2 SYNOPSIS

NAME OF COMPANY: Topotarget A/S, CuraGen, and Spectrum Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Belinostat Injection 50 mg/mL	Volume:	
NAME OF ACTIVE INGREDIENT: Belinostat (PXD101)	Page:	

TITLE OF STUDY: A Phase 1/2 Safety, Pharmacodynamic, and Pharmacokinetic Study of Intravenously Administered PXD101 Plus Carboplatin or Paclitaxel or Both in Patients with Advanced Solid Tumors

INVESTIGATORS:
Coordinating Investigator (Site 001): Dr. Ulrik Lassen, Department of Oncology, The Finsen Center, Copenhagen University Hospital, Copenhagen, DK.
Principal Investigators:
Site 002: Dr, Johann de Bono.
Site 003: Dr. Robert John Jones.
Site 004: Dr. Lisa Sengeløv.
Site 101: Dr. Richard Penson.
Site 102: Dr Don Dizon.
Site 105: Dr. James Hoffman.
Site 106: Dr. John Micha.
Site 108: Dr. Neil Finkler.
Site 109 Dr. Patricia Braly.
Site 111: Dr. Paul Celano.

STUDY CENTERS:
Part A: The Phase 1 part (advanced tumor) was conducted at:
- Site 001: The Finsen Center, Copenhagen University Hospital, DK
- Site 002: The Royal Marsden NHS Trust, Cancer Research, UK
- Site 101: Massachusetts General Hospital Cancer center, Boston, US

Part B: The Phase 2 part, MTD expansion phase (ovarian cancer) was conducted at:
- Site 001: The Finsen Center, Copenhagen University Hospital, DK
- Site 002: The Royal Marsden NHS Trust, Cancer Research, UK
- Site 003: The Beatson West of Scotland Cancer Centre, Glasgow, UK
- Site 101: Massachusetts General Hospital, Boston, Massachusetts, US
- Site 102: Women & Infants Hospital, Providence, Richmond, Rhode Island, US
- Site 105: The hospital of Central Connecticut at New Great Britain General, Connecticut, US
- Site 106: Gynecologic Oncology Associates, Newport Beach, California, US
- Site 108: Florida Hospital Cancer Institute, Orlando, Florida, US
- Site 109: Hematology and Oncology Specialists, LLC, Metairie and Covington, Louisiana, US
- Site 111: Greater Baltimore Medical Center (GBMC), Baltimore, Maryland, US

Part C: The site specific study: Safety and PK/PHDY study after 3 and 6 hour IV infusion (refractory solid tumors) was conducted at:
- Site 001: The Finsen Center, Copenhagen University Hospital, DK

Part D: The site specific study: Safety and PK/PHDY study (urothelial [transitional cell] carcinoma of the bladder) was conducted at:
- Site 001: The Finsen Centre, Copenhagen University Hospital, DK
- Site 002: The Royal Marsden NHS Trust. Cancer Research, UK
- Site 003: The Beatson West of Scotland Cancer Centre, Glasgow, UK
- Site 004: Department of Oncology, Herlev Hospital, DK

PUBLICATION (REFERENCE):
D. S. Dizon, L. Damstrup, N. J. Finkler, U. Lassen, P. Celano, R. Glasspool, E. Crowley, H.S. Lichenstein, P.

Knoblauch, and R. T. Penson: "Phase II activity of belinostat (PXD-101), carboplatin, and paclitaxel in women with previously treated ovarian cancer" Int J Gynecol Cancer. 2012 Jun 12.

U Lassen, LR Molife, M Sorensen, S-A Engelholm, L Vidal, R Sinha, RT Penson, P Buhl-Jensen, E Crowley, J Tjornelund, P Knoblauch and JS de Bono: "A phase I study of the safety and pharmacokinetics of the histone deacetylase inhibitor belinostat administered in combination with carboplatin and/or paclitaxel in patients with solid tumours" British Journal of Cancer (2010) 103, 12 – 17.

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Neil J. Finkler, Don S. Dizon, Patricia Braly, John Micha, Ulrik Lassen, Paul Celano, Roslind Glasspool, Elizabeth Crowley, Peter Buhl-Jensen, Richard T. Penson: "Phase II multicenter trial of the histone deacetylase inhibitor (HDACi) belinostat, carboplatin and paclitaxel (BelCaP) in patients with relapsed epithelial ovarian cancer" ASCO[2], 2008.

