SYNOPSIS

NAME OF COMPANY Topotarget A/S and CuraCen Corporation	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 II Clinical Trial of PXD101 in Patients with Advanced Multiple Myeloma

INVESTIGATORS:

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STUDY CENTERS:

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PUBLICATION (REFERENCE): No applicable

STUDY PERIOD: First patient enrolled: 26 Jan 2005 Last Patient End of Study: 02 Jan 2007	**PHASE OF DEVELOPMENT:** 2

OBJECTIVES:

Primary Objective:

In patients with advanced myeloma, to assess the efficacy of PXD101 treatment as measured by response rate (CR=complete response; PR=partial response; MR=minimal response; NC/SD=no change/stable disease; PD=progressive disease) using the Bladé response criteria (Bladé 1998).

Secondary Objectives:

Study Part A:

- To examine time to response, duration of response, time to progression, and survival following single agent PXD101 therapy.
- To examine safety following single agent PXD101 therapy.

Study Part B:

- To examine the chemotherapy sensitizing effect of PXD101 by assessing the efficacy (response rate, duration of response, time to progression and survival) and safety of a combination of dexamethasone and PXD101.
- To determine the pharmacokinetic parameters of the intravenous administration of PXD101 followed by oral dexamethasone on Days 1 and 4.
- To investigate the pharmacodynamic effects of belinostat in blood mononuclear cells on Days 1 and 4, and when possible in tumor biopsies (bone marrow), in patients receiving PXD101 in combination with dexamethasone.

METHODOLOGY:

The PXD101-301-G study was an open-label, non-randomized, multicenter, Phase 2 study to assess the efficacy and safety of PXD101 (belinostat) monotherapy and, in non-responders, for the combination of belinostat with dexamethasone. The study consisted of a study Part A and study Part B.

Study Part A:
Cycle 1: Belinostat was administered as a 30-minute intravenous (IV) infusion of 900 mg/m^2/day (amendment 1 and 2) or 1000 mg/m^2/day (amendment 3 and 4) every 24 hours (± 2 hours) on Day 1-5 followed by 2 weeks of observation.
Cycle 2: On Day 22, a second 5-day cycle of treatment with belinostat was administered, followed by 2 weeks of observation. During study Week 6 (Cycle 2, Day 15-21), patients were evaluated for response (complete response [CR], partial response [PR], minimal response [MR], no change [NC] / stable disease [SD], or progressive disease [PD]) on study Day 43.

Study Part A – continued:
Patients with CR, PR, MR or NC/SD continued belinostat monotherapy in study Part A until PD or until receipt of a maximum of 8 cycles including the two initial cycles. Patients with PD continued treatment according to study Part B. Response evaluation occurred after every 2 cycles. There was no dose escalation for belinostat.

Study Part B
Patients with PD on study Day 43 or in later cycles continued in study Part B – a combination of belinostat and dexamethasone.
Cycle 3: Belinostat was administered as in Cycle 1 and 2 in combination with oral dexamethasone 40 mg daily on cycle Days 2-5 and Days 10-13. On cycle Days 2-5, dexamethasone was administered 2 hours after

the belinostat infusion. On cycle Days 10-13, dexamethasone was administered in the morning. Patients received a minimum of two cycles of combined therapy. Patients with PD after four cycles were taken off study.
Response evaluation occurred after every 2 cycles. Completion of 8 cycles was considered the standard duration, but patients who achieved a clinical benefit from the treatment (objective response or stable disease) continued treatment beyond Cycle 8 according to the investigator's advice.
The study design utilized a Simon Two-Stage design where initially 21 patients were planned for enrollment in Part A of the study. If two or fewer responses were observed after 2 cycles, the study should be terminated (although patients would be given the option of continuing dual therapy). Otherwise, accrual was to continue to a maximum of 50 patients.
Blood samples were collected and analyzed for belinostat in plasma during mono- and combination therapy.
Adverse events (AEs) were recorded throughout the study and up to 30 days after the last treatment administration.

