Synopsis

Title of the study: A multinational, randomized, double blind, controlled phase II trial of ombrabulin with taxane and platinum combination administered every three weeks, in first line treatment of patients with metastatic Non-Small-Cell Lung Cancer (NSCLC) (EFC10259/DISRUPT)

Principal Investigator: [redacted]

Study center(s): 44 centers in 13 countries worldwide

Publications (reference): Joachim von Pawel, Vera Gorbounova, Martin Reck, Dariusz M Kowalski, Aurore Allard, Mustapha Chadjaa, Augustin Rey, Jaafar Bennouna, Francesco Grossi on behalf of the DISRUPT Investigators. DISRUPT: A randomized phase 2 trial of ombrabulin (AVE8062) combined with a taxane-platinum regimen in the first-line treatment of metastatic non-small cell lung cancer (NSCLC). Annals Oncol. 2012; 23 (suppl) ESMO 2012: abstract 1250P

Study period:

Date first patient enrolled: 15 February 2011

Study data cut-off date: 05 March 2012 (primary analysis)
19 October 2012 (addendum cut-off)

Study completion date (last patient last visit): 02 October 2012

Phase of development: 2

Objectives: The primary objective was to demonstrate progression-free survival (PFS) improvement for ombrabulin compared to placebo, in combination with taxane and platinum, as first line treatment for patients with metastatic NSCLC.

The secondary objectives were:

- To compare the overall survival (OS) between ombrabulin and placebo, in combination with taxane and platinum
- To compare the objective response rate (ORR) between ombrabulin and placebo, in combination with taxane and platinum, according to the Response Evaluation Criteria In Solid Tumors
- To assess the safety profile of ombrabulin in combination with taxane and platinum
- Analyses of potential biomarkers in tumor and blood samples
- To assess the pharmacokinetics (PK) of ombrabulin and its main metabolite, RPR258063, using a population approach

Methodology: Multinational, randomized, double-blind, placebo-controlled phase 2 study comparing the efficacy based on PFS of ombrabulin or placebo combined with background chemotherapy (taxane + platinum) in patients with NSCLC.

Number of patients: Planned: 170 (85 per treatment group); Randomized: 176, Treated: 176

Evaluated: Efficacy: 176; Safety: 176; PK: 49; Pharmacodynamics: 104

Diagnosis and criteria for inclusion:

Histologically proven metastatic non-small cell lung cancer (stage IV, according to Tumor, Node, Metastasis [TNM] classification 7th edition) and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1); >18 years of age; Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1

Study treatments

Investigational medicinal products: Ombrabulin hydrochloride, placebo

Formulation: Ombrabulin hydrochloride: 50 mg/10 mL (on anhydrous and solvent free basis)

Placebo: Sterile saline solution for injection 10 mL.

Route of administration: Intravenous (IV)

Dose regimen: 35 mg/m^2 every 3 weeks on Day 1; 30 minute IV infusion

Batch numbers: Ombrabulin: [redacted]; Placebo: [redacted]

Noninvestigational medicinal product: docetaxel, cisplatin, paclitaxel, carboplatin

Formulation: commercial vials labeled according to the country. For more information, see manufacturer's product information

Route of administration: IV

Dose regimen: Day 2 of each 3-week cycle

Docetaxel 75 mg/m² administered as a 60 minutes IV infusion followed by cisplatin 75 mg/m² as a 120 minutes IV infusion, 24 hours after the end of ombrabulin infusion.

or

Paclitaxel 200 mg/m² administered as a 180 minutes IV infusion followed by carboplatin AUC 6 as a 30 minutes IV infusion, 24 hours after the end of ombrabulin infusion.

Batch numbers: Not applicable

Duration of treatment: Each patient was to be treated for a maximum of 6 cycles, in the absence of unacceptable toxicity or disease progression, or consent withdrawal.

