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		
NAME OF ACTIVE INGREDIENT Belinostat (PXD101)		

TITLE OF STUDY: A Phase 1/2 Clinical Trial of PXD101 in Combination with Doxorubicin in Patients with Soft Tissue Sarcomas

INVESTIGATORS:

Three principal investigators at 3 sites, including the international coordinating investigator who was responsible for approval of the clinical study protocol and report on behalf of all Investigators: Ole Steen Nielsen.

- Site 001: Ole Steen Nielsen and Akmal Ahmed Safwat
- Site 002: Ian Judson
- Site 003: Anders Krarup Hansen

Study coordination: Topotarget A/S

STUDY CENTERS:

The study was conducted at 2 centers in Denmark and at one center in United Kingdom:

- Site 001: Aarhus Hospital, Department of Oncology, Noerrebrogade 44, Building 5, 8000 Aarhus C, DK.
- Site 002: The Royal Marsden Hospital, NHS Trust Institute of Cancer Research, Sycamore House, Downs Road, Sutton Surrey, SM2 5PT, UK.
- Site 003: Herlev Hospital, Clinical Research Unit 54B1, Oncological Department, 2730 Herlev, DK.

PUBLICATION (REFERENCE):
André Brunetto, Anders Krarup-Hansen, Ole Steen Nielsen, Anni Norman, Akmal Safwat, Jette Tjørnelund and Ian Judson : A Phase I Clinical Trial of Belinostat (PXD101) in Combination with Doxorubicin (BelDox) in Patients with Advanced Solid Tumours including Soft Tissue Sarcomas (STS), both as Poster and Abstract at EORT-NCI-AACR October 2008.

STUDY PERIOD: 23 Apr 2007 (first patient informed consent) to 23 Oct 2012 (last patient last visit)	**PHASE OF DEVELOPMENT:** 1/2

OBJECTIVES:

Primary Objective

To determine the tolerance (Maximum Tolerated Dose (MTD)), the Dose-Limiting Toxicity (DLT) and the efficacy of belinostat and doxorubicin combination treatment as measured by response rate (complete response (CR) or partial response (PR) using the Response Evaluation Criteria in Solid Tumors (RECIST).

Secondary Objectives

- To examine the time to response, the duration of response, and survival following belinostat combination therapy.

- To examine disease control rate (CR+PR+Stable Disease [SD]).
- To examine the pharmakokinectic (PK) of belinostat and doxorubicin in the combination.
- To examine pharmacodynamic (PHDY) aspects of the treatment.

METHODOLOGY: The PXD101-CLN-14 study was an open-label, multicenter, dose-escalation, Phase 1/2 study to evaluate safety, efficacy, PHDY, and PK of the combination of belinostat with doxorubicin (BelDox) in patients with advanced solid tumors. Belinostat was to be administered as a 30-minute IV infusion every 24 hours (± 2 hours) on Days 1 to 5, followed by 2 weeks of observation. Doxorubicin was administered IV on Day 5. This cycle of belinostat plus doxorubicin treatment was repeated every 3 weeks, as long as there was no evidence of significant treatment-related toxicities or progressive disease (PD). All patients were planned to receive at least 2 cycles of therapy.

Doxorubicin cumulated dose was to be followed and dosing was to follow the cardiotoxicity guidelines. Completion of 6 complete cycles of belinostat treatment was considered the standard study duration for each patient. Patients who achieved a clinical benefit from the treatment (objective response or SD) could have continued belinostat treatment beyond the 6th cycle according to the Investigator's advice. If the cumulative upper dose of doxorubicin (450 mg/m^2) was exceeded the treatment would have continued with belinostat as monotherapy. This extension was considered as the long-term follow-up phase of the study with continued assessments of anti-tumor effects and abbreviated assessments of safety.

Safety assessments were to be performed at every cycle, and efficacy assessments every 2 cycles. Dose escalation was planned for belinostat using 600, 800, and 1000 mg/m²/d (day) doses, whereas the dose of doxorubicin was evaluated in 2 dose steps, 50 mg/m^2 and 75 mg/m^2. Escalation decisions were made based on a minimum of 3 weeks data from Cycle 1 for all patients in a given cohort.