NUMBER OF PATIENTS (PLANNED AND ANALYSED):

Up to 50 patients planned, 25 included in Part A; of these, 10 patients were treated in Part B.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

1. Signed informed consent.
2. A confirmed diagnosis of multiple myeloma, diagnostic criteria as follows, in patients who have failed at least 2 prior lines of therapy. Diagnostic criteria for multiple myeloma:

   A Monoclonal immunoglobulin (M-component) in serum of IgG-type > 30 g/L, of IgA type > 20 g/L, of IgD type or IgE type of any concentration and/or excretion of M-component in the urine of type k or l type > 1 g/24 hours.

   B M-component in serum and/or urine in lower concentration than indicated above in 'A'.

   C 10% or more plasma cells in bone marrow aspirate or plasmocytosis in biopsy from bone marrow or soft tissue tumor.

   D Osteolytic bone lesions.

   The diagnosis of multiple myeloma demands one of the following combinations: **A**+**C**, **A**+**D**, or **B**+**C**+**D**.
3. Evaluable disease (as described above)
4. Adequate bone marrow and hepatic function including the following:

   White blood cells (WBC) > 2.5×10^9/L.

   Absolute neutrophil count ≥ 1.5×10^9/L.

   Platelets ≥ 50×10^9/L (≥ 80×10^9/L for protocol version 1.0).

   Total bilirubin ≤ 1.5 × upper normal limits (UNL).

   Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) ≤2.5× ULN.
5. Serum potassium within normal range (for protocol version 2.0, 3.0 and 4.0).
6. Age ≥ 18 years.
7. ECOG performance status (PS) ≤ 2.
8. Estimated life expectancy greater than 3 months.
9. Female patients with reproductive potential with a negative serum pregnancy test within the last 7 days before study enrollment and use a safe contraceptive during and for a period of sixty (60)

days after the study. Fertile female partners to male participants must likewise use contraceptive.

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

Belinostat Injection 50 mg/mL; batch numbers: 05J20, 06B03, 06H10, P04505, P06505, P07104, P07804, P07904, and P09404.
Dexamethasone 4 mg tablets commercially available and provided by the Sponsor.

DURATION OF TREATMENT:

A minimum of two 3-week cycles in Part A. Patients with CR, PR, MR or NC/SD continued belinostat monotherapy in study Part A until PD or until receipt of a maximum of 8 cycles including the two initial cycles.
Patients with PD on study Day 43 or in later cycles began study Part B. Patients received a minimum of two cycles of combined therapy. Patients with PD after 4 cycles were taken off study. Completion of 8 cycles was considered the standard duration, but patients who achieved a clinical benefit from the treatment (objective response or stable disease) continued treatment beyond Cycle 8 according to the investigator's advice.

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

No other therapy

CRITERIA FOR EVALUATION:

EFFICACY:
Response (efficacy) assessments were based on the European Group for Blood and Marrow Transplantation (EBMT) criteria (Bladé 1998), with the following modifications:

- Confirmation of response < 6 weeks apart was allowed.
- In the absence of 24-hour urine M-component data, response was based on serum M-component alone.
- If no confirmation data was available, a conservative assessment of the next lower level of response was made.

For responses after belinostat + dexamethasone treatment, baseline M-component value is the value obtained in the cycle immediately preceding addition of dexamethasone.

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

SAFETY:
Assessments included analysis of AEs, clinical laboratory results (including hematology, coagulation parameters, serum chemistry, and urine analysis), vital signs, performance status, physical examination and electrocardiogram (ECG) results. The Medical Dictionary for Regulatory Activities (MedDRA, version 9.1) 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. Frequency tables were generated for patient's assessment of tolerability.
Efficacy was evaluated for efficacy population treated with belinostat monotherapy (N=23) and for patients who received at least 2 cycles of belinostat and dexamethasone in combination (N=8).
Safety was evaluated for patients who received at least one treatment with belinostat (N=25). Safety data were analyzed on the total safety population, not separately for patients treated with belinostat only and those treated with belinostat + dexamethasone.

