SYNOPSIS

NAME OF COMPANY Topotarget A/S 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 I/II Clinical Trial of PXD101 in Combination with Idarubicin in Patients with AML Not Suitable for Standard Intensive Therapy

INVESTIGATORS:

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STUDY CENTERS:

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PUBLICATION (REFERENCE): Richard Schlenk, Kristina Sohlbach, Marie Luise Hütter et al: Interim Results of a Phase I/II Clinical Trial of Belinostat in Combination with Idarubicin in Patients with AML Not Suitable for Standard Intensive Therapy, ASH Dec 2008

STUDY PERIOD: First patient enrolled: 17-Aug-2007 Last Patient Last Visit: 26-May-2009	**PHASE OF DEVELOPMENT:** 1/2

OBJECTIVES:

Primary Objective:

For PXD101 and idarubicin combination (Schedule A and Schedule B):

- To determine the safety and tolerance (maximum tolerated dose, dose limiting toxicity).

- To explore the efficacy (response rate (CR [complete response] or PR [partial response]), using the response criteria of the International Working Group [Cheson et al 2003]). (CR will in this protocol include CRi, CRc, CRm[1]).

Secondary Objective:

- To examine the time to response, response duration, overall survival, relapse-free survival, event-free survival and remission duration following PXD101 combination therapy.
- To examine aspects of pharmacokinetics (PK) and pharmacodynamics (PHDY) of PXD101 in combination with idarubicin in the two PXD101 schedules.

METHODOLOGY:

The PXD101-CLN-15 study was an open-label, multi-center, dose-escalation Phase 1/2 study to evaluate safety, explore efficacy, gene expression profiling (PHDY), and PK of belinostat and idarubicin combination in patients with acute myeloid leukemia (AML). Belinostat (PXD101) plus idarubicin treatment was repeated every 3 weeks for Schedule A (belinostat 30-minute infusion Day 1-5) and every 2 weeks for Schedule B (belinostat 48-hour infusion) depending upon toxicities or disease progression. Eligible patients were allocated by the Sponsor to Schedule A or B. Up to 35 patients could be included in each Schedule A or B (or up to a total of 70 patients).

In Schedule A belinostat was administered as a 30-minute intravenous (IV) infusion of 1000 mg/m²/day every 24-hours (± 2 hours) for 5 consecutive days, followed by 2 weeks of observation. Idarubicin was administered on Day 5 (first steps) or Days 4 and 5 (later steps) using a standard dose escalation program from 5 mg to 10 mg/m²/day for two days. Treatment cycles were repeated every 21 days.
On study Day 43 (Cycle 3, Day 1) response was assessed as CR, PR or progressive disease (PD). Patients experiencing PD after the first 2 cycles had their treatment terminated. Patients with CR or PR after 2 cycles continued to receive the drugs until a diagnosis of PD. Patients with recurrence after a CR could be retreated (based upon investigators decision). Patients were evaluated after every cycle while on therapy. If patient obtained CR or PR at the end of the Cycle 6 the patient was evaluated every month (limited response and safety assessment) afterwards until disease progression.

In Schedule B belinostat monotherapy administered by continuous intravenous infusion (CIV) over 24-48 hours was dose escalated (Step 1-6), and idarubicin was added after 48 hours (Step 7) and after 24 and 48 hours (Step 8-10). The second cycle started on Day 15 but under observation of possible myelotoxicity or other toxicity. For safety reasons the first dose steps were belinostat alone. Following each step the sponsors and the principal investigators decided next step based upon observed toxicity.
Accelerated titration design (ATD) for belinostat monotherapy was used from Step 1 to 6:

- Only one patient was needed per dose step for the first 6 steps.
- If only toxicity of Grade 0 or 1 was seen in Cycle 1 an intra-patient dose escalation from Cycle 1 to Cycle 2 was permitted.
- A Grade 2 or higher toxicity required another patient entered at that dose.
- If no patient with a first cycle dose limiting toxicity (DLT) or no Grade 2 toxicity in 2 patients was observed at a dose step the following patient started at the next dose step.
- If a DLT was observed in Cycle 1 or a Grade 2 or higher toxicity was observed in 2 patients the escalation proceeded to the traditional 3+3 design from this step on.

