2 SYNOPSIS

NAME OF COMPANY Onxeo DK, Filial af Onxeo S.A., Frankrig (Topotarget A/S merged as of 01August 2014 to become Onxeo DK) and Spectrum Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Belinostat Injection 50 mg/mL Belinostat Capsules 250 mg		
NAME OF ACTIVE INGREDIENT Belinostat (PXD101)		
TITLE OF STUDY: An Open-Label Randomized Phase 2 Trial of Belinostat (PXD101) in Combination with Carboplatin and Paclitaxel (BelCaP) Compared to Carboplatin and Paclitaxel in Patients with Previously Untreated Carcinoma of Unknown Primary		

INVESTIGATORS and STUDY CENTERS

The study was conducted at 23 sites in 4 countries; Denmark (1 site), Germany (4 sites), France (7 sites) and the United States (US) (11 sites).
Coordinating Investigator: John Hainsworth, Nashville, Tennessee, US.

Site number	Principal Investigator	Site Address
Site 100	Gedske Daugaard	Rigshospitalet, Finsen Center, Department of Oncology, Copenhagen, Denmark
Site 140	Gerdt Hübner	Ostholstein-Onkologie-Onkologische Schwerpunktpraxis, Oldenburg/Holstein, Germany
Site 141	Michael Stahl	Kliniken Essen-Mitte, Department of Internal Medicine/Oncology, Essen, Germany
Site 143	Christian Meyer zum Büschenfelde	Asklepios Klinik Altona, Medical Department (Hematology/Oncology), Hamburg, Germany
Site 145	Gunnar Folprecht	Carl-Gustav-Carus, Medical Department I, Dresden, Germany
Site 160	Karim Fizazi	Institut Gustave Roussy, IGR, Villejuif, France
Site 161	Marianne Leheurteur	Centre Henri Becquerel, Rouen, France
Site 162	Djelila Allouache	Centre Francois Baclesse, Oncologie medicale, Caen, France
Site 163	Christelle de la Fouchardiere	Centre Léon Bérard, Lyon, France
Site 165	Thierry Lesimple	Centre Eugène Marquis, Rennes, France
Site 166	Nicolas Penel	Centre Oscar Lambret, Lille, France
Site 167	Yacine Merrouche	Institut de Cancerologie de la Loire, Department d'Oncologie Medicale, Saint Priest en Jarez, France
Site 900	John Hainsworth	Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN, US
Site 901	Edward Arrowsmith	Chattanooga Oncology & Hematology Associates, Chattanooga, TN, US
Site 902	James Rubinsak	Florida Cancer Specialists, Venice, FL, US

Site 903	Seaborn McDonald Wade	Virginia Cancer Institute, Richmond, VA, US
Site 904	Fred Kudrik	South Carolina Oncology Associates, Colombia, SC, US
Site 905	Robert Hermann	Northwest Georgia Oncology Centers, P.C., Marietta, GA, US
Site 906	Gladys Rodriguez	South Texas Oncology and Hematology, San Antonio, TX, US
Site 907	Irfan Firdaus	Oncology Hematology Care, Inc., Cincinnati, OH, US
Site 908	Ralph Boccia	Center for Cancer and Blood Disorders, Bethesda, MD, US
Site 910	Michael Castine, III	Baton Rouge Medical Center, Hematology/Oncology Clinic, Baton Rouge, LA, US
Site 914	Jaswinder Singh	Research Medical Center, Cancer Center, Kansas City, MO, US

PUBLICATION (REFERENCE): Not applicable (N/A)

STUDY PERIOD: 14 Apr 2009 to 31 Dec 2012 | **PHASE OF DEVELOPMENT:** 2

OBJECTIVES

Primary Objective:

- To provide an estimate of the hazard ratio (HR) of treatment effect when belinostat in combination with carboplatin and paclitaxel (BelCaP) is compared with the combination of carboplatin and paclitaxel (CaP) in terms of progression-free survival for patients with Cancer of Unknown Primary (CUP) site.

Secondary Objectives:

- To evaluate and compare further efficacy parameters (overall survival [OS], objective response rate [ORR] according to response evaluation criteria in solid tumors [RECIST] criteria, time to response [TTR], duration of response [DOR], and time to progression [TTP]) in the randomized treatment groups receiving BelCaP or CaP.
- To evaluate and compare the safety profiles of the same randomized treatment groups using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (version 3.0).