Duration of observation: Patients were followed for disease progression documentation until the study cut-off date, and for patient status (death or alive) for up to one year after this date.

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint was the PFS, defined as the time interval from the date of randomization to the date of occurrence of the first documented tumor progression (defined according to RECIST version 1.1) or death due to any cause, whichever occurred first. In the absence of confirmation of disease progression or death, the time of PFS was censored at the earliest date between the date of last valid tumor assessment without evidence of tumor progression and the cut-off date, regardless of initiation of a post-study anticancer therapy.

The secondary efficacy endpoints included

- To compare the OS between ombrabulin and placebo, in combination with taxane and platinum. OS was defined as the time interval from the date of randomization to the date of death from any cause. In the absence of death before the cut-off date, the time of OS was censored at the earliest date between the last date the patient was known to be alive and the cut-off date.
- To compare the ORR between ombrabulin and placebo, in combination with taxane and platinum, according to the RECIST 1.1 criteria. ORR was defined as the proportion of patients with confirmed complete response or confirmed partial response relative to the total number of patients in the modified intent-to-treat (mITT) population. The analysis of ORR included tumor assessments performed up to the initiation of a post-study anticancer therapy.

Safety:

Safety was assessed by assessments including AEs, clinical laboratory evaluations, physical examinations, vital signs measurements, left ventricular ejection fraction (LVEF), concomitant medications, and ECOG PS. Laboratory abnormalities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events v.4.03.

Pharmacokinetics:

A limited sampling strategy with 4 plasma samples collected per patient was implemented to assess plasma concentrations of ombrabulin and RPR258063, its main metabolite. PK samples were collected at selected sites to include a total of 100 patients.

Pharmacodynamics:

Potential biomarkers were assessed using blood and (original) tumor samples.

Statistical methods:

The analysis cut-off date was event-driven and corresponded to the date when 123 PFS events had occurred (ie, 05 March 2012)

Analysis populations:

The intent-to-treat (ITT) population included all patients who gave their informed consent and for whom there was confirmation of successful allocation of a randomization number through the study treatment allocation system. All analyses using this population were based on the treatment group allocated by randomization.

The mITT population was comprised of patients in the ITT population who had measurable disease at baseline and at least one valid post-baseline tumor assessment. All analyses using this population were based on the treatment group allocated at randomization.

The safety population was comprised of patients in the ITT population who received at least one dose of study medication. This was the primary population for all safety parameters. All analyses using this population were based on the treatment actually received.

Analysis of primary efficacy endpoint:

Analysis of the primary efficacy endpoint (PFS) was performed based on the ITT population. PFS was compared between the two treatments by the log-rank test procedure stratified by histology type and background therapy as specified at the time of randomization (as per IVRS). The overall one-sided α level was 0.20. The estimates of the hazard ratio (HR) and corresponding 60% and 95% confidence interval (CI) were provided using a Cox proportional hazard model stratified by histology subtype and by background therapy as specified at the time of randomization.

The PFS curves were estimated using Kaplan-Meier estimates.

Analysis of secondary efficacy endpoints:

OS: The OS analysis was performed on the ITT population. The estimates of the HR and corresponding 60% and 95% CIs for OS were provided using a Cox proportional hazard model stratified histological type and background chemotherapy specified at the time of randomization (as per IVRS). Survival curves were presented for each treatment group using non-parametric Kaplan-Meier estimate.

ORR: ORR was summarized by treatment group for the mITT population using descriptive statistics and presented with 60% and 95% exact binomial CIs (Clopper-Pearson).

Analysis of safety:

Safety parameters were summarized for the safety population using descriptive statistics.

Interim Analysis: An interim analysis of efficacy was conducted when 69 PFS events (56% of the targeted PFS events) had occurred. At the interim analysis, the median PFS was 4.8 months in the placebo arm and 6.3 months in the ombrabulin arm. The estimated stratified hazard ratio was 0.821 (60% CI=0.668-1.009). Patients with non-squamous histology appeared to have achieved greater benefit. The stratified hazard ratio between ombrabulin and placebo in patients with non-squamous histology was estimated to be 0.66 (60% CI=0.517-0.841).

