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Sponsor / Company: Sanofi **Drug substance(s):** AVE8062 (ombrabulin)	**Study Identifiers:** NCT01293630, UTN U1111-1115-2568 **Study code:** TCD11270
Title of the study: An open-label, dose-escalation, safety and pharmacokinetics Phase 1 study of ombrabulin in combination with paclitaxel and carboplatin every 3 weeks in patients with advanced solid tumors (TCD11270)	
Study centers: 2 investigational centers in Japan	
Study period: Date first patient enrolled: 12/Jan/2011 Date last patient completed: 21/Oct/2013	
Phase of development: Phase 1	

Objectives:

Primary:

The primary objective of the study was to determine the maximum tolerated dose (MTD) based on the incidence of dose-limiting toxicity (DLT) and the maximum administered dose (MAD) of ombrabulin combined with paclitaxel and carboplatin administered every 3 weeks in patients with advanced solid tumors.

Secondary:

- To assess the overall safety profiles of the combination therapy.
- To characterize the pharmacokinetic (PK) profile of ombrabulin, its active metabolite RPR258063, paclitaxel, and carboplatin when used in combination.
- To document the objective tumor response.

Methodology:

This was an open-label, non-randomized, dose escalation and PK, Phase 1 study of ombrabulin in combination with paclitaxel and carboplatin in patients with advanced solid tumors.

Sequential cohorts of 3 or 6 patients with malignant solid tumor were to be treated with successively higher doses of ombrabulin based on the DLT occurrence.

Initially, 3 patients were to be enrolled at Level 1, and assessed for DLT during Cycle 1. After evaluation of safety data of 3 patients in Cycle 1, if none of the 3 patients experienced a DLT, then dose escalation to the next level (Level 2) could occur; however, if 1 patient out of the initial 3 patients experienced a DLT in the first cycle, then additional 3 patients were to be enrolled at the same dose level (Level 1).

If no more than 1 out of 6 patients experienced a DLT, patient enrollment to the next dose level (Level 2) could start. The same procedure was to be conducted in subsequent dose level. When more than 1 patient experienced DLT, the dose level was considered MAD and additional patients were to be evaluated in the previous dose level until at least a total of 6 patients could be evaluated.

If no more than 1 DLT (out of 3 or 6 patients) was observed at the highest dose level (ie, MAD was not achieved), further dose escalation was not to be conducted and this dose level was considered as the MTD for the combination. Six patients were to be treated at this dose level.

Although the dose escalation process was guided by the safety evaluation during Cycle 1, the global safety profile of ombrabulin at each completed dose level was to be considered and discussed with the investigators before increasing doses.

Number of patients**:**	Planned: 18 to 30 Screened: 18 Treated: 18 Evaluated: 18 Efficacy: 18 Safety: 18 Pharmacokinetics: 18

Diagnosis and criteria for inclusion:

Patients over 20 years and less than 75 years of age with advanced solid tumor for which paclitaxel-carboplatin doublet regimen is approved such as non-small cell lung cancer or epithelial ovary cancer, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and life expectancy of at least 12 weeks.

Study treatments

Investigational medicinal products: Ombrabulin (AVE8062), paclitaxel, carboplatin

Formulation:

Ombrabulin (AVE8062): ombrabulin was supplied as a single-dose vial containing a total of 53.0 mg of ombrabulin in a 10.6 mL aqueous solution at the concentration of 5 mg/mL of ombrabulin.

Paclitaxel: Commercial vials were used.

Carboplatin: Commercial vials were used.

Route of administration: Intravenous (IV) infusion

Dose regimen: 3 doses of ombrabulin (25, 30, and 35 mg/m^2) with carboplatin at area under the curve (AUC) 5 or AUC 6 and paclitaxel 175 or 200 mg/m^2 were to be administered. Ombrabulin 20 mg/m^2 could be also tested.

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), paclitaxel was administered as a 180-minute IV infusion followed by carboplatin as a 30-minute IV infusion.

Duration of treatment: The treatment could be continued unless disease progression or unacceptable toxicity or patient refusal.

Duration of observation: The duration of the study for each patient included an up to 4-week screening phase, 21-day study treatment cycles, an end of treatment visit, and a follow-up period. The period of observation for collection of adverse events extended from the time of informed consent signature until 30 days after the final dose of study drugs.

Criteria for evaluation:

Efficacy: Objective tumor response as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria in evaluable patients.