At least 3 patients should be treated with each of these dose levels. If a DLT was found in one of these cohorts it was to be expanded to a total of 6 patients. If DLTs were found in ≥ 2 patients in Cohort 1, then the accrual would have been suspended and the study design would have been modified after review of the safety data. If there was no DLT in 3 patients or ≤ 1 DLT in 6 patients in each of the cohorts, the study was to proceed to the next dose level. If ≥ 2 DLTs were found at a dose level, it would have been declared above the MTD and the MTD would have been defined as the preceding dose level after its expansion to a minimum of 6 patients. Thus, 3 to 6 patients were assessed for each of the 4 different dose levels of belinostat/doxorubicin. The escalation decision was made by review of all available data in consultation between the Sponsor and the Investigator. Once the MTD had been established, up to a total of 20-40 patients with STS were to be enrolled at the MTD dose level (Phase 2) to examine efficacy and safety in this specific patient population. The study was to have been stopped if no more than 2 responses of CR or PR were seen among the first 20 of these patients in Phase 2.

NUMBER OF PATIENTS (PLANNED AND ANALYSED):

It was planned to enroll 2-6 patients in each cohort and 20-40 patients with STS at the MTD dose level.
A total of 41 patients were enrolled into the study, 25 patients were enrolled in the dose escalation Phase 1 of the study and 16 STS patients were enrolled in the MTD expansion Phase 2 of the study.

Six patients were treated in Cohort 4, which was declared the MTD. Among these 6 patients 4 soft tissue sarcoma patients were included in the evaluation of the decision rule for the stage two of the Simon design.

Sixteen patients were enrolled in Phase 2, and together with the 4 patients mentioned above these were grouped as the first stage of the MTD expansion phase. There was only one responder within the first 2 cycles; as at least 3 responders were required according to the decision rule to warrant the enrolment of another 20 patients, the study was stopped after these 16 patients had been enrolled into Phase 2.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

- Signed consent of an Independent Ethics Committee (IEC) approved informed consent form (ICF).
- **A**. For the dose escalation phase: Patients with histological or cytological confirmed solid tumours (including sarcomas), for which there was no known curative therapy.
- **B**. For the MTD expansion phase: Patients with an established diagnosis of soft tissue sarcoma who

were in need of first line chemotherapy and with measurable disease.

- Performance status Eastern Cooperative Oncology Group (ECOG) ≤ 2.
- Life expectancy of at least 3 months.
- Age ≥ 18 years.
- Acceptable liver, renal, and bone marrow function including the following:
  a) Bilirubin ≤ 1.5 times upper limit of normal (ULN).
  b) Aspartate aminotransferase AST (SGOT), alanine aminotransferase ALT (SGPT), and alkaline phosphatase ≤ 3 times upper limit of normal (if liver metastases were present, then ≤ 5 × ULN was allowed).
  c) Serum creatinine ≤ 1.5 times ULN).
  d) Leucocytes > 2.5×10^9/L, neutrophils > 1.0×10^9/L, platelets > 100×10^9/L.
  e) Hemoglobin > 9.0 g/dL or > 5.6 mmol/L.
- Acceptable coagulation status: prothrombin time (ProTime) and activated partial thromboplastin time (APTT) within ≤ 1.5 x ULN or in the therapeutic range if on anticoagulation.
- A negative pregnancy test for women of childbearing potential. For men and women of child-producing potential, the use of effective contraceptive methods during the study was required.
- Serum potassium within normal range.

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

Belinostat: presented as a concentrate for solution for infusion and supplied in single use 10 mL glass vials containing 500 mg belinostat in a concentration of 50 mg/mL of belinostat and 100 mg/mL L-arginine. The drug was diluted with 250 mL of 5% glucose or 0.9% saline before infusion. Infusion administered using 0.22 µm in-line filters. Batch numbers: P07205 (TPTP13), 06H10 (24596), 07A27 (24890), 07E24 (25026), 07H21 (25058), 09C06 (25869), 09J16 (26070), 10A28 (26172), 10C14 (26256), 11B04 (26584), and 11H29 (26803).

Belinostat and doxorubicin were handled and administered according to the regulations concerning cytotoxic anti-cancer agents and obtained from the hospital pharmacy.