Clinical study report (CSR): The CSR data cutoff date was event-driven and corresponded to the date when 123 PFS events occurred, determined as 05 March 2012. Database lock for the initial study report was performed on 28 April 2012. All patients alive at cutoff date for primary efficacy analysis with ongoing serious adverse events (SAEs) or ongoing treatment-related AEs were to be followed-up until recovery or stabilization of the events. Patients receiving ombrabulin treatment were allowed to continue ombrabulin beyond the cut-off date.

An addendum to the initial CSR was done that includes safety updates for the 10 patients who were on treatment at the time of primary cut-off date as well as safety update for patients who were in follow-up period with an ongoing SAE, or related AE. The last patient last visit occurred on 02 October 2012 and the final database lock (DBL) took place 19 October 2012.

Summary:

Population characteristics:

A total of 176 chemotherapy naive patients (88 per arm) with stage IV NSCLC were randomized to receive placebo or ombrabulin in combination with taxane and platinum therapy. Males represented 76.1% of the patients. Median age was 61.5 years, with 64.2% of the patients below 65. Overall, 94.9% of the patients were Caucasian/White. Non squamous and squamous histology were reported (per IVRS) in 66.5% and 33.5% of the patients, respectively. Background chemotherapy was paclitaxel+carboplatin and docetaxel+cisplatin for 51.7% and 48.3% of the patients, respectively. Patients received a median of 6 treatment cycles in both the placebo and ombrabulin arms.

Efficacy results:

The primary population for efficacy was the ITT population, comprised of all patients who gave their informed consent and were randomized. Analyses using this population were based on the treatment assigned by randomization. The analyses for ORR were performed on the mITT population which included patients in the ITT population with measurable disease at baseline and at least one valid post-baseline tumor assessment.

The analysis of the primary endpoint, PFS, was based on a total of 124 PFS events: 61 in the ombrabulin arm and 63 in the placebo arm. The majority of PFS events were objective radiological progression (61.4% in ombrabulin arm and 64.8% in placebo arm) followed by death (8.0% in ombrabulin arm and 6.8% in placebo arm).

There was no significant difference in PFS between ombrabulin and placebo arms. The median PFS was 5.65 months and 5.45 months in the ombrabulin and placebo treatment arms, respectively. Hence, the one-sided stratified log-rank p-value for ombrabulin versus placebo (p=0.3857) exceeded the pre-specified one-sided significance level of 0.2, and the stratified HR was 0.948 with a 60% CI ranging from 0.813 to 1.106.

No significant interaction between treatment group and histology, background chemotherapy, demographic variables or patient's characteristics at study entry were observed. The treatment effect was consistent across all subgroups except for patients without weight loss ≥5% during the past 3 months and patients with >2 organs involved.

Secondary endpoints:

- OS analysis was based on a total of 56 deaths: 28 in the ombrabulin group and 28 in the placebo treatment group. The median OS was the same in both treatment groups (11.01 months; stratified HR 0.962 [60% CI: 0.764 to 1.211]).
- The ORR was similar in both groups: 31.3% in the placebo arm (60% CI: 26.7% to 36.4%) and 32.1% in the ombrabulin arm (60% CI: 27.5% to 37.2%) based on the mITT population.

Exploratory endpoint: The best overall change in tumor size was similar between the 2 treatment groups.

Overall, the number of patients receiving further antitumor therapy and the type of therapies were similar between the treatment groups.

Safety results:

Patients received a median of 5 and 4 treatment cycles in the placebo and ombrabulin arms, respectively.