The 3+3 design was used belinostat and idarubicin in combination from Step 7 to 10:

[1] CRi: Morphologic CR with incomplete blood count recovery.
CRc: Cytogenetic complete remission.
CRm: Molecular complete remission.

- If 1 out of 3 in a dose level cohort experienced DLT during the first cycle, three more patients were added to that cohort.
- If 2 or more patients in a cohort of up to 6 patients experienced DLTs during their cycle of treatment, the previous lower dose was the recommended dose for the final expansion phase.
- Idarubicin was evaluated in three dose steps, 5, 7.5 or 10 mg/m²/day

An interim safety assessment was performed after maximum tolerated dose (MTD) for belinostat 48-hour infusion was reached and before adding idarubicin. Treatment cycles were repeated every 14 days for up to 6 cycles.
Clinical response evaluation took place after Cycle 1 and Cycle 2, and then after every second cycle. Treatment cycles of both schedules were repeated until disease progression or evidence of significant treatment-related toxicities. Completion of 6 cycles of belinostat treatment was standard study duration. Patients who achieved a clinical benefit from the treatment (objective response) could continue treatment beyond Cycle 6 according to the investigators advice and with continued abbreviated assessments of antileukemic effects and safety.
Patients with DLTs who had documented clinical benefit (objective response) could continue treatment with the belinostat and idarubicin combination at the prior dose level if toxicity has resolved to less than Grade 2 (except for alopecia). Once the MTD for Schedule A or B was defined, the patient cohort at the MTD could be expanded with up to 12 patients. If one or less responders were observed within these 12 patients the Schedule A or B part of the study was to be stopped. Otherwise, accrual could continue to a maximum of 35 patients in each Schedule (70 in total).

NUMBER OF PATIENTS (PLANNED AND ANALYSED):

Up to 35 patients were planned in each schedule; 18 patients were analysed in Schedule A and 23 patients were analysed in Schedule B.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

1. Signed consent of an IEC-approved informed consent form.
2. AML patients evaluable for efficacy:
   a. Patients above 60 years in first relapse or refractory.
   b. Patients 18-60 years 2nd relapse or refractory to at least two intensive chemotherapy cycles.
   c. Patients above 60 years with high risk features (cytogenetics, secondary or treatment related AML).
   d. Patients above 60 years with myelodysplastic syndrome with >10% blasts in bone marrow (would health organization - refractory anemia with excess of blasts [WHO RAEB-2]). For patients below 60 years potential curative treatments should have been exhausted.
3. Performance status (ECOG) ≤ 2.
4. Age above 18 years.
5. Acceptable liver, renal and bone marrow function including the following:
   a. Bilirubin below or equal 1.5 times upper limit of normal (ULN).
   b. Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or Alanine aminotransferase (ALT)/serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase ≤ 3 UNL.
   c. Serum creatinine ≤ 1.5 ULN.

6. Serum potassium within normal range.
7. Acceptable coagulation status: activated partial thromboplastin time (APTT) and prothrombin time (PT) or international normalized ratio (INR) within ≤1.5 times UNL or in the therapeutic range if on anticoagulation.
8. Female patients with reproductive potential with a negative pregnancy test within the last 7 days before study enrollment had to use a safe contraceptive during and for a period of 60 days after the study. Fertile female partners to male participants likewise had to use contraceptive.

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

Belinostat injection 50 mg/mL; batch numbers: 06K08, 07A27, 07E24.
Idarubicin, sterile pyrogen-free, orange-red freeze-dried powder, in vials containing 5 or 10 mg of idarubicin hydrochloride with 50 or 100 mg of lactose, respectively, obtained from the hospital pharmacy.

DURATION OF TREATMENT:

Schedule A: 3-week cycles (at least 2 cycles). Termination if progressive disease (PD) after Cycle 2. Patients with CR or PR after 2 cycles continued to receive the drugs until a diagnosis of PD. Patients were evaluated after every cycle.

