phenylbutyrate compound, N-hydroxy-4-(4-phenylbutyrylamino)benzamide (HTPB), displayed nanomolar potency in inhibiting HDAC activity. Exposure of several cancer cell lines to HTPB at the submicromolar level showed reduced cell proliferation accompanied by histone hyperacetylation and elevated p21(WAF/CIP1) expression, which are hallmark features associated with intracellular HDAC inhibition.

540 POSTER

Clinical phase II development of resminostat, a novel HDAC inhibitor

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Resminostat (4SC-201) is a promising, oral pan-HDAC inhibitor being under clinical phase II development. It has shown excellent anti-tumour activity in a wide panel of preclinical models.
A First-in-Man study yielded a favourable safety profile, together with superior pharmacokinetic characteristics and a consistent modulation of the HDAC target. After 4 treatment cycles (2 months), a stabilization of tumour diseases was observed in the majority of patients with various late-stage solid tumours.
Currently, a clinical phase II programme with resminostat explores its therapeutic activity in a spectrum of indications as follows:
(I) Hepatocellular carcinoma (HCC). A phase II trial (SHELTER study) in patients with advanced HCC investigates the therapeutic efficacy in an exploratory second-line setting after treatment failure of first-line standard therapy with sorafenib. In the study, patients are treated with the combination of resminostat and sorafenib (including MTD determination) or with resminostat as monotherapy. Study endpoints are the estimation of the progression-free survival, overall survival, response rate, and the analyses of safety, PK and biomarkers.
(II) Hodgkin's lymphoma (HL). A phase II trial (SAPHIRE study) evaluates the therapeutic activity of resminostat in relapsed or refractory HL patients. Resminostat is applied as monotherapy in an open-label, single-arm, Simon-two stage design. Primary endpoint is the overall response rate (ORR), the secondary endpoints are similar to the SHELTER study.
(III) Colorectal carcinoma (CRC). A phase II study in patients with advanced k-ras mutant CRC is to be commenced shortly. Resminostat will be administered in combination with the standard FOLFIRI chemotherapy regimen to patients being refractory to a 5-FU-comprising first-line therapy. Following a dose escalation part of the combination treatment, patients will be randomized into two study arms, receiving either the resminostat/FOLFIRI combination or FOLFIRI alone. Primary end point is the estimation of progression-free survival (PFS), the secondary endpoints correspond to the SHELTER study.
Clinical data from this development program of resminostat will be presented at the conference.

541 POSTER

ERBB3 promoter polymorphisms and mRNA expression associated with lung cancer risk in Korean lung cancer patients

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Lung cancer has been the leading cause of cancer-related deaths in Korea, and its incidence continues to rise. Recent therapeutic strategies have focused on the development of "targeted therapies" that aims to specifically disrupt critical oncogenic mechanisms. The EGFR is one such target, because it is known to promote growth of cells and function as an oncogene, expressing in up to 80−90% of NSCLC.
The ERBB3 is unique among the EGFR families in that it has been shown to have weak or no tyrosine kinase activity. The correlation between ERBB3 protein expression and distant metastasis in lung cancer was reported.
To evaluate the role of ERBB3 gene in lung cancer risk, genotypes of the ERBB3 promoter region (−536 A/G and −276 C/T) were determined in 430 lung cancer patients and 429 normal subjects by TaqMan assay. Furthermore, to examine potential effects of the common haplotypes (A-T and A-C haplotypes) on ERBB3 transcriptional activity, luciferase reporter assays were performed in H2009 and H358 cells. The ERBB3 mRNA expressions were quantified by real-time PCR using immortal lymphocytes originated from lung cancer patients. The genotypes of ERBB3 polymorphisms showed no association with susceptibility to the lung cancer risk. However, in the analysis stratified by smoking status, the effect of −276 C/T on the lung cancer risk was found in non-smokers (OR: 0.11, 95% CI: 0.02–0.87) in the recessive model. And, the subsequent analysis revealed that A-C haplotype was associated with susceptibility to the lung cancer risk in codominant model (OR: 1.31, 95% CI: 1.01–1.70). In particular, the A-C haplotype showed an increased risk of lung cancer in non-smokers (dominant OR: 8.82, 95% CI: 1.14–68.36) and the A-T haplotype showed a decreased risk of lung cancer in non-smokers (codominant OR: 0.63, 95% CI: 0.41–0.98). Interestingly, A-C haplotype induced transcriptional activity by 30% compared with A-T haplotype. And, the ERBB3 mRNA levels were higher in A-C haplotype (0.51 ± 0.09) than in A-T haplotype (0.25 ± 0.05). These results suggest that ERBB3 promoter polymorphisms affect ERBB3 mRNA expression, further contributing to the genetic susceptibility to lung cancer.
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Centralised analysis of phase I ECG dataset of resminostat, a new oral histone deacetylase inhibitor (HDACi)