The overall incidence of treatment emergent adverse events (TEAEs) was generally similar between the placebo and ombrabulin treatment arms (94.3% and 92.1%). While grade 3-4 TEAEs occurred less frequently in the placebo arm than in the ombrabulin arm (51.7% versus 57.3%), discontinuations caused by TEAEs (23.0% versus 19.1%), serious TEAEs (39.1% versus 32.6%), and TEAEs leading to death (9.2% versus 4.5%) were more frequent in the placebo arm.

TEAEs reported in at least 10% of patients in either arm were nausea, alopecia, fatigue, diarrhea, vomiting, myalgia, arthralgia, polyneuropathy, decreased appetite, pain in extremity, asthenia, dyspnea, cough, peripheral neuropathy, anemia, constipation, neutropenia, pyrexia, paresthesia, and headache. Of these, paresthesia and headache were the only TEAEs reported at least twice as frequently in the ombrabulin arm compared with placebo. Less common TEAEs reported at least twice as frequently with ombrabulin were dysgeusia, insomnia, chest pain, and hypertension.

With the exception of anemia, the most common grade 3-4 TEAEs were all reported more frequently in the ombrabulin arm compared with placebo and included neutropenia, febrile neutropenia, nausea, and diarrhea.

Overall, 28 patients died in each arm died during the on-treatment and post-treatment periods, including 5 patients in the placebo arm and 3 in the ombrabulin arm who died during the treatment phase. Two patients in each arm died because of TEAEs during the on-treatment period that were not considered to be drug related (purulent pericarditis and respiratory failure in the placebo arm and tumor hemorrhage and pulmonary embolism in the ombrabulin arm).

The most common treatment-emergent SAEs reported more frequently in the ombrabulin arm compared with the placebo arm and included febrile neutropenia, pyrexia, non-cardiac chest pain, nausea, and vomiting.

In the ombrabulin arm, grade 3-4 neutropenia was the most common TEAE leading to treatment discontinuation. Dose reductions and delays in both treatment arms were most frequently the result of neutropenia, thrombocytopenia, and anemia.

LVEF decreases ≤10% and below the lower limit of normal (LLN) between 10% and 20%, and within the LLN occurred more frequently in the ombrabulin arm than with placebo.

Two (2.2%) patients in the ombrabulin arm had diastolic blood pressure of ≤45 mmHg and concurrent decrease from baseline ≥ 10 mmHg, versus none in the placebo arm. Potentially significant changes in systolic blood pressure occurred with similar incidence in the 2 treatment arms.

On the basis of these findings, the overall safety profile demonstrated by ombrabulin in combination with background chemotherapy was not substantially worse than the safety profile of the background therapy alone, and the adverse reactions associated with ombrabulin in this study could be anticipated on the basis of prior clinical experience and were manageable.

Overall, the safety analysis at final DBL did not lead to any change in the safety conclusions from the primary analysis.

Pharmacokinetic results:

Plasma concentrations of ombrabulin and its main metabolite, RPR258063, were assessed; however, the planned PK analyses were not performed at the time of this abbreviated report, because the clinical results of the study did not provide evidence in support of efficacy of ombrabulin in NSCLC.

Pharmacodynamic results:

The treatment effects on PFS, OS, and ORR in the tumor and blood biomarker evaluable populations were not consistent with those observed in the ITT population and as well as those for evaluable and nonevaluable patients. This suggests the possibility of a substantial ascertainment bias. A few pharmacodynamic biomarkers seemed to be associated with individual efficacy measures (PFS, OS, and ORR), but there were no consistent associations across measures. Taken individually, no predictive tumor and blood biomarkers could be identified for any efficacy measure. Some tumor and blood biomarkers could be identified as predictive biomarkers of efficacy endpoints in multivariate analyses but no consistent conclusion could be drawn across measures. Few prognostic tumor biomarkers could be identified in ombrabulin-treated patients. However, this cannot be generalized in the overall population, as the results of the planned analyses may be confounded and have questionable external validity (due to the ascertainment bias).

Conclusions: [redacted]
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