Schedule B: 2-week cycles. Dose escalation based on toxicity.

Completion of 6 cycles of belinostat treatment was standard study duration. Patients who achieved a clinical benefit from the treatment (objective response) could continue treatment beyond Cycle 6 according to the investigators advice.

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

No other therapy

CRITERIA FOR EVALUATION:

EFFICACY:
Response and progression of AML were evaluated from blood and bone marrow examination using the "Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia" (Cheson et al. 2003)).

PHARMACODYNAMICS:
Blood samples were taken into primary cultures and studied by conventional chromosome banding analysis. Karyotype- and molecular markers were correlated to objective responses. Gene expression profiling was performed on samples obtained at site 030. Histone acetylase analysis was planned, but not successful.

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

SAFETY:
Assessments included analysis of adverse events (AEs), clinical laboratory results (including hematology, coagulation parameters, and serum chemistry), vital signs, performance status, physical examination, urine analysis and electrocardiograms (ECGs) results. The Medical Dictionary for Regulatory Activities (MedDRA, version 10) 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.
All patients who received at least one dose of study drug were included in the efficacy and safety analyses.

Pharmacodynamic analysis was performed and reported by site 030 and at Medical Prognosis Institute.
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, eResearchTechnology, Inc. (ERT, Philadelphia, PA, US) for a blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment.
The statistical analysis were performed by CE3, Guilford, CT, US)

SUMMARIES – CONCLUSIONS:

A total of 41 patients were enrolled in the study and received the study drug and treated as follows:

Eighteen patients were treated in Schedule A: belinostat at 1000 mg/m², 30-minute IV infusion Day 1-5 plus idarubicin IV, Day 5, every 3 weeks

- Step 1: idarubicin at 5 mg/m², Day 5 (n=3).
- Step 2: idarubicin at 10 mg/m², Day 5, (n=3).
- Step 3: idarubicin IV at 7.5 mg/m², Day 4 and 5, (n=3).
- Step 4: idarubicin IV at 10 mg/m², Day 4 and 5, (n=9).

Seven patients were treated in Schedule B, monotherapy CIV, every 2 weeks

- Step 1: 25 mg/m²/24 hour, 24-hour CIV, (n=1).
- Step 2: 50 mg/m²/24 hour, 24-hour CIV, (n=1).
- Step 3: 100 mg/m²/24 hour, 48-hour CIV, (n=1).
- Step 4: 200 mg/m²/24 hour, 48-hour CIV, (n=1).
- Step 5: 400 mg/m²/24 hour, 48-hour CIV, (n=1).
- Step 6: 800 mg/m²/24 hour, 48-hour CIV, (n=2).

Sixteen patients were treated in Schedule B: belinostat at 1000 mg/m², 48-hour CIV starting Day 1 plus idarubicin IV after 24 and/or 48 hours, every 2-weeks

- Step 7: idarubicin at 5 mg/m² after 48 hours, (n=3).
- Step 8: idarubicin at 5 mg/m² after 24 and 48 hours, (n=6).
- Step 9: idarubicin at 7.5 mg/m² after 24 and 48 hours, (n=7).

The predominant reason for study discontinuation was PD observed in 30 out of 41 treated patients.

EFFICACY RESULTS:

In the 5-day regimen (Schedule A), 3 out of 18 patients (17%) achieved CR/CRi, and in the CIV regimen (Schedule B) 5 responders (2CR/CRi, 3 PR) among 16 patients (31%) were observed.
After belinostat monotherapy (Schedule B, Step 6) at 800 mg/m²/day 48-hour CIV anti-leukemic effect was demonstrated (1 PR, 1 SD).

PHARMACODYNAMICS:

Karyotype analysis in 41 patients indicated that low/intermediate risk cytogenetic karyotypes seemed to respond better to a belinostat containing therapy than high risk AML cases with complex karyotypic changes.
Gene expression profiling was performed successfully in samples from 13 patients (4 responders, 9 non-responders). A blinded response prediction based on in vitro data indicated that patient selection based on gene expression analysis could potentially increase the response rate to study treatment. The gene expression analysis of 19564 genes comparing responders versus non responders revealed a significant ($p<0.05$ level, univariate test) gene expression pattern associated with the response to belinostat comprising 1905 genes.
No interpretable histone deacetylase results were obtained.