SUMMARIES – CONCLUSIONS:

A total of 25 patients were enrolled in the study and received the study drug and treated as follows:
Twenty-five patients were treated in Part A:

- Belinostat 900 mg/m^2/day×5 (N=8).
- Belinostat 1000 mg/m^2/day×5 (N=17).

Ten patients continued to Part B:

- Belinostat 1000 mg/m^2/day Day 1-5 + dexamethasone 40 mg/day on cycle Days 2-5 and Days 10-13.

Primary reason for treatment discontinuation was disease progression (12 out of 25 patients).

EFFICACY RESULTS:

Objective responses were not observed in the 23 evaluable patients treated with belinostat monotherapy. In accordance with the pre-defined futility analysis based on the Simon two-stage design, the study was not expanded.
Nine patients (39%) had SD while on monotherapy, one for 5 cycles, seven for 2 cycles, and one for 1 cycle.
Fourteen patients (61%) had PD as best response.
The response evaluation for belinostat and dexamethasone in combination was based on 8 patients. Four patients (50%) had objective responses (PR or MR) for 3-8 cycles. In addition, 4 out of 8 evaluable patients (50%) achieved an SD (50%) while treated for up to 17 cycles (13 months).

PHARMACOKINETICS:

The pharmacokinetic analysis populations were too small for reliable statistical comparison between the belinostat and belinostat and dexamethasone in combination. No statistical conclusive trends were observed.

SAFETY RESULTS:

The treatment was generally well tolerated. The most common AEs related to study drug were nausea (84%), vomiting (48%), diarrhea (40%), and fatigue (28%).
Seven patients died on study; 4 due to progressive disease. The remaining 3 patients died of respiratory failure, gastrointestinal hemorrhage, and a blood borne *Pseudomonas aeruginosa* infection. All deaths were assessed as not related to study drug by the investigator.
Twenty-two serious adverse events (SAEs) were reported in 12 patients. A total of six SAEs reported in four patients were assessed by the investigator to be probably, possibly or definitely related to study drug. One Grade 4 SAE (transaminases increased), four Grade 3 SAEs (×2 pneumonia, sepsis and pulmonary hypertension), and one Grade 2 SAE (hypersensitivity) were assessed as related to study drug. Four patients discontinued due to SAE/AEs assessed as related to study drug.
Grade 4 laboratory parameters observed were thrombocytopenia (7 patients) and decreased calcium, increased calcium, decreased WBCs, and increased uric acid (each in 1 patient).
Grade 3 or 4 changes in laboratory parameters seen in more than 10% of patients were thrombocytopenia (12 patients), decreased sodium (5 patients), and increased glucose (4 patients).
Thrombocytopenia and low WBC counts were predominantly observed in patients who already had low counts at baseline due to the advanced stage of their disease.
Observed changes in hematology and serum chemistry clinical laboratory test results raised no concerns with relationship to study drug.
ECG data for Part A revealed no evidence of any significant changes.

CONCLUSION:

Due to lack of efficacy, the PXD101-301-G study was stopped before complete enrollment of the planned number of patients. Among 25 heavily pre-treated patients enrolled and treated with belinostat, 23 patients were evaluable for efficacy of belinostat monotherapy. There were no objective responses after belinostat monotherapy, although stabilization of disease was observed in 9 patients (SD in 39 % of evaluable patients).
When belinostat therapy was continued in combination with dexamethasone, objective responses (PR+MR) were observed in 4 out of 8 evaluable patients (50%). In addition, 4 out of 8 evaluable patients (50%) achieved an SD while treated with belinostat and dexamethasone for up to 17 cycles (13 months).
Belinostat alone or in combination with dexamethasone was generally well tolerated with the most common adverse events being nausea, vomiting, diarrhea and fatigue.
In conclusion, belinostat monotherapy resulted in stabilization of advanced disease in some patients. This observation does not warrant further clinical investigations of belinostat monotherapy in patients with multiple myeloma. The observations support the continued exploration of belinostat in combination with dexamethasone and other agents for the treatment of multiple myeloma.

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