METHODOLOGY

The PXD101-CLN17 trial was an open-label, multi-national, multi-center, randomized, comparative efficacy and safety trial in previously untreated patients with CUP. Patients were randomized to treatment with either BelCaP (Group A) or CaP (Group B).
Patients in Group A were to receive up to 6 cycles of treatment after which they were to continue treatment on belinostat monotherapy at a dose of 750 mg (flat dose) administered orally (PO) once daily on days 1 to 14, every 3 weeks until disease progression or treatment-related toxicities. Patients in Group B stopped trial treatment after 6 cycles, unless toxicity or progression was seen earlier.
The protocol allowed patients in both treatment groups to continue chemotherapy treatment beyond 6 cycles where the Investigator judged this to be in the best interest of the patient.
Adverse events (AEs) were recorded throughout the trial and up to 30 days after the last treatment administration.
The study was terminated 31 Dec 2012 as of amendment 4 after having conducted the primary efficacy analysis and prior to the planned 5 year follow-up period.

NUMBER OF PATIENTS (PLANNED AND ANALYSED)

Approximately 44 patients were planned to be randomized to each treatment group. A total of 89 patients

were included in the study; 44 patients in Group A (BelCaP) and 45 patients in Group B (CaP).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

- Patients with CUP where the primary site had not been revealed by complete history, physical examination (including gynecological examination when appropriate), computed tomography scan of the chest, abdomen, and pelvis, bilateral mammography (in women with adenocarcinoma or poorly differentiated carcinoma), routine laboratory studies (complete blood cell counts, electrolytes, urinalysis, liver and renal function tests), and directed work-up of any other symptomatic areas.
- Light microscopic pathologic diagnosis of adenocarcinoma (including poorly differentiated), squamous cell carcinoma, or poorly differentiated carcinoma. Patients with poorly differentiated carcinoma had to have immunohistochemical stains to confirm the diagnosis of carcinoma, and to rule out other tumor types. Note, patients with a light microscopic histology diagnosis of "poorly differentiated neoplasm, not otherwise classified" did not fulfill the criteria for inclusion, unless immunohistochemical staining confirmed the diagnosis of carcinoma.
- Signed consent of an Independent Ethics Committee/Institutional Review Board (IEC/IRB) approved Informed Consent Form (ICF).
- At least one measurable lesion according to RECIST criteria. Note, target lesions could only be selected within previously irradiated areas if newly arising or clearly progressing after irradiation as proven by repeat scanning.
- Performance status Eastern Cooperative Oncology Group (ECOG) ≤ 2.
- Age ≥ 18 years.
- A negative serum or urine pregnancy test for women of childbearing potential. Postmenopausal women must have been amenorrheic for ≥ 12 months to be considered of non-childbearing potential.
- Serum potassium within normal range.
- Acceptable coagulation status: prothrombin time or International Normalized Ratio (INR), and activated partial thromboplastin time (APTT) ≤ 1.5 x upper limit of normal (ULN) or in the therapeutic range if on anticoagulation therapy.
- Acceptable liver, renal, and bone marrow function including the following:
  - Bilirubin ≤ 1.5 times ULN; if liver metastases were present, then ≤ 3 x ULN was allowed.
  - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine amino transferase/serum glutamic pyruvic transaminase (ALT/SGPT), and alkaline phosphatase ≤ 3 times ULN; if liver metastases were present, then ≤ 5 x ULN was allowed.
  - An estimated creatinine clearance ≥ 45 mL/min using an appropriate formula, or measured ethylenediaminetetraacetic acid (EDTA) renal clearance ≥ 45 mL/min.
  - Absolute neutrophils count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L.
  - Hemoglobin ≥ 9.0g/dL or ≥ 5.6 mmol/L (patients with chronic anemia due to underlying disease and its treatment could undergo blood transfusion prior to treatment in order to meet this criteria).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER

Belinostat Injection 50 mg/mL (intravenous [IV]); batch numbers: 07E24, 07F29, 07H21, 09C06, 09J16, 10A28 and 10C14.
Belinostat Capsules 250 mg; batch numbers: 237496, 244600, 247885, 259543, 256751, 311262, 327594,

332481, 337565.
CaP (IV) were commercially available and to be obtained from the local pharmacy.

DURATION OF TREATMENT

Group A: Belinostat IV (1000 mg/m^2) administered on Days 1, 2, and 3. Subsequently belinostat 2000 mg (flat dose) administered PO on Days 4 and 5, every 3-weeks for up to 6 cycles, in combination with paclitaxel (175 mg/m^2) administered IV following the infusion of belinostat on Cycle Day 3, and IV carboplatin at target area under the curve of 6 minutes × mg/mL (AUC 6) administered directly after the paclitaxel administration on Cycle Day 3. After 6 cycles of treatment, patients in Group A continued treatment on belinostat monotherapy administered PO on Days 1 to 14, every 3 weeks until disease progression or treatment-related toxicities.