PHARMACOKINETICS:

The PK profile of belinostat 30-minute IV infusion plus idarubicin was similar to the previous reported PK profile after belinostat 30-minute IV infusion monotherapy. The PK of intravenous idarubicin, at doses of 5, 7.5 and 10 mg/m², given during two alternative regimens of IV belinostat treatment, were similar to those

previously reported for IV idarubicin at this range of doses. No evidence of a PK drug interaction between belinostat and idarubicin was found in the present study. Median steady-state levels at 1,167 ng/mL or 3.66 μM were achived during 48-hour belinostat infusion. A relationship between high belinostat exposure and achievement of OR was indicated for patients in Schedule B.

SAFETY RESULTS:

Schedule A:

No instances of DLT were observed. The most common related AEs (observed in >20 % of patients) with the highest dose given (Step 4) regardless of severity werewere nausea and febrile bone marrow aplasia (22% of patients each). Two patients (Schedule A, Step 4) discontinued treatment due to related AEs: one due to a febrile bone marrow aplasia (Grade 4) and one due to a left ventricular dysfunction (Grade 2).

In Schedule B:

No instances of DLT were observed. The safety of belinostat CIV monothearapy was acceptable. Recruitment was stopped after Step 9 (belinostat plus idarubicin [7.5 mg/m² after 24 and 48 hours]), when two of the seven patients died from sepsis assessed as related to treatment. Two cases of tumor lysis syndrome were observed in Schedule B, Step 8 and Step 9. These were not considered as DLTs since tumor lysis is a desired effect of the treatment. The most common related AEs (observed in >20 % of patients) at Step 8 and 9 regardless of severity were diarrhea (83% and 71% of patients), vomiting (67% and 57% of patients), nausea (67% and 43% of patients), dysgeusia (50% and 29% of patients). The investigators found that the general toxicity observed at Step 9 was unacceptable.

Belinostat/idarubicine combination using standard belinostat 30-minute infusion Day 1-5 (Schedule A) caused lower incidences of diarrhea, vomiting and nausea than belinostat as 48-hour CIV (Schedule B). Also cardiac toxicity (QT prolongation) and tumor lysis syndrome observed with combination therapy in Schedule B were not observed in Schedule A.

Hematological toxicity in white blood cells as observed is a known adverse reaction to treatment with an anthracyclin and was similar for the belinostat/idarubicin combination in Schedules A and B. The abnormal serum chemistry values observed were possibly signs of tumor lysis syndrome.

The ECG analysis revealed no clear effect on heart rate or PR or QRS duration. There was a clear change in QTcF duration at the higher doses used in this study. The QTc effect was specifically observed in the subgroups of Schedule B/Step 8 and Step 9 treated with belinostat 1000 mg/m² 48-hour CIV and idarubicin 5 or 7.5 mg/m² after 24 and 48 hours.

CONCLUSION:

In conclusion, the recommended idarubicin dose for future combination studies with belinostat standard 5-day regimen is 10 mg/m², Day 4 and 5. For future combination studies with belinostat 48-hour CIV every 2-weeks the recommended idarubicin dose is 5 mg/m² given 24 and 48 hours after belinostat infusion start.

Belinostat monotherapy administered as 48-hour CIV every 2-weeks up to 800 mg/m²/24 hour demonstrated an anti-leukemic effect and an acceptable safety profile.

Objective response rate for combination therapy was higher for belinostat CIV (31%) (Schedule B) than for belinostat standard regimen (17%) (Schedule A); however, at the highest idarubicin dose level (Schedule B, Step 9) the responses were associated with unacceptable general toxicity.

No evidence of a PK drug interaction between belinostat and idarubicin was observed. Median steady-state levels at 1,167 ng/mL or 3.66 μM were achived during 48-hour belinostat infusion A relationship between high belinostat exposure and achievement of OR was indicated for patients in Schedule B.

DATE OF THE REPORT: 11-Sept-2012