Morten Sørensen, Jette Tjørnelund, Peter Buhl Jensen, and Ulrik Lassen: "A phase I safety and pharmacokinetic (pk) study of 3 and 6 hours intravenously administered belinostat (PXD101) Plus carboplatin (C) and paclitaxel (P) in patients with advanced solid tumours" EORTC-NCI-AACR[3], 2008.

U. Lassen, P. Braly, J.S. de Bono, P. Celano, D. Dizon, R. Glasspool, J. Micha, R.T. Penson, N. Finkler: "Phase (Ph) I/II study of the histone deacetylase inhibitor belinostat (bel) in combination with carboplatin (ca) and paclitaxel (p) in advanced solid tumors (Ph I) and relapsed ovarian cancer (Ph II)" ESMO[4], 2008.

R. Sinha, R. Moliffe, M. Scurr, L. Vidal, S. A. Engelholm, P. Buhl Jensen, A. Normann, S. Li, J. De Bono, U. Lassen: " A phase I/II study of the safety and anti-cancer activity of IV-administered belinostat (PXD101) plus carboplatin (C) or paclitaxel (P), or both in patients with advanced solid tumors" ASCO, 2007.

Neil J. Finkler, Don Dizon, John Micha, Patricia Braly, Ulrik Lassen, S. A. Sngelholm, Rosalind Glasspool, Elizabeth Crowley, Shu-Xia Li, Peter Buhl-Jensen, Richard Penson: "Phase II multicenter trial of belinostat (PXD101) in combination with carboplatin and paclitaxel (BelCaP) for patients (pts) with relapsed ovarian cancer" AACR-NCI-EORTC, 2007.

Ulrik Lassen, Morten Sørensen, Johann de Bono, Rhoda Molife, Laura Vidal, Sarah Settatree, Michael V. Seiden, Shu-Xia Li, Peter Buhl Jensen: "A Phase I Safety, Pharmacokinetic and Pharmacodynamic Study of Intravenously Administered PXD101 Plus carboplatin or paclitaxel or Both in Patients with Advanced Solid Tumors" EORTC-NCI-AACR, 2006.

STUDY PERIOD:	**PHASE OF DEVELOPMENT: 1/2**
First Patient Enrolled: 29-Aug-2005 Last Patient Last Visit: 27-Feb-2009	

OBJECTIVES:

Primary Objective:

- To determine the maximum tolerated dose (MTD) and the dose limiting toxicity (DLT) of

[1] ECCO: European Multidisciplinary Cancer Congress
[2] ASCO: American Society of Clinical Oncology
[3] EORTC: European Organization for Research and Treatment of Cancer, NCI: National Cancer Institute, AACR: American Association of Cancer Research.
[4] ESMO: European Socity for Medical Oncology

belinostat (in doses up to 1000 mg/m²/d) administered in combination with standard doses of carboplatin at a target Area Under the Curve (AUC) of 5 mg/mL/min [5]or paclitaxel at a dose of 175 mg/m^2 or both to patients with solid tumors.

- To confirm safety of the belinostat, carboplatin and paclitaxel combination delivered at the MTD defined in the initial part of the study in patients with urothelial (transitional cell) carcinoma of the bladder (Amendment 2 13 Dec 2006, Part D).

Secondary Objectives:

- To determine the pharmacokinetics of belinostat and its effect on carboplatin and paclitaxel pharmacokinetics. Carboplatin and paclitaxel baselines were to be defined from historical and/or literature data.
- To determine the pharmacodynamic (PHDY) effect of belinostat in combination with carboplatin and/or paclitaxel on histone acetylation in peripheral mononuclear blood cells (selected sites).
- To observe patients for any evidence of anti-tumor activity. *This objective was replaced with:* To explore anti-tumor activity of the combination of belinostat plus carboplatin and paclitaxel in patients with advanced solid tumors and in the MTD expansion arm in patients with ovarian cancer in need of relapse treatment (protocol Global version 4).
- To explore the safety, efficacy, pharmacokinetics (PK), PHDY of a prolonged infusion (3 or 6 hours) of belinostat in patients with refractory solid tumor other than ovarian cancer settings (Amendment 31-Oct-2006, Part C).
- To assess PK, PHDY and to make a preliminary assessment of therapeutic efficacy in patients with urothelial (transitional cell) carcinoma of the bladder (Amendment 2 13-Dec-2006, Part D).