Group B: Paclitaxel IV (175 mg/m^2) directly followed by carboplatin (AUC 6) administered IV on Cycle Day 1 of a 3-weekly cycle for up to 6 cycles. After 6 cycles of chemotherapy treatment patients in Group B discontinued treatment.

It was, however, recognized that there may have been circumstances in individual patients that might have made it complex to justify stopping chemotherapy after 6 cycles of treatment in Group B, if no progression or relevant toxicity was observed. Thus, Protocol Amendment 3 allowed for continued chemotherapy of Group B patients beyond 6 cycles. If treatment was continued the Investigator was to clearly document in the patient's Case Report Form (CRF) why it was in the best interest of the individual patient to continue chemotherapy treatment beyond 6 cycles.

REFERENCE THERAPIES, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER

CaP (IV) were commercially available from the local pharmacy.

CRITERIA FOR EVALUATION

EFFICACY

The primary end-point of this study was progression free survival (PFS). PFS was defined as the time from the date of randomization to the day of documented disease progression or death due to any cause. The PFS was based on the tumor assessments as provided by the Investigators. Patients with neither disease progression nor death were censored at the last tumor assessment date they were known not to have progressed. Patients with no tumor assessments after baseline but who were still alive at the time of the clinical cut-off were censored at Day 1. If several response evaluations for a patient were progressive disease (PD), the first of these measurements were used in the analysis of PFS. In the rare event that a patient would undergo curative surgery after experiencing a sufficient shrinkage of tumor lesion(s), any relapse, new occurrence of tumor lesion(s), or death were to be considered as an event. Patients undergoing surgery without any such event occurring were censored at the date of the last tumor assessment that documented that neither a relapse nor a new tumor lesion had occurred.

The secondary end-points included:

- OS: time from the date of randomization to the date of death. Patients who were not reported as having died at the time of the analysis were censored using the date they were last known to be alive).
- ORR: the best overall response of complete response (CR) or partial response (PR) recorded from the start of the treatment until disease progression/recurrence in an individual patient according to RECIST criteria.
- TTR: for patients with overall best response of either CR or PR, TTR was measured as the time from randomization to the first time when the measurement criteria for CR or PR (whichever status was recorded first) were met.
- Duration of complete / overall response: measured from the time that measurement criteria were first met for CR / CR or PR until the first date that PD or death was documented.
- TTP: the time from the date of randomization to the time of disease progression. Patients

without disease progression were censored at the last date they were known not to have progressed. TTP differed from PFS only in terms of whether death was an event: PFS treated all-cause death as events, while TTP only treated death caused by disease progression as an event.

SAFETY

Assessments included analysis of AEs, clinical laboratory results (including hematology, coagulation parameters, and blood chemistry), vital signs, performance status, physical examination, and electrocardiogram (ECG) results. The Medical Dictionary for Regulatory Activities (MedDRA, version 14) was used for assigning system organ classes (SOCs) and preferred terms (PTs).

STATISTICAL METHODS

Numerical data are presented in summary tables by number of patients, arithmetic mean, median, standard deviation, minimum, and maximum. Categorical data are presented by number and percent of patients as well as number events (where applicable).

Demography and other baseline characteristics are summarized using descriptive statistics for each treatment group in the intention to treat (ITT) dataset.

The primary analysis was based on the ITT population and took into account all tumor assessments obtained during the treatment and follow-up phases of the study.

A stratified log-rank test (one-sided) was used for comparing the PFS distributions of the 2 treatment groups. The test used a one-sided significance level of 10%. The test and estimation of HR was conducted using a stratified Cox-regression with treatment as a sole covariate. The stratification was based on ECOG status, lactate dehydrogenase (LDH) status, and study country.

The clinical cut-off for the primary analysis was 60 progression or death events in the intent-to treat population across both treatment groups. The analysis was repeated as a secondary analysis based on the complete data available upon termination of the study.

In addition, PFS was evaluated as a secondary analysis that included only tumor assessments and death events that occurred no later than 28 days after the last confirmed intake of chemotherapy components of the study medication (i.e. paclitaxel or carboplatin). The median PFS and its 95% confidence interval (CI), number of progressions, and censoring were summarized based on the general approach and the on-treatment approach for both ITT and per protocol (PP) populations. Cox proportional hazard modelling results for different combination of populations (ITT and PP), and evaluation approaches (general and on-treatment) was summarized. In addition to the treatment group, pairwise comparison based on the stratification factors (ECOG status, LDH status, and study countries) were included.