Safety: Treatment-related adverse events (AEs) defined as DLTs at Cycle 1 (primary endpoint), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities, vital signs, electrocardiogram (ECG) in all cycles and chest X-ray, echocardiography and cardiac makers every 2 cycles. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 was to be used in this study to grade clinical and laboratory adverse events. Safety profile was based on incidence, severity, and cumulative nature of TEAEs.

Pharmacokinetics:

Pharmacokinetic parameters of ombrabulin, its active metabolite RPR258063, paclitaxel, and total and free platinum:

- Ombrabulin: time to reach maximum concentration (t_{max}), maximum concentration (C_{max}), area under the concentration-time curve from time zero to the time of the last concentration (AUC_{last}), AUC, clearance (CL), volume of distribution at steady state (V_{ss}), and biological half-life ($t_{1/2z}$)
- RPR258063: t_{max}, C_{max}, AUC_{last}, AUC, $t_{1/2z}$, and metabolic ratio for C_{max} and AUC
- Paclitaxel: t_{max}, C_{max}, AUC_{last}, AUC, CL, V_{ss}, and $t_{1/2z}$
- Carboplatin (free and total platinum): t_{max}, C_{max}, AUC_{last} , AUC, CL, V_{ss}, and $t_{1/2z}$

Pharmacokinetic sampling times and bioanalytical methods:

Sampling times:

A series of blood samples was collected at the following time points at Cycle 1:

- Ombrabulin and RPR258063: 2 mL blood of samples were collected before infusion, immediately prior to the end of ombrabulin infusion, and 5, 10, 25, and 45 minutes and 1, 2, 4, 6, 8.5 and 24 hours post ombrabulin infusion at Cycle 1 (ie, approximately 24 mL of blood).
- Paclitaxel: For paclitaxel data: 2 mL of blood samples were collected pre-start of ombrabulin infusion, 90 minutes after start of paclitaxel, and just before end of paclitaxel infusion, 30 minutes and 1, 2, 4, 6 and 24 hours post paclitaxel infusion (ie, a total of 18 mL of blood).
- Free and total platinum: 5.5 mL blood samples for total and free measurement carboplatin and 2 mL blood samples for total carboplatin measurement (time points with*) measurement were collected before ombrabulin infusion*, immediately prior to the end of carboplatin infusion, and 30 min, and 1.5, 3.5 and 23.5 hours post carboplatin infusion (ie, approximately 29.5 mL of blood).

Bioanalytical assay methods:

- Ombrabulin and RPR258063: concentrations of both analytes were determined in plasma by a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 2.00 ng/mL.
- Paclitaxel: concentrations were measured in plasma by a validated LC-MS/MS method with a LLOQ of 5.00 ng/mL.
- Free and total platinum: concentrations were determined by a validated inductively coupled with plasma mass spectrometry (ICP-MS) method; for total carboplatin in plasma with a LLOQ of 100 ng/mL and for free carboplatin, in ultrafiltrate plasma with a LLOQ of 1.00 ng/mL.

Genotyping:

For those patients who signed the specific pharmacogenetic analysis informed consent form, blood samples were collected for investigation on pharmacogenetic questions that could emerge related to ombrabulin. Blood sampling for pharmacogenetic purpose was performed in one center but no samples were analyzed.

Statistical methods:

Sample size determination:

Cohorts of 3 or 6 patients were screened, and treated at each dose level. The actual sample size could vary depending on the incidence of DLT during Cycle 1 at a given dose level. Maximum number of patients treated on each dose level was six. Since 5 dose levels of ombrabulin with carboplatin and paclitaxel were planned to be tested, the maximum number of enrolled patients was expected to be 30.

Analysis population:

All-treated/safety population: The all-treated population was defined as all registered patients exposed to at least 1 of the investigational drug (ombrabulin, carboplatin or paclitaxel), regardless of the amount of treatment administered.

Dose-limiting toxicity population: The patients evaluable for DLT assessment were all the patients who received at least 1 (even if incomplete) infusion of ombrabulin, paclitaxel or carboplatin and had no major protocol deviations such as ineligible patient, poor compliance of ombrabulin at Cycle 1 and a lack of safety assessment at Cycle 1.

Pharmacokinetics population: The PK population was defined as the subset of patients from all treated population with at least 1 PK parameter and PK-related documents forms during the Cycle 1. In case of missing data, incomplete data or any important protocol deviations which influenced PK evaluation, the patient was not to be evaluable for PK.