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Background: Resminostat (4SC-201) is a newly developed, specific, potent, pan-HDAC inhibitor with broad anti-tumour activity in preclinical models and promising clinical characteristics. The compound is in phase II clinical development in various oncological indications.
Methods: 19 Patients with advanced solid tumours were treated in a first-in-human trial at increasing oral daily dose levels from 100 mg to 800 mg in repeated 14-day cycles consisting of 5 consecutive treatment days followed by a 9-day rest period. Cardiac function was monitored by pulse rate, blood pressure, troponin levels and continuous ECG telemetry. In addition, standard 12-lead rest ECGs were conducted frequently to aid in the determination of potential effects on QT interval prolongation. An intensive profile consisting of 18 single ECGs was performed from Day 1 to 5 during Cycle 1, and a reduced number of ECGs in the following cycles, if there were no clinically relevant findings. Subsequent to the on-site clinical assessment, ECGs were sent to a core lab for further analysis by a trained cardiologist. PR, QRS and QT intervals and heart rate (HR) were measured in lead II across 3 consecutive beats using markers for the respective ECG intervals.
Results: No signal for drug-induced prolongation of QTc was observed. A maximum mean HR increase of up to 22 beats per minute and a corresponding shortening of the PR and QT interval was found in a dose-dependent manner. HR correction with Fridericia's formula did not reveal consistent changes in QTc. The incidence of QTcF outliers was very small. The results suggest that resminostat does not affect the duration of myocardial repolarisation. At doses $\geqslant$ 400 mg, unspecific flattening of the T-wave and slight depression of the ST-segment were observed frequently. However, in some patients such findings were already observed at baseline. No dose-limiting toxicities were seen with regard to cardiac safety in all dose cohorts.
Conclusions: Centralised analysis of phase I ECG data did not reveal a drug-induced prolongation of the QTc interval. Drug administration was frequently associated with moderate increases in HR. At doses levels $\geqslant$ 400 mg, unspecific changes in T-wave morphology and slight ST-segment depression were observed.

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Human transcription factors regulated by SET protein

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Background: Transcription factors exhibit three essential functions: binding to specific DNA sequence, transcription control and response to regulatory signals. The SET/TAF-1β protein, also termed I2PP2A, interacts with several proteins involved in the regulation of cell cycle and apoptosis. In addition, SET is a member of INHAT complex, responsible for inhibiting the activity of the histone acetyltransferase (HAT) proteins by binding to histones and blocking the association between HATs and histones. Consequently, SET influences the state of histone acetylation and affects chromatin structure, promoting epigenetic alterations and gene transcriptional silencing. We previously identified SET protein accumulated in oral scamous cell carcinoma (OSCC). Here, we addressed the impact of SET accumulation on transcription factors expression. Material and Methods: HEK293 cells were transfected with pCMV vector containing SET full length cDNA or empty vector. Small interference RNA (siRNA) was performed in OSCC-HN13 (origin: tongue) cells using oligos against SET or a negative control. After transfection, to promote *SET* overexpression or knockdown, the mRNA was extracted by TriZol reagent and the