Doxorubicin was to be administered IV 2 hours following the infusion of belinostat on cycle Day 5.

DURATION OF TREATMENT:

The combination treatment of belinostat (Days 1-5) and doxorubicin (Day 5) was to be repeated every 3 weeks, until evidence of significant treatment-related toxicities or PD. All patients were planned to receive at least 2 cycles of therapy.
Completion of 6 cycles of belinostat treatment was considered the standard study duration for each patient. Patients who achieved a clinical benefit from the treatment (objective response or SD) could have continued belinostat treatment beyond the 6th cycle according to the Investigator's advice.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

Doxorubicin intravenous (IV) was commercially available from the hospital pharmacy.

CRITERIA FOR EVALUATION:

EFFICACY AND PHARMACOKINETICS:
The primary efficacy variable was the best overall objective response (CR and PR) following up to 6 cycles of treatment with confirmation according to the RECIST criteria.
The secondary efficacy variable was the disease control rate (objective response [OR] and SD) following up to 6 cycles of treatment with confirmation according to the RECIST criteria.
The pharmacokinetic objective of the study was to examine the pharmacokinetics of belinostat and doxorubicin in the combination.
SAFETY:
Assessments included analysis of adverse events, clinical laboratory results (including hematology, coagulation parameters, and clinical chemistry, urinalysis), 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 (SOC) and preferred terms (PT).

STATISTICAL METHODS:

The full-analysis set (FAS) was defined as all patients enrolled in the study who received at least 1 dose of study drug, and for whom at least 1 tumor assessment was performed post-baseline.

The safety analysis set was defined as all patients who received at least 1 dose of study drug.

The efficacy variables were evaluated for the FAS using descriptive statistics.

Safety parameters were evaluated for the safety analysis data set. No formal statistical analysis was planned for safety data and safety data were summarized using descriptive statistics.

SUMMARIES – CONCLUSIONS:

EFFICACY CONCLUSION

The primary efficacy endpoint was best overall objective response (CR and PR) following up to 6 cycles of treatment with confirmation according to the RECIST criteria. There were 2 patients among 25 in the dose escalation Phase 1 with an objective response, and similarly 2 patients among 16 in the MTD expansion phase with an OR. The response rates were 8% and 12.5% in the 2 phases with 95% confidence intervals of (1.0 %, 26.0 %) and (1.6 %, 38.8%), respectively.

With 1 objective responding patient at tumor evaluation after Cycle 2 (003-031) among the Phase 2 STS patients treated at the MTD (4 STS patients in Phase 1/Cohort 4 plus 16 STS patients in MTD expansion phase) the decision not to enter Stage two of the Simon stage design was made.

Three patients with OR and 11 patients with SD were observed among STS patients treated with 30-minute IV belinostat at 1000 mg/m^2 on Days 1-5 every 3-weeks in combination with doxorubicin 75 mg/m^2 IV on Day 5. This corresponds to a response rate of 15% (3/20 patients), and a disease control rate of 70% (14/20 patients).

The median time to progression was 3.7 months in the dose escalation Phase 1 (95% CI: 3.0-5.6 months), and 6.0 months in the MTD expansion phase (95% CI: 1.6-9.7 months).

The time to response for the 3 responders among STS patients ranged from 1.8 to 3.5 months, and duration of response ranged from 135 to 345 days.

Belinostat appeared to exhibit dose-proportional pharmacokinetics across the dose range studied. In addition, there was no evidence that co administration with doxorubicin had any effect on belinostat exposure in consideration of the between-patient variability (16.2 to 43.2% for $AUC_{0\text{-}tlast}$ and 13.6 to 69.2% for C_{max}).

SAFETY CONCLUSIONS:

Twenty-five patients were enrolled and treated with belinostat in dose escalation Phase 1; 3 patients in Cohort 1 (BelDox: 600/50 mg/m^2), 7 patients in Cohort 2 (BelDox: 600/75 mg/m^2), 9 patients in Cohort 3 (BelDox: 800/75 mg/m^2), and 6 patients in Cohort 4 (BelDox: 1000/75 mg/m^2). Sixteen patients were enrolled and treated in the MTD expansion phase and treated with BelDox: 1000/75 mg/m^2. No DLTs were observed. Thus a formal MTD was not reached and the MTD was declared at the highest tested dose level: 30-minute IV infusion with belinostat at 1000 mg/m^2 on Days 1-5 in combination with doxorubicin IV at 75 mg/m^2 on Day 5 every 21-days.