Efficacy population: The efficacy population was defined as all registered patients who had received at least 1 administration of ombrabulin and provided a baseline and at least 1 postbaseline assessment for tumor that was performed according to RECIST guidelines. The patients with an early progression as per RECIST 1.1 were also included in this population.

Safety analyses:

Analyses were descriptive and performed based on the all-treated population. Continuous data were summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each dose level. Categorical and ordinal data were summarized using number and percentage of patients in each dose level.

The primary safety analysis assessed DLTs for Cycle 1 in each patient. The secondary safety analysis summarized TEAEs by actual dose level in the all-treated patients.

Adverse events were summarized with respect to frequency, incidence, intensity/severity (as graded by the NCI CTCAE, version 3.0). All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) system. Serious AEs and deaths were documented.

Pharmacokinetic analysis:

Pharmacokinetic parameters were summarized with descriptive statistics.

Efficacy analysis:

Antitumor activity as assessed by the best overall response using RECIST 1.1 criteria was descriptively presented by the actual dose level received.

Summary:

Twenty-three patients were screened, and 18 patients were registered and treated in the study. All these patients were included in the all-treated population/safety population, and all patients were evaluable for DLT.

All patients discontinued the study treatment: 10 patients discontinued because of TEAEs, 7 patients because of disease progression, and 1 patient requested to stop the treatment as she wanted to live by her own way without any treatment.

Population characteristics:

All patients were Asian/Oriental. There were 5 male (27.8%) and 13 female patients (72.2%). Patients' mean age was 56.3 years (between 40 and 74 years). Among the 18 patients treated, 5 patients (27.8%) were ≥65 years old. None of the patients had an ECOG performance status of 2 and in total, 55.6% of patients had an ECOG PS of 0 and 44.4% patients had an ECOG PS of 1.

The most frequent primary tumor sites at baseline were cervix and other (22.2% each) and ovaries and uterus (16.7% each). Two patients had muscle/soft tissue cancer (1 patient with unclassified spindle and round cell sarcoma and the other one with leiomyosarcoma) and one patient had brain cancer. The most common initial pathology cell type was adenocarcinoma (61.1%). Two patients had squamous cell carcinoma (11.1%) and 5 patients had other histology type (27.8%). The median time from diagnosis to first study treatment infusion was 16 months (ranging from 23 days to 9.2 years).

Seventeen patients (94.4%) had metastatic disease and 1 patient (5.6%) had locally advanced disease at baseline. Fifteen patients (83.3%) had at least 2 organs involved including 1 patient (5.6%) with 6 organs involved. The most frequent organs with lesions (where a patient could have multiple lesions in different organs) were lungs (55.6%), bone (33.3%), and lymph nodes and paraaortic organs (27.8% each).

Most patients had received prior chemotherapy (83.3%) and surgery (66.7%) before entering the study. Other prior anticancer therapy included radiotherapy (22.2%).

Safety results:

Regardless of the dose group, the patients received between 1 and 24 cycles of treatment. The mean (SD) number of cycles administered ranged from 3.0 (0.0) cycles in patient treated with ombrabulin 30 mg/m^2 in combination with carboplatin AUC 5 and paclitaxel 175 mg/m^2 to 12.0 (9.1) cycles in patients treated with ombrabulin 35 mg/m^2 in combination with carboplatin AUC 6 and paclitaxel 200 mg/m^2 (117 cycles in 12 patients treated on 35 mg/m^2 versus 21 cycles in 6 patients treated on 25 or 30 mg/m^2).

Mean (SD) relative dose intensity of ombrabulin was 0.807 (0.147), ranging from 0.694 in patients treated with ombrabulin 25 mg/m^2 in combination with carboplatin AUC 5 and paclitaxel 175 mg/m^2 to 0.881 in patients treated with ombrabulin 35 mg/m^2 in combination with carboplatin AUC 5 and paclitaxel 175 mg/m^2.

Mean (SD) relative dose intensity of paclitaxel was 0.802 (0.136), ranging from 0.724 in patients treated with ombrabulin 25 mg/m^2 in combination with carboplatin AUC 5 and paclitaxel 175 mg/m^2 to 0.875 in patient treated with ombrabulin 35 mg/m^2 in combination with carboplatin AUC 5 and paclitaxel 175 mg/m^2.

