Belinostat abstracts at ASCO 2013

Topotarget announces that abstracts on belinostat clinical data were released for ASCO 2013 on May 15, 2013 at 6.00 pm EDT.

Below are the abstracts that are now available on ASCO’s website (www.asco.org).

**Phase I trial of belinostat in combination with cisplatin (Cis) and etoposide (Etop).**


Background: Histone deacetylase inhibitors (HDIs) are epigenetic therapies in development. To exploit the unique activity in impairing DNA repair, HDIs have been combined with chemotherapy. Belinostat is a potent HDI combined with Cis and Etop based on enhanced DNA damage and apoptosis in small cell lung cancer (SCLC) cells. Methods: Patients with relapsed/refractory cancer or previously untreated advanced stage SCLC were eligible. Belinostat was administered by continuous infusion (CIV) over 48h, from 400 mg/m²/24h, in cohorts of 3. Cis was administered on day 1 and Etop daily X3. Belinostat pharmacokinetics (PK) and several pharmacodynamic (PD) measures were assessed, including lysine acetylation in peripheral blood mononuclear cells (PBMCs) and γH2Ax staining in PBMCs and in hair follicles. Results: Five dose levels were explored in 20 patients with solid tumors, including 5 patients with SCLC, two who had no prior therapy. At the first dose level, dose-limiting toxicities (DLT) of gr 4 ANC in 1, and gr 3 HTN in 1 were observed. Cis and Etop were reduced to 60 mg/m² and 80 mg/m², respectively, and the dose level repeated without DLT. At the next dose level, 800 mg/m²/24h belinostat, grade 3 HTN and grade 4 pneumonitis were observed. At the MTD of 600 mg/m²/24h belinostat, DLT was seen in 1 of 6 pts; however, all 6 pts required later dose reductions. We thus considered 500 mg/m²/24h in combination with Cis and Etop to be the recommended Phase II dose; confirmation ongoing. PKs show belinostat levels at 1 uM over the 48h infusion, decreasing rapidly to the 60h timepoint. In total 11 pts, 3 with SCLC, completed 6 cycles. PR was seen in 6 pts (3 with SCLC). PD studies confirmed γH2AX staining in PBMCs and hair follicles, peaking at 36h and 60h, respectively. Tubulin and lysine acetylation (Ac-K) in PBMCs peaked at 36h; Ac-K recovered more rapidly than tubulin, mirroring γH2AX.

Conclusions: The MTD of belinostat over 48h by CIV was 600 mg/m²/24h, in combination with Cis 60 mg/m² on day 1 and Etop 80 mg/m² on days 1 - 3. PD endpoints indicate that belinostat is active in promoting both acetylation and DNA damage. The HDI combined with chemotherapy requires dose reduction and likely represents an on-target increase in DNA damage.
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PhI-53: (NCI#7251): Phase I Trial of Belinostat (PXD101) in Combination with 13-cis-Retinoic Acid (13c-RA) in Advanced Solid Tumor Malignancies; A California Cancer Consortium NCI/CTEP Sponsored Trial.


Background: Belinostat has a reported maximum tolerated dose (MTD) of 1,000 mg/m² given days 1 to 5 every 21 days as a single agent, although in one study in hepatocellular carcinoma belinostat was given at 1,400 mg/m² on the same schedule. Pre-clinical evidence suggests HDAC inhibitors enhance retinoic acid signaling with a synergistic impact in a variety of solid tumors. We conducted a phase I study of belinostat and 13c-RA in advanced solid tumors. Methods: Dose limiting toxicity (DLT) was defined as cycle 1 hematologic toxicity: ≥grade 3 that not resolved to <grade 1 within 1 week or non-hematologic toxicity: ≥grade 3. We sought the MTD of belinostat days 1-5 with 13c-RA days 1-14, every 21 days, in patients (pt) with advanced solid tumors. Eligibility criteria included normal organ function and QT/QTc interval; 4 weeks from previous therapy. Results: 51 pt were treated: median age 61 (range 40-80); 29 men; 57% ECOG 0, 41% ECOG 1, 2% ECOG 2; 13 lung, 11 breast, 8 colorectal, 3 pancreatic. 11 dose levels (DL) were tested starting from belinostat 600 mg/m²/day and 13c-RA 50 mg/m²/day to belinostat 2000 mg/m²/day and 13c-RA 100 mg/m²/day. Only two DLTs were observed: a grade 3 hypersensitivity reaction with dizziness and hypoxia at DL 8 (belinostat 1700 mg/m²/day, 13c-RA 100 mg/m²/day); and a grade 3 allergic reaction in a patient with an ECOG PS 2 at DL 11 (belinostat 2000 mg/m²/day, 13c-RA 100 mg/m²/day). The MTD was not reached. Pharmacokinetics of belinostat suggests dose proportionality. Median number of cycles: 2 (range 1-56). 10 patients had SD including: 1 neuroendocrine pancreatic stable for 56 cycles; 1 breast pt for 12 cycles; 1 lung pt 8 cycles. 2 pt had PRs: a keratinizing squamous cell carcinoma (tonsil) and a lung cancer pt. Conclusions: Belinostat 2000 mg/m² days 1-5 and 13-cis-Retinoic acid 100 mg/m² days 1-14, every 21 days, was well-tolerated and an MTD was not reached despite doubling the established single agent MTD. Future studies building on this combination to belinostat are warranted. Support: U01CA062505 and P30CA033572 (City of Hope); U01CA099168 and P30CA047904 (University of Pittsburgh).

An abstract on the CLN-19 BELIEF study in PTCL was furthermore released for presentation on ASCO 2013 on May 15, 2013 – for more information hereon, please refer to company announcement 15-13.

Topotarget A/S

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Background information

About Topotarget
Topotarget (NASDAQ OMX: TOPO) is a Scandinavian-based biopharmaceutical company headquartered in Copenhagen, Denmark, dedicated to clinical development and registration of oncology products. In collaboration with Spectrum Pharmaceuticals, Inc., Topotarget focuses on the development of its lead drug candidate, belinostat, which has shown positive results in the treatment of hematological malignancies and solid tumors, obtained by both mono- and combination therapy. For more information, please refer to www.topotarget.com.
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