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Videnskablige belinostat resuméer på ASCO's årsmøde 2011

København, Danmark – 19. maj 2011 – Topotarget A/S (NASDAQ OMX: TOPO.CO) har i dag meddelt, at kliniske data (videnskablige resuméer) vil blive præsenteret på ASCO's 2011 årsmøde (American Society of Clinical Oncology). Mødet afholdes i Chicago, the McCormick Place Convention Center fra den 3. juni til den 7. juni 2011.

Neden for er en liste over de videnskabelige resuméer der der nu er tilgængelige for gennemsyn på ASCO's hjemmeside (www.asco.org).

A phase I and pharmacodynamic (PD) study of the histone deacetylase (HDAC) inhibitor belinostat (BEL) plus azacitidine (AZC) in advanced myeloid malignancies.

Abstract No: 6521

Session: Leukemia, Myelodysplasia, and Transplantation. Type: Poster Discussion Session, Time: Friday June 3, 2:00 PM to 6:00 PM. Location: McCormick Place E450b
Discussion Time: Friday June 3, 5:00 PM to 6:00 PM. Location: McCormick Place Arie Crown Theater.

Author(s): O. Odenike, L. A. Godley, J. Madzo, T. Karrison, M. Green, A. S. Artz, R. J. Mattison, K. W. L. Yee, M. Bennett, N. Fulton, G. Koval, G. Malnassy, R. A. Larson, M. J. Ratain, W. Stock; The University of Chicago, Chicago, IL; University of Wisconsin, Madison, WI; Princess Margaret Hospital, Toronto, ON, Canada.

Abstract:

Background: We hypothesized that targeting two mechanisms of epigenetic silencing with a potent HDAC inhibitor BEL plus the DNA methyltransferase inhibitor AZC would be additive or synergistic with regard to transcriptional de-repression and up-regulation of specific target genes.

Methods: Part 1 of the study was a dose escalation phase to establish the MTD of BEL in combination with a fixed dose of AZC. 3 to 6 pts were enrolled per dose level in the absence of a DLT or until the 1000mg/m2 dose level of BEL was attained. AZC was given at a dose of 75mg/m2/d SC on days 1-5, with escalating doses of BEL given IV over 30 minutes on the same days in a 28 day cycle. In part 2, pts were randomized during cycle 1 to AZC alone, or BEL/AZC at the established MTD of BEL. Part 2 was designed to evaluate the relative contribution of BEL to the combination, based on change in PD variables analyzed at day 5 of therapy in comparison to baseline, in cycle 1. In subsequent cycles all pts could receive BEL/AZC.

Results: 56 pts were enrolled, part 1 (n=24), part 2 (n=32). Median age 68, range (42-83). AML de novo=53% t- AML/MDS=18%, MDS/CMML=27%, PMF=2%; 68% had primary refractory or relapsed disease, 43% had poor risk cytogenetics. In part 1, dose escalation was feasible up to the 1000mg/m2 dose level of BEL, without first course DLT. In part 2, 18 pts (9 in each arm) had marrow samples at baseline and at day 5 for q-RT-PCR analysis for *p21*, *MDR1* and *HIST1H3H* transcript levels. At day 5, *MDR1* was significantly upregulated in the BEL/AZC arm when compared with AZC alone arm (p=0.0089), in contrast to *p21* and *HIST1H3H* which were not significantly different between the 2 arms. There were18 responses (CR=6, marrow CR =2, PR= 1, HI-P=7, HI-N=2); 13 of these occurred at the 1000mg/m2 dose level of BEL.

Conclusions: The combination of BEL and AZC is feasible, responses have been observed in several pts at the RP2D of 1000mg/m2 of BEL plus 75mg/m2 AZC. A significant upregulation in *MDR1* was observed in the BEL/AZC arm at day 5 compared with the AZC alone arm, suggesting a relative biologic contribution of BEL to the combination. The clinical correlates of these observations require evaluation in the context of a larger trial.

Management of thymic epithelial tumors (TETs) at the National Cancer Institute (NCI).

Abstract No: e17511

Publication-only abstracts (abstract number preceded by an "e"), published in conjunction with the 2011 Annual Meeting but not presented at the Meeting, can be found online only. The publication-only abstracts are not included in the print or USB versions of the *ASCO Annual Meeting Proceedings Part I*, but they are citable to the *Journal of Clinical Oncology.*

Author(s): A. Rajan, R. J. Kelly, A. Lopez-Chavez, C. A. Carter, E. Szabo, B. Scepura, M. J. Manu, A. W. Berman, G. Giaccone; National Cancer Institute, Bethesda, MD.

Abstract:

Background: TETs are very rare anterior mediastinal tumors.

Methods: We performed a retrospective review of patients (pts.) with TETs presenting to the NCI for enrollment in ongoing clinical trials, standard-of-care therapy or a second opinion.