Mean (SD) relative dose intensity of carboplatin was 0.767 (0.168), ranging from 0.680 in patient treated with ombrabulin 30 mg/m^2 in combination with carboplatin AUC 5 and paclitaxel 175 mg/m^2 to 0.887 in patient treated with ombrabulin 35 mg/m^2 in combination with carboplatin AUC 5 and paclitaxel 175 mg/m^2.

One DLT at Cycle 1 (non-serious Grade 3 related *Escherichia coli* urinary tract infection) was reported in a patient treated with ombrabulin 35 mg/m^2 in combination with carboplatin AUC 6 and paclitaxel 200 mg/m^2. The patient received corrective treatments (levofloxacin, paracetamol, and Lactec G [calcium chloride anhydrous/potassium chloride/sodium chloride/sodium lactate/sorbitol]) and recovered 11 days later. No action was taken with the investigational product (IP).

The dose escalation was stopped after administration of the highest ombrabulin dose level (35 mg/m^2) in combination with paclitaxel 200 mg/m² and carboplatin AUC 6. This ombrabulin dose level was then considered to be the MTD.

All patients experienced at least 1 related TEAE. Fifteen patients (83.3%) experienced at least 1 Grade 3 to 4 TEAE including 14 patients with at least 1 Grade 3 to 4 related TEAE. Serious TEAEs were reported in 2 patients: 1 patient treated with ombrabulin 35 mg/m^2 in combination with carboplatin AUC 6 and paclitaxel 175 mg/m^2 experienced Grade 3 pulmonary embolism leading to treatment discontinuation (recovering) and another patient treated with 35 mg/m^2 in combination with carboplatin AUC 6 and paclitaxel 200 mg/m^2 experienced Grade 3 drug hypersensitivity (recovered). Both events were considered to be related to the IP. No TEAEs leading to death were reported. Nine patients (50%) discontinued the study treatment because of a TEAE.

The most common TEAEs across all ombrabulin treatment groups were by decreasing order: alopecia (83.3%), neutropenia and fatigue (72.2% for each), decreased appetite, arthralgia, myalgia, nausea, and diarrhea (66.7% each), dysgeusia and constipation (50.0% each), and vomiting and injection site pain (38.9% each).

The most common TEAEs related to the IP across all ombrabulin treatment groups were: alopecia (83.3%), neutropenia and fatigue (72.2% each), decreased appetite, arthralgia, myalgia, nausea, and diarrhea (66.7% each), dysgeusia and constipation (50.0% each).

Overall, 15 patients had Grade 3 to 4 TEAEs: Grade 3 or 4 neutropenia (11 patients, 61.1%), Grade 3 pulmonary embolism,(1 patient), Grade 3 E. coli urinary tract infection (1 patient), Grade 3 hypersensitivity carboplatin (1 patient), Grade 3 syncope (1 patient) , and Grade 3 left hydronephrosis (1 patient).

During the treatment period, 9 patients (50%) discontinued treatment because of related TEAE (peripheral neuropathies not elsewhere classified [NEC, high-level term] and neutropenia in 2 patients, and drug hypersensitivity, pulmonary embolism, thrombocytopenia, creatinine renal clearance decreased, and cystitis in 1 patient each). Among these 9 patients, 6 patients had received ombrabulin 35 mg/m^2.

Seventeen patients had dose modifications (reduction, delay or interruption) because of TEAEs (12 patients with Grade 3 to 4 TEAEs).

Five patients experienced cardiac Grade 1 to 2 related TEAEs including sinus bradycardia (3 patients), sinus tachycardia (2 patients), palpitation (1 patient), and ventricular hypokinesia (1 patient).

Vascular disorders were reported in 8 patients including 4 patients who developed hypertension (no corrective treatment). All these TEAEs were Grade <3 and were considered to be IP-related. One patient treated with ombrabulin 35 mg/m^2 in combination with carboplatin AUC 6 and paclitaxel 175 mg/m^2 had Grade 3 related pulmonary embolism that led to permanent discontinuation.

Four patients had Grade <3 renal TEAEs considered to be related to the IP: pollakiuria (1 patient), proteinuria (2 patients), and urinary incontinence (1 patient). One patient experienced Grade 3 not related hydronephrosis.

Overall, all patients had at least one hematological abnormality: 15 patients (83.3%) had Grade 3 to 4 neutropenia, 10 patients (55.6%) had Grade 3 to 4 leukopenia, 5 patients (27.8%) had Grade 3 lymphopenia, and 1 patient (5.6%) had Grade 3 anemia. No Grade 3 to 4 thrombocytopenia was reported.