Subgroup analyses of HR of treatment Group A vs. B based on stratification factors were summarized and presented graphically for ITT and PP populations.

The PFS rate and corresponding 95% CI at 6, 12, 18 and 24 months for each treatment group evaluated using either a general approach or on-treatment approach for ITT and PP population were be summarized. All patients' PFS were listed.

The OS was analyzed using Cox-proportional hazard regression, the HR together with the 95% CI was reported, in addition to Kaplan-Meier estimates of the survival curves for each treatment arm (including medians and OS rates at 6, 12, 18, and 24 months with 95% CIs). In addition, the results of log-rank tests (both stratified and non-stratified) were provided. The results (using trial treatment as sole covariate as well as together with the stratification variables) were summarized for the ITT as well as the PP populations. The first analysis of OS was conducted at the time of the primary analysis of PFS. A follow-up survival analysis was carried out following the end of trial dated 31 Dec 2012 as of Protocol Amendment 4.

For the analysis of the binary version of the best overall response, a simple test of the odds ratio of the response rates in the two groups was used. Superiority was concluded if the lower limit of the 95% CI for the odds ratio was above 1.

For secondary efficacy parameters TTR and duration of complete / overall response the results of the analyses were summarized by Kaplan-Meier plots. Medians as well as associated 95% CIs were presented for

each treatment group.

All analyses performed for PFS was applied for the assessment of TTP using the same presentation.

All patients who received at least one dose of belinostat, paclitaxel, or carboplatin were included in the safety population. Safety parameters were summarized and listed based on the safety population, but no formal statistical analysis was planned for safety data.

SUMMARIES – CONCLUSIONS

EFFICACY RESULTS

The primary efficacy analysis of PFS for BelCaP versus CaP in ITT, did not show statistical significance at the designated 10% level for the stratified, one-sided log-rank test. The median PFS was 5.4 months (95% CI of 3.0 – 6.0) in the BelCaP group and 5.3 months (95% CI of 2.8 – 6.7) in the CaP group. The primary efficacy result yielded a HR of 1.034 (95% CI at 0.631 – 1.694) with a one-sided p-value of 0.5526.

The top-line OS results for PP had the lowest p-value among the analyses of PFS and OS across the ITT and PP analysis. The median of the top-line OS in the PP analysis set was 11.5 months (95% CI of 7.4 – 18) in the BelCaP group and 9.1 months (95% CI of 6.6 – 11) in the CaP group. The HR was 0.771 with a 95% CI of [0.447, 1.330]. The p-value was 0.1744 and still outside the area where statistical significance is achieved.

Landmark analyses of OS at 6, 12, 18, and 24 months found statistically significant effect at the 10% level (p-value = 0.0991) for 12 month survival rates of 47.6% and 30.2% in the BelCaP and CaP arm, respectively, for the final OS results in PP.

The TTP result yielded HRs close to 1 and did not indicate any statistically significant treatment difference.

In the ITT Analysis Set there were 19 responders (43.2%) in BelCaP group versus 10 responders (22.2%) in the CaP group, the ORR was statistically significant with a p-value of 0.0252, and yielded an odds ratio, at 2.85 (95% CI at 1.12 – 7.27) for BelCaP versus CaP. Thus the ORRs exhibited a statistically significant treatment difference in favor of the BelCaP arm. Most of the responses occurred within 3 months after first study treatment with the majority of responses occurring within 6 months from first study treatment. The results did not indicate any significant difference in DOR.

SAFETY RESULTS

The two groups are fairly balanced, as no statistically significant differences between incidence rates, time to first onset, and duration of selected AEs were found. There was a non-statistically significant trend towards a higher incidence rate of thromboembolic events in Group A compared to Group B. Weaker trends for higher incidence were seen for treatment related vomiting and nausea in patients in Group A compared to Group B. There were no clinically relevant findings for the safety laboratory variables, as the majorities were within normal ranges throughout the study for the majority of patients.

CONCLUSION

The primary efficacy analysis of PFS for BelCaP versus CaP in ITT yielded a median PFS of 5.4 months in the BelCaP, and 5.3 months in the CaP group, which was not statistically significant. No statistically significant treatment difference was seen for secondary efficacy analysis for OS and TTP for BelCaP compared to CaP.

A statistically significant difference for ORR in favor of BelCaP treatment was observed. Most of the responses occurred within 3 months after first study treatment, and all but 3 responses occurred within 6 months from first study treatment. The results did not indicate any significant difference in DOR.

Overall, the combination of belinostat, paclitaxel, and carboplatin was well tolerated and the safety profile was comparable between the two treatment groups.

DATE OF THE REPORT: 30 Oct 2014