Results: Seventy-three pts. were seen between 12/2007 and 12/2010; 43 males (41%), median age at diagnosis: 48 years (range, 17 - 81). Fifty-four pts. were Caucasian (74%), 7 (10%) African-American, 8 (11%) Asian and 4 (6%) Hispanic. Histology: B1 5 (7%), B2 13 (18%), B2/B3 1 (1%), B3 9 (12%), thymic carcinoma (TC) 35 (48%), atypical carcinoid 2 (3%) and unclassified thymoma 8 (11%). Fifty pts. were enrolled in clinical trials: 28 on a phase II study of the HDAC inhibitor, belinostat (B), 27 on a phase II study of the IGF -1R inhibitor cixutumumab (C) (including 10 previously on B), 3 on a phase I study of chemotherapy (PAC) plus B and 2 on a phase II study of the cyclin-dependant kinase inhibitor PHA-848125AC. Median number of previous systemic therapy regimen that had been administered was 2 (range, 0-10). Forty-three pts. (59%) had extra-thoracic metastases; liver, bone and lymph nodes were the most common sites. Fourteen pts. (19%) had at least one autoimmune disease; myasthenia gravis (10%) was the most common. Three out of six pts. with TC with neuroendocrine features had Cushing's syndrome. Eleven pts. (15%) had opportunistic infections including shingles (8%) and candidiasis (4%). Forty-eight pts. On clinical trials were evaluable for response: B: 2PR, 18SD, 8PD; C: 1PR, 16SD, 8PD; PACB: 1PR, 2SD; PHA: 2SD.

Median survival for all pts. was 117 months (T - not reached; TC - 56 months). Among 28 pts. enrolled on B, the only clinical predictor of response and survival was presence of intra-thoracic disease only. Of 12 tumors (B1-1, B2-2, B3-1, C-7, atypical carcinoid-1) evaluated for overexpression of HER2 by IHC, none was positive. One patient with TC had a c-KIT mutation in exon 11.

Conclusions: Histologic diagnosis of thymoma and the presence of intra-thoracic disease only predicts for longer survival in pts. with TETs. Targeted drugs can induce prolonged disease stabilization and few responses in heavily pretreated patients. Molecular profiling of tumors will be necessary in order to advance the field.

Dagens meddelelse ændrer ikke Topotargets finansielle forventninger for helåret 2011.

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Baggrundsoplysninger

Om belinostat
Belinostat er en lovende molekyle HDAC-hæmmer, som undersøges for sin rolle i behandlingen af en lang række solide tumorer og blodkræftsygdomme, enten alene eller i kombination med andre aktive antikræft-midler, herunder carboplatin, paclitaxel, doxorubicin, idarubicin, cis-retinoidsyre, azacitidin, 5-FU, etoposid og Velcade® (bortezomib) til injektion. HDAC-hæmmere udgør en ny mekanistisk klasse antikræftmidler, som er rettet mod HDAC-enzymerne, og de har vist sig at: stoppe kræftcellernes vækst (herunder undertyper, der er resistente over for lægemidler), inducere apoptose (programmeret celledød), fremme differentiering, hæmme angiogenese (dannelse af blodkar), og sensibilisere kræftcellerne til ikke længere at være resistente, når de anvendes i kombination med andre antikræftmidler.

Intravenøst indgivet belinostat undersøges i øjeblikket i et pivotalstudie til behandling af perifert T-celle lymfekræft (PTCL) og undersøges i en række kliniske undersøgelser som en potentiel behandling af kræft med ukendt primærtumor (CUP), kræft i æggestokkene, småcellet lungekræft, tymom, leverkræft, bløddelssarkom, lymfekræft, AML samt myelodysplastisk syndrom (MDS), enten alene eller i kombination med andre antikræftbehandlinger. Konstant intravenøs infusion (CIV) evalueres i kliniske undersøgelser til behandling af både solide tumorer og AML. Topotarget har indgået en Clinical Trial Agreement (CTA) med NCI omkring kliniske studier med belinostat for bedre at kunne forstå stoffets antitumoraktivitet.

Om Topotarget
Topotarget (NASDAQ OMX: TOPO.CO) er en skandinavisk-baseret international biotekvirksomhed med hovedkontor i Danmark dedikeret til at forbedre behandlinger mod kræft. I samarbejde med Spectrum Pharmaceuticals, Inc. fokuserer Topotarget i øjeblikket på udviklingen i de pivotale studier af dets førende lægemiddelkandidat, belinostat, som har vist en tydelig antineoplastisk effekt i behandlingen af såvel blodkræftsygdomme som solide kræftsvulster. Belinostat kan anvendes i kombination med fulde doser kemoterapi og er i registreringsfase i PTCL (perifert T-celle lymfekræft) samt i fase II i kræft med ukendt primærtumor (CUP). Topotargets primære kræftbehandlings-targets er HDAC, NAD+ og topoisomerase II. Totect® er et markedsført produkt, som er udviklet fra Topotargets forskningsteknologi. Totect® markedsføres af selskabets egne salgsspecialister i USA. De europæiske rettigheder til Savene® blev frasolgt i marts 2010 som resultat af selskabets fokus på at udvikle og kommercialisere belinostat. For yderligere oplysninger henvises til www.topotarget.com.

Topotarget Safe Harbour Statement

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