No Grade 3 to 4 liver, renal, or metabolic function abnormality was observed in laboratory data during the treatment period. No Grade 3 to 4 electrolytes abnormalities were reported.

All patients were assessed for urinalysis: 11 patients showed positive results for protein in urine including 7 patients with Grade 1 to 2 proteinuria.

Regarding cardiac markers, 1 patient without medical history of cardiac disease or concomitant TEAE had transient troponin I values higher than the upper limit of normal (0.9 ng/mL). No concomitant abnormality was observed on ECG or on cardiac examination. Troponin I increased resolved one week later. This patient was treated with ombrabulin 35 mg/m^2 in combination with carboplatin AUC 6 and paclitaxel 200 mg/m^2.

Four patients had Grade 1 creatinine phosphokinase (CPK) abnormalities: 1 patient had CPK abnormalities at baseline which did not resolve while transient CPK abnormalities were reported in the 3 other patients. Among these 3 patients, echocardiography and cardiovascular examination transient abnormalities were reported in 1 patient each. These abnormalities were not concomitant to CPK abnormalities. No other cardiac abnormalities were reported in these patients.

Creatinine kinase MB abnormalities were reported in 10 patients. All were treated in the same investigational centers. These abnormalities were observed from baseline to the end of study. No medical history of cardiac disease or concomitant TEAE was reported in these patients.

With respect to systolic blood pressure (SBP) abnormalities, 8 patients had a SBP ≤90 mmHg and a SBP decrease from baseline ≥20 mmHg, and 1 patient had a SBP ≥180 mmHg and a SBP increase from baseline ≥20 mmHg.

Regarding DBP abnormalities, 6 patients had DBP ≤45 mmHg and a DBP decrease from baseline ≥10 mmHg.

These blood pressure abnormalities were transient and all patients recovered. These abnormalities were observed at different cycles and mainly on the day of treatment administration.

Pharmacokinetic results:

Mean (coefficient of variation [CV]%) PK parameters of ombrabulin and RPR258063 are presented in the table below:

Mean (CV%) PK parameters	**Ombrabulin**			**RPR258063**		
Treatment	**Ombrabulin 20 mg/m²**	**Ombrabulin 30 mg/m²**	**Ombrabulin 35 mg/m²**	**Ombrabulin 20 mg/m²**	**Ombrabulin 30 mg/m²**	**Ombrabulin 35 mg/m²**
N	3	3	12	3	3	12
C_{max} (ng/mL)	960 (20)	1370 (27)	1710 (34)	244 (1)	254 (24)	271 (15)
T_{last}[a] (h)	2.45 (1.52 - 2.55)	2.47 (2.45 - 2.50)	1.54 (1.45 - 4.48)	24.53 (24.38 – 24.53)	24.48 (24.43 – 24.50)	24.48 (24.38 – 24.67)
t_{max}[a] (h)	0.52 (0.50 - 0.55)	0.48 (0.47 - 0.52)	0.50 (0.47 - 0.58)	0.55 (0.52 - 0.63)	0.60 (0.57 - 0.72)	0.58 (0.48 - 0.67)
AUClast (ng•h/mL)	433 (6)	561 (25)	681 (31)	617 (27)	669 (22)	730 (18)
AUC (ng•h/mL)	436 (6)	562 (25)	684 (31)	676 (31)	732 (22)	829 (22)
$t_{1/2z}$ (min or h [b])	20.7 (36)	21.4 (12)	17.5 (41)	8.14 (19)	8.02 (29)	9.68 (28)

[a] Median (Min - Max)

[b] Expressed as minutes for ombrabulin and hours for RPR258063

Mean (CV%) PK parameters of ombrabulin and RPR258063 are presented in the table below (continued):

Mean (CV%) PK parameters	**Ombrabulin**			**RPR258063**		
Treatment	**Ombrabulin 20 mg/m²**	**Ombrabulin 30 mg/m²**	**Ombrabulin 35 mg/m²**	**Ombrabulin 20 mg/m²**	**Ombrabulin 30 mg/m²**	**Ombrabulin 35 mg/m²**
N	3	3	12	3	3	12
CL/BSA (L/h/m²)	52.8 (5)	51.5 (28)	51.9 (34)	-	-	-
V_{ss}/BSA (L/m²)	19.7 (15)	17.4 (35)	16.2 (33)	-	-	-
Rmet $_{(Cmax)}$ [c]	-	-	-	0.260 (17)	0.206 (55)	0.174 (34)
Rmet $_{(AUC)}$ [c]	-	-	-	1.54 (27	1.41 (48)	1.30 (34)