In phase 2 belinostat and/or doxorubicin dose reduction was observed in 15 out of 20 patients and was most frequent from Cycle 2. For all patients, except one, the reason for dose modification was associated with decrease in neutrophilic counts.

All 41 exposed patients experienced at least one TEAE, and in total, 1059 TEAEs were reported.

The most frequent events were fatigue (39 patients; 95%), nausea (31 patients; 76%), alopecia (26 patients; 63%), vomiting (24 patients; 59%), constipation, neutropenia, dyspnea and decreased appetite (all experienced by 22 patients; 54%), , mucosal inflammation (20 patients; 49%), headache (18 patients; 44%)

and injection site reaction (16 patients; 39%).

The majority of worst grade per patient TEAEs were classified as Grade 1 (275/562) or Grade 2 (207/562). Fifty-five events in 29 patients were Grade 3, 24 events in 18 patients were Grade 4, and 1 event was Grade 5.

In total, 332 TEAEs (worst grade per patient) were assessed by the Investigator as related to study drug. The majority of related TEAEs were mild (Grade 1 [152]) or moderate (Grade 2 [125]).

Of the 41 patients enrolled and dosed in the study, one patient died. A 51-year-old male patient in Cohort 3 had an AE (disease progression) with a fatal outcome. The event was evaluated by the Investigator as unrelated to study drug.

In total, 23 of 41 patients (56.1%) experienced 34 serious TEAEs during the study, and 15 of the serious TEAEs in 13 patients were judged by the Investigator as related to the study drug. These related SAEs included 5 events of febrile neutropenia, 2 events of neutropenia, and single events of bacteremia, abdominal abscess, vomiting, nausea, hemoglobin decreased, neutropenic sepsis, hypersensitivity, and pneumonia. The reported outcome in all patients was 'recovered' or 'resolved'.

Three patients discontinued from the study due to serious TEAEs (fatigue/febrile neutropenia [related], neutropenic sepsis [related], and myocardial ischemia [not related]).

As expected when combining with doxorubicin, myelotoxicity was reported with decrease in neutrophilic cells (neutropenia, febrile neutropenia, neutrophil count, neutrophil count decrease) being the most frequent (> 50 % of the patients) and represented by several reports of Grade 3/4 events. Anemia was the second most frequent (> 25% of the patients), but less severe.

The ECG data revealed no clear change in heart rate, PR interval duration or QRS interval duration. While some new morphological changes were noted their attribution to belinostat was unlikely. While the sample size in the cardiac safety report was small, no clear dose related changes could be observed for the effect of belinostat on cardiac repolarization (QTcF changes). The most important analysis in light of the small sample sizes and lack of control groups was the effect exposure model which did not suggest a clinically relevant change to QTcF related to belinostat. The data comparing belinostat administered alone versus the combination of belinostat and doxorubicin did not suggest any clear differences in ECG effects but this conclusion should be viewed with caution in light of the study design, small sample sizes and lack of controls. In conclusion, the ECG analysis did not show any clear signal of effect of belinostat on ECG parameters.

The hematological findings indicated myelotoxicity and supported reported TEAEs of decreases in neutrophilic cells (neutropenia, febrile neutropenia, neutrophil count, neutrophil count decrease) and anemia.

Most clinical chemistry parameters and the majority of coagulation parameters were within normal ranges throughout the treatment period, and there are no apparent cumulative effects or patterns in shifts of level.

No changes in physical examination findings or vital signs suggested an increased safety risk with belinostat.

CONCLUSION:

No DLTs were observed. The MTD was declared at the highest tested dose level: 30-minute IV infusion with belinostat at 1000 mg/m^2 on Days 1-5 in combination with doxorubicin IV at 75 mg/m^2 on Day 5 every 21-days. However, the well known pronounced myelotoxicity of doxorubicin was observed and is considered a safety concern when belinostat is combined with doxorubicin.

The study was terminated after treatment of 20 STS patients at the MTD dose level

DATE OF THE REPORT: 12 Feb 2015