METHODOLOGY:

The study was an open-labeled, multicenter, dose-escalation Phase 1/2 study in patients with solid tumors confirmed by histology or cytology for whom there was no standard therapy (Part A), and an additional MTD expansion arm (Part B), where recruitment was limited to women with a history of epithelial ovarian cancer. The study was designed to evaluate the safety, PHDY, PK and preliminary assessments of efficacy in patients with advanced solid tumors, when belinostat was administered intravenous (IV) and in combination with carboplatin and paclitaxel every 3 weeks. The protocol was amended to also include safety, PK/PHDY and preliminary efficacy study of patients with urothelial (transitional cell) carcinoma of the bladder treated with belinostat, carboplatin and paclitaxel combination at the MTD expansion level (Part D). In addition, the protocol was amended to include additional patients with advanced solid tumors in a safety, PK/PHDY and preliminary efficacy study of 3-6 hour IV belinostat infusion in combination with carboplatin and paclitaxel to examine prolonged IV infusion of belinostat (Part C).

NUMBER OF PATIENTS (PLANNED AND ANALYSED):

Phase 1:

Part A: Advanced solid tumors, dose escalation: 30 patients planned, 27 enrolled, and 23 treated.

Phase 2:

Part B: Ovarian cancer, MTD: 18-32 planned, 35 enrolled, and 35 treated.

Part C: Refractory solid tumor, other than ovarian cancer, 3 or 6 hour infusion: 10-12 patients planned, 7

[5] Note: unit for AUC should read mg×min/mL not mg/ml/min. Calvert formula: total Dose (mg) = target AUC (mg×min/mL) x [estimated GFR (mL/min) + 25].

enrolled, and 7 treated.

Part D: Bladder cancer, MTD: 15 patients planned, 16 enrolled, and 15 treated.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Inclusion criteria

For patients to qualify for participation in this study they must meet the following criteria:

1. Signed consent of an IRB approved consent form.
2. Patients with histologically confirmed solid carcinomas, for which there is no known curative therapy.
3. Performance status (Eastern Cooperative Oncology Group [ECOG]) ≤ 2.
4. Life expectancy of at least 3 months.
5. Age ≥ 18 years.
6. Acceptable liver, renal and bone marrow function including the following:
   a. Bilirubin ≤ 1.5 times upper limit of normal (ULN).
   b. Aspartate amino transferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine amino transferase (ALT) /serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase ≤ 3 times ULN (if liver metastases are present, then ≤ 5 x ULN is allowed).
   c. Measured Ethylenediaminetetraacetic acid (EDTA) renal clearance ≥ 45 mL/min (EU sites). At the US sites calculated creatinine clearance ≥ 45 mL/min using the Jeliffe formula.
   d. Leukocytes > 2.5×10^9/L, neutrophils > $1.0\text{x}10^9$/L, platelets > 100×10^9/L.
   e. Hemoglobin > 9.0 g/dL or > 5.6 mmol/L.
7. Acceptable coagulation status: prothrombin time-international normalized ratio (PT-INR)/ activated partial thromboplastin time (APTT) ≤ 1.5 × ULN or in the therapeutic range if on anticoagulation therapy
8. 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 is required.
9. Serum potassium within normal range (added in protocol Global version 3.0)

Additional Eligibility Criteria at the MTD Expansion only

10. Patients with epithelial ovarian cancer in need of relapse treatment. Changed with protocol Global version 3 to: Patients with epithelial ovarian, primary peritoneal, fallopian tube or mixed mullerian tumors of ovarian origin in need of relapse treatment.

Or

11. Patients with urothelial (transitional cell) carcinoma of the bladder who have received up to a maximum of 3 previous chemotherapy regimens in the advanced disease setting (neoadjuvant chemotherapy is not included in the total of chemotherapy regimens), applies only for patients enrolled in Part D.
12. At least one uni-dimensional measurable lesion. Lesions must be measured by CT scan or MRI

according to Response Evaluation Criteria in Solid Tumors (RECIST) (Added with protocol Global version 4).

13. Eligibility Criteria for the Site Specific Amendment (Part C) - Advanced solid tumors only

14. Patients with refractory solid tumors other than ovarian cancer.

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

Belinostat injection 50 mg/mL; batch numbers EU: P02505 (TPTP08), P02705 (TPTP09), P04505 (TPTP10), P04605 (TPTP11), P06505 (TPTP12), P07205 (TPTP13), 05J20 (244020), 06B03 (24516), 06H10 (24596), 06K08 (24801), 07A27 (24890), 07E24 (25026) and 07H21 (25058).