[c] Metabolic ratio did not take into account molecular weights

- = Not applicable

Mean (CV%) PK parameters of paclitaxel, total and free platinum are presented in the table below:

Mean (CV%) PK parameters	Paclitaxel		Carboplatin			
	175 mg/m²	200 mg/m²	Total platinum		Free platinum	
			AUC5	AUC6	AUC5	AUC6
N	11[b]	6	9	9	9	9
C_{max} (ng/mL)	5600 (36)	6360 (15)	20200 (13)	23200 (22)	21400 (15)	58800 (47)
t_{max}[a] (h)	3.00 (2.97 - 3.28)	3.03 (2.98 - 3.22)	0.52 (0.47 - 0.98)	0.50 (0.45 - 2.87)	0.52 (0.47 - 0.55)	0.50 (0.45 - 0.55)
AUC_{last} (ng•h/mL)	18100 (24)	22500 (12)	80200 (26)	103000 (22)	65100 (17)	121000 (33)
AUC (ng•h/mL)	18700 (24)	23100 (12)	87600 (26)	111000 (22)	65400 (17)	121000 (33)
$t_{1/2z}$ (h)	6.72 (9)	6.41 (2)	7.12 (3)	7.68 (14)	3.32 (8)	3.28 (7)
CL (L/h/m²)	9.91 (24)	8.80 (13)	3.86 (30)	3.80 (29)	5.01 (24)	3.64 (31)
V_{ss} (L/m²)	46.4 (28)	38.8 (14)	26.4 (27)	30.0 (39)	13.0 (15)	7.87 (44)

[a] Median (Min - Max)

[b] 1 patient excluded due to an interruption of paclitaxel infusion impacting PK parameters accuracy

Following a first infusion of ombrabulin (salt) at 25, 30 or 35 mg/m² in combination with paclitaxel at 175 or 200 mg/m² and carboplatin at AUC 5 or AUC 6, a high clearance (52 L/h/m²), a short $t_{1/2z}$ (20 min) and a medium volume of distribution at steady state (V_{ss} = 17 L/m²) were observed for ombrabulin, regardless of dose. Exposure to RPR258063, its active metabolite, increased with ombrabulin dose increase. Compared to the parent compound, RPR258063 AUC was 1.3 to 1.5-fold higher while C_{max} was 3.8 to 5.7-fold lower and the $t_{1/2z}$ was longer (8 to 10 h).

The pharmacokinetics of paclitaxel, whatever the dose administered, was characterized by a low clearance (9 to10 L/h/m²), a large V_{ss} (39 to 46 L/m²), and a medium $t_{1/2z}$ (6 h).

The pharmacokinetics of total platinum, whatever the dose administered of carboplatin, was characterized by a low clearance (3.8 L/h/m²), a large V_{ss} (30 L/m²), and a medium $t_{1/2z}$ (7 h). That of free platinum showed a low clearance (3.6 to 5 L/h/m²), a moderate V_{ss} (8 to 13 L/m²), and a $t_{1/2z}$ around 2-fold lower than the total platinum (3.3 h).

Total variability observed on all PK parameters of all ombrabulin, RPR258063, paclitaxel, total and free platinum was low to moderate (CV% range: 1 to 47%).

Efficacy results:

All 18 patients were evaluable for antitumor activity assessment: 1 patient (5.6%) had complete response (CR), 6 patients (33.3%) had partial response (PR), 7 (38.9%) had stable disease (SD) and 2 (11.1%) had progressive disease (PD). Two patients (11.1%) had non-CR/non-PD.

Complete response was observed in 1 patient with ovarian cancer who received 24 cycles of ombrabulin 35 mg/m² in combination with carboplatin AUC 6 and paclitaxel 200 mg/m². This patient had previously undergone surgery and had received carboplatin as adjuvant chemotherapy. Partial responses were observed in patients with ovarian (1 patient), muscle/soft tissue (1 patient), cervix (2 patients), and other (peritoneum, 2 patients) cancers. These patients received between 3 and 20 cycles of study treatment.

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