in both arms (range: 1 to 17 cycles in the placebo, 1 to 41 cycles in the ombrabulin).

Treatment-emergent adverse events

The overall incidence of TEAEs was generally similar between the placebo and ombrabulin treatment arms (74 patients [97.4%] and 73 patients [94.8%]). The incidence of Grade 3-4 TEAEs was higher in the ombrabulin arm than in the placebo arm (placebo: 34 patients [44.7%]; ombrabulin: 42 patients [54.5%]).

Overall, TEAEs related to study treatment were reported more frequently in the ombrabulin arm (57 patients [74%]) compared with the placebo arm (36 patients [47.4%]), as was the incidence of Grade 3-4 TEAEs related to study treatment (11 patients [14.5%] in the placebo arm and 20 patients [26.0%] in the ombrabulin arm).

The most common TEAEs (reported in at least ≥10% of patients in either arm) were nausea, diarrhea, vomiting, abdominal pain, constipation, abdominal pain upper, fatigue, asthenia, pyrexia, alopecia, neutropenia, thrombocytopenia, anemia, arthralgia, myalgia, neuropathy peripheral, headache, paresthesia, peripheral sensory neuropathy, polyneuropathy, cough, drug hypersensitivity, and decreased appetite. Of these, myalgia, headache, paresthesia, cough, and drug hypersensitivity were reported at least twice as frequently in the ombrabulin arm compared with the placebo arm. The 5 most frequently reported TEAEs were alopecia (placebo: 44 patients [57.9%]; ombrabulin: 48 patients [62.3%]), nausea (placebo: 33 patients [43.4%]; ombrabulin: 32 patients [41.6%]), neutropenia (placebo: 25 patients [32.9%]; ombrabulin: 32 patients [41.6%]), diarrhea (placebo: 21 patients [27.6%]; ombrabulin: 30 patients [39.0%]), arthralgia (placebo: 20 patients [26.3%]; ombrabulin: 26 patients [33.8%]). Less common TEAEs (5% to <10% incidence) reported at least twice as frequently with ombrabulin compared with placebo were erythema, rash, dyspnea, nasopharyngitis, urinary tract infection, and depression, and that reported at least twice as frequently with placebo compared with ombrabulin were chills, epistaxis, respiratory tract infection viral, and dysuria. Most of TEAEs were Grade 1-2.

The most common Grade 3-4 TEAE was neutropenia, which occurred more frequently in the ombrabulin arm (23 patients [29.9%]) than in the placebo arm (10 patients [13.2%]).

Death results:

No patient died during the on-treatment period. A total of 6 patients in the placebo arm and 13 patients in the ombrabulin arm died during the posttreatment period. All deaths were due to disease progression.

Serious adverse events

Overall, treatment-emergent SAEs were reported more frequently in the ombrabulin arm (placebo: 14 patients [18.4%]; ombrabulin: 20 patients [26.0%]), as was the incidence of Grade 3-4 treatment-emergent SAEs (placebo: 10 patients [13.2%]; ombrabulin: 14 patients [18.2%]). The most common treatment-emergent SAEs (reported in >3% of patients in either arm) were vomiting (placebo: 3 patients [3.9%]; ombrabulin: 0 patient) and drug hypersensitivity (placebo: 0 patient; ombrabulin: 3 patients [3.9%]).

Treatment-emergent adverse events leading to discontinuation

Overall, 20 patients (26.3%) and 23 patients (29.9%) in the placebo and ombrabulin arms, respectively, discontinued due to

TEAEs; of these 12 patients (15.8%) and 11 patients (14.3%), respectively, had Grade 3-4 TEAEs. The most common TEAEs leading to treatment discontinuation (reported in >2% of patients in either arm) were fatigue (placebo: 0 patient; ombrabulin: 2 patients [2.6%]), asthenia (placebo: 1 patient [1.3%]; ombrabulin: 5 patients [6.5%]), neutropenia (placebo: 4 patients [5.3%]; ombrabulin: 4 patients [5.2%]), thrombocytopenia (placebo: 5 patients [6.6%]; ombrabulin: 3 patients [3.9%]), anemia (placebo: 2 patients [2.6%], ombrabulin: 1 patient [1.3%]), pancytopenia (placebo: 2 patients [2.6%], ombrabulin: 0 patient), neuropathy peripheral (placebo: 4 patients [5.3%]; ombrabulin: 3 patients [3.9%]), anaphylactic reaction (placebo: 0 patient; ombrabulin: 2 patients [2.6%]), and alanine aminotransferase increased (placebo: 2 patients [2.6%], ombrabulin: 1 patient [1.3%]) ; of these TEAEs, only fatigue, asthenia, and anaphylactic reaction were reported more frequently in the ombrabulin arm compared with the placebo arm.

Laboratory results:

Grade 3-4 hematologic abnormalities of hemoglobin (placebo: 9 patients [12.0%]; ombrabulin: 10 patients [13.0%]), leukocytes (placebo: 9 patients [12.0%]; ombrabulin: 12 patients [15.6%]), and neutrophils (placebo: 17 patients [22.7%]; ombrabulin: 29 patients [37.7%]) occurred more frequently in the ombrabulin arm than in the placebo arm, with the exception of abnormalities in platelets (placebo: 7 patients [9.3%]; ombrabulin: 6 patients [7.8%]). Grade 3-4 liver abnormalities included alanine aminotransferase (ALT) (placebo: 2 patients [2.6%]; ombrabulin: 4 patients [5.2%]), aspartate aminotransferase (AST) (placebo: 2 patients [2.6%]; ombrabulin: 1 patient [1.3%]), and alkaline phosphatase (placebo: 0 patient; ombrabulin: 1 patient [1.3%]). No patient had a concurrent ALT>3 upper normal limit (ULN) and total bilirubin >2 ULN. Grade 3-4 electrolyte abnormalities occurred infrequently, and the incidence was generally similar between the 2 treatment arms. Any clinically significant laboratory abnormalities were to have been reported as AEs.

Vital signs, physical findings, and other safety observations:

Vital signs, ECOG PS, LVEF, and ECG were collected during the study but not analyzed.

Pharmacokinetic results:

Plasma concentrations of ombrabulin and its main metabolite, RPR258063, were assessed in 108 patients (57 and 51 in ombrabulin and placebo treatment arms, respectively). However, the planned PK analyses were not performed at the time of this synopsis report because the clinical results of the study did not provide evidence in support of efficacy of ombrabulin in ovarian cancer. AVE8062 and RPR258063 concentrations were determined in 434 human plasma samples that included 57 patients from the ombrabulin treatment arm. All concentrations measured in patients from the placebo arm were below the limit of quantification for both compounds (ie, <1 ng/mL) except in one patient with concentration of 2.08 ng/mL for ombrabulin. All the other ombrabulin and RPR258063 samples for this patient were below the limit of quantifications. There were 2 patients from the ombrabulin treatment arm that had ombrabulin and RPR258063 concentrations below the limit of quantification for all samples. Individual plasma concentrations of ombrabulin and its main metabolite, RPR258063, are provided in the bioanalytical report.

Pharmacodynamic results:

Overall, 82 biopsies were collected. Following early study termination, only 43 biopsies were read but not analyzed.

The following biomarkers were measured in blood samples: free VEGF was measured in 268 out of 369 samples received; MMP-9 was measured in 194 out of 394 samples received; SDF1-alpha was measured in 193 out of 393 samples received; and G-CSF was measured in 230 out of 392 samples received. Following early study termination, all biomarkers were not analyzed. All data are on file with the Sponsor.

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