Batch numbers US: 05J20 (244020), 06K08 (24801), 07A27 (24890), and 2H5660.

DURATION OF TREATMENT:

Part A: Belinostat (600, 800 or 1000 mg/m²) was administered as a 30-minute IV infusion every 24 hours (± 2 hours) for 5 days on Day 1-5 every 3 weeks. In each cycle carboplatin (AUC of 5) or paclitaxel (175 mg/m²) or both were to be administered 2-3 hours following the infusion of belinostat on cycle Day 3. The carboplatin dose was determined using a target AUC of 5 mg/mL/min and the paclitaxel dose was 175 mg/m2. The series were repeated every 3 weeks and all patients are planned to receive at least 2 cycles of therapy.

Part B/D: Belinostat (1000 mg/m²) was administered as a 30-minute IV infusion every 24 hours (± 2 hours) for 5 days on Day 1-5 every 3 weeks in combination with carboplatin (AUC 5 IV) and paclitaxel (175 mg/m² IV) both administered 2-3 hours following the infusion of belinostat on cycle Day 3 (paclitaxel followed by carboplatin) to patient with ovarian cancer or urothelial (transitional cell) carcinoma of the bladder.

Part C: Belinostat (1000 mg/m²) was administered as a 3- or 6-hour IV infusion every 24 hours (± 2 hours) for 5 days on Day 1-5 every 3 weeks in combination with carboplatin (AUC of 5 IV) and paclitaxel (175 mg/m² IV) both administered 2-3 hours following the infusion of belinostat on cycle Day 3 (paclitaxel followed by carboplatin) to patient with refractory solid tumor.

Treatment cycles of the belinostat combinations were repeated every 3 weeks until disease progression or evidence of significant treatment-related toxicities. 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 stable disease) might continue treatment beyond the 6th cycle according to the investigators advice. This extension was considered as the long-term follow-up phase of the study.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER: No other therapy

CRITERIA FOR EVALUATION:

EFFICACY: Response and progression were evaluated in measurable disease according to the RECIST criteria and CA-125 response was evaluated in patients with ovarian cancer (part B).

PHARMACODYNAMICS:
Histone acetylase analysis was planned, but not successful due to technical issues with the method.

PHARMACOKINETICS:
Blood samples were collected and analyzed for belinostat in plasma during mono- and combination therapy and for carboplatin and paclitaxel during combination therapy.

SAFETY: Assessments included analysis of adverse events (AEs), vital signs, physical examination results, electrocardiograms (ECGs), and clinical laboratory results (including hematology, coagulation parameters, serum chemistry). The Medical Dictionary for Regulatory Activities (MedDRA) was used for assigning system organ classes and preferred terms.

STATISTICAL METHODS:

Descriptive statistics were used to describe the study population and the observed antineoplastic effect. All patients who received at least one dose of study drug were included in the efficacy and safety analyses. Frequency tables were generated for patient's assessment of tolerability. Data were summarized using SAS version 9.1 or later.
Standard pharmacokinetic and statistical calculations were performed using Microsoft® Office Excel® 2007, version 12.0 and Analyse-it for Excel 12+, version 2.20.
The ECGs were recorded at the sites and ECGs were sent to a central laboratory, eResearch Technology (eRT) Inc. (Philadelphia, PA, USA) for a blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment.

SUMMARIES – CONCLUSIONS:

EFFICACY RESULTS:
Part B (ovarian cancer treated at MTD): overall response rate was 54% (95% confidence interval [CI] 37 to 71%) and the overall disease control rate was 80% (95% CI 63 to 92%). The median time to progression was 5.8 months, the median time to response was 4.1 months and the median response duration was 5.3 months. There was no apparent relationship between platinum sensitivity and time to event parameters. In total 48%, 12% and 6% of the patients obtained more than 6-, 12- or 18-month progression free survival (PFS), respectively. Patients classified as being sensitive to most recent platinum regimen given had significantly higher overall response and prolonged PFS compared to patients being platinum resistant.
Part C (prolonged belinostat infusion): 6 patients (two colorectal cancer, one cancer of unknown primary, one liver cancer, and two stomach cancer patients were evaluated for response. None of the patients treated in Part C obtained objective response (OR). Four patients obtained stable disease (SD).
Part D (bladder cancer treated at MTD): overall response rate was 27% (95% CI 8 to 55%) and the overall disease control rate was 93% (95% CI 68 to 100%). Median time to progression was 136 days and median time to response was 35 days.
SAFETY RESULTS:
Part A: DLT did not occur. A total of 27 serious adverse events (SAEs) were reported for 17 (74%) patients; none except one were assessed as drug related by the investigator. One patient had cardiac ischemia judged as a probably related SAE and study drug was discontinued. ECGs were submitted for a manual digital analysis to eRT for analysis, which indicated that no corrected QT interval (QTc) above 405 milliseconds (msec) could be observed, that the patient was in sinus tachycardia with T-waves flattening and observation of ST segment depression confirming the non-specific ST-T wave changes. MTD was declared at the highest tested dose level: belinostat 1000 mg/m²/day, 30-minute IV infusion on Day 1-5, every 3 weeks in combination with standard, carboplatin/paclitaxel (5 AUC/175 mg/m^2) IV on Day 3. This dose was the recommended Phase 2 dose and used for Parts B-D.
Part B/D: One patient died during study due to progressive disease (Part B). Two patients discontinued from study due to related AEs; one with increase in ALT and AST liver parameters and one with myocardial ischemia/syncope. Dose was reduced for belinostat in 14 patients, for carboplatin in 11 patients, and for paclitaxel in 21 patients. The most common AEs assessed as related to study drugs - were nausea, fatigue, vomiting, diarrhea, and alopecia. Incidence of peripheral sensory neuropathy was 53.3% in bladder cancer patients, while less than 20% in ovarian cancer patients. Approximately half of the patients experienced SAEs of which about 1/4 were assessed as related to study drug. In ovarian cancer patients five related SAEs were Grade 3 (three drug hypersensitivity, one ischemia, and one hemorrhagic disorder) and two were Grade 2 (dehydration, anemia) events. In all three cases, the observed drug hypersensitivity was associated to carboplatin treatment. In bladder cancer patients related SAEs were one Grade 3 (neutropenic sepsis), three Grade 2 (myocardial ischemia, chest pain, peripheral sensory neuropathy), and one Grade 1 (electrocardiogram T wave inversion). The incidence of injection site injury was 20-30%. The incidence of anemia was 53-69%, neutropenia/leukopenia was 33-63% and thrombocytopenia was 6.7-43%. More than 80% of the patient had no or limited (one grade shift) in platelet counts during treatment. Central analysis of electrocardiograms judged it unlikely that belinostat alone or in combination with carboplatin and paclitaxel causes a change in heart rate, PR-interval or QRS duration. A similar effect of belinostat alone or in combination on QTc duration was demonstrated. It was found to be above 5 msec, which is considered the

regulatory threshold, but probably <15 msec using the upper confidence interval from the effect exposure model.

PHARMACOKINETIC RESULTS:

Belinostat pharmacokinetic parameters were similar to those previously reported for IV belinostat in this patient population. The PK of paclitaxel and carboplatin administered following belinostat treatment on Day 3, were similar to those previously reported for these agents. The PK profiles of paclitaxel and carboplatin did not appear to change as the belinostat dose was increased from 600 to 1000 mg/m^2, and the co-administration of these drugs did not appear to alter the PKs of belinostat at the MTD.

CONCLUSIONS:

In conclusion, belinostat in combination with standard doses of carboplatin and paclitaxel is well tolerated representing a safety profile consistent of that observed with carboplatin/paclitaxel alone. The recommended dose of belinostat in combination with standard dose carboplatin and paclitaxel is 1000 mg/m^2/day, 30-minute IV infusion on Day 1-5, every 3 weeks. Anti-tumor activity of belinostat in combination with carboplatin/paclitaxel was demonstrated in ovarian cancer patient both platinum sensitive or resistant, with best response in patients sensitive to the most recent platinum regimen given. In bladder cancer patients, anti-tumor activity was observed as the disease control rate was near 100%. The PK profiles for belinostat, paclitaxel and carboplatin when given in combination was similar to single agent PK profiles indicating no pharmacokinetic interaction between belinostat and carboplatin/paclitaxel. When belinostat was given as prolonged infusion, plasma levels peaked later, and at lower levels, with reduction of C_{max} , but with highest AUC following a 3-hour infusion.

DATE OF THE REPORT: 27 Aug 2012