clinicopathological findings. Next, we used human HCC cell lines to know estimatethe endogenous AFP secretion and response to exogenous AFP. We applied introduced AFP siRNA in HuH7 and HepG2 cells to examine whether it can could inhibit AFP secretion on HuH7 and HepG2 cells.
Results: Post-operative serum AFP correlates to both disease free and overall survival. Further, that value is an independent prognostic factor in HCC patients. Five HCC cell lines, including HepG2 and HuH7, secreted AFP. Human cord blood and AFP can make could induce HCC cells proliferatione on a dose-dependently in vitro manner. AFP inhibited apoptosis induced by 5-fluorouracil (5-FU) on in several cell lines. When we introduced AFP specific siRNA in HepG2 and HuH7, AFP mRNA and protein secretion were significantly inhibited. AFP siRNA could inhibited the proliferation of HCC lines significantly. Furthermore, AFP siRNA induced apoptosis on in these cells co-culture with 5-FU.
Conclusions: These results indicate that AFP inhibition of AFP by siRNA may be effective to in inhibiting the HCC progression.

Drug Development

Poster presentations (Thu, 27 Sep, 08:00−11:00)
Drug development

700 POSTER

Outcome of the Clinical Trials Directive on clinical cancer research in Europe: a 3-years'-follow-up analysis

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Background: The implementation of the Clinical Trials Directive 2001/20/EC (CTD 2001/20) between 2004 and 2006 in each EU Member State marks a watershed in European clinical research. The Directive, which set-up a mandatory framework for clinical trial registration, ethical review and regulatory approval by national authorities, requires sponsors of commercial like non-commercial trials to respect GCP requirements and to follow a meticulous set-up, supervision and reporting scheme for any drug trial. Perceived as a particular obstacle for non-commercial trials due to rising administrative complexity and increased costs, investigators, sponsors and analysts have forecasted a sharp decline in clinical research. Nevertheless, no accurate data have been published so far allowing to quantify the impact of the CTD 2001/20 on clinical cancer research at EU level.
Methods: This study constitutes a follow-up analysis to results presented in November 2005 at ECCO 13 (Abstract 528), aimed to provide reliable figures on the impact of the CTD 2001/20 on clinical cancer research three years after its coming-into force on 1 May 2004. For this purpose, clinical trial application charts from European (EMEA) and national authorities in half a dozen relevant EU Member states were evaluated. Whenever possible, data for commercial and non-commercial clinical trials were tracked separately as well as figures for oncology and paediatric oncology studies. In addition, heads of coordinating ethics committees in the respective EU member states as well as cancer research associations were contacted in order to collect comparative data. Descriptive statistics were applied for data presentation. Standard methods were used to test for statistical significance of differences or means.
Results: The CTD 2001/20 formally changed the categorisation of clinical trials. Hence, the authorities have revised their monthly/annual reporting. As a result, the pre- and post-implementation statistics are not fully comparable. The most reliable data arise from Italy, where an official trial reporting system is in place since 2000. Like for Italy, data from other countries confirm a marked decline of academic clinical cancer research activity of around one-third, although the overall figures for the set-up of cancer trials remained rather stable between 2000 and 2006 with a short post-implementation nadir in each country. Paediatric oncology, much affected by the CTD 2001/20, may be revived by the Paediatrics Regulation, which came in force in January 2007.
Conclusion: The CTD 2001/20 has resulted into a drop of non-commercial clinical cancer research within the EU. Representing 25% of all clinical trials prior to implementation, actually only 18% of new trials are conducted by academic sponsors. Efforts of all stakeholders are necessary to prevent a lasting cutback of interest in, commitment to and funding for clinical research.

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Phase I study of oral LBH589 in advanced solid tumours and non-Hodgkin's lymphoma

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Background: LBH589 is a highly potent deacetylase inhibitor. We evaluated the safety, tolerability, and preliminary efficacy of oral LBH589 in a phase 1 study in patients with refractory advanced solid tumors or non-Hodgkin's lymphoma (NHL).
Material and Methods: LBH589 was given orally every Monday, Wednesday, and Friday (MWF) until there was disease progression or unacceptable toxicity. Histone acetylation (HA) was studied using Western blots on total cell lysates from peripheral blood lymphocytes. Plasma pharmacokinetic (PK) profiles were analyzed on days 1 and 15. Noncompartmental analysis was used to determine PK parameters derived from plasma concentration time curves. Thirty-two patients (pts) received either the initial dose level of 15 mg MWF weekly, dose-limiting toxicity (DLT) level of 30 mg MWF weekly, or maximum tolerated dose (MTD) of 20 mg MWF weekly for cutaneous T-cell lymphoma (CTCL), renal cell carcinoma (RCC), melanoma, rhabodomyosarcoma, mesothelioma, prostate, hepatic, colon, bladder, or other malignancies.
Results: Three dose-limiting toxicities (DLTs) were reported: G3 diarrhea and transient G4 thrombocytopenia in the 30 mg cohort and G3 fatigue in the 20 mg cohort. Anorexia, nausea, fatigue, diarrhea, and transient thrombocytopenia were the most common adverse events. Of 1057 ECGs analyzed, 1 patient in the 20 mg cohort had a QTcF >500 ms (503 ms), which was an isolated event after the first dose with no recurrence with continued LBH589 therapy. Mean change in QTcF from baseline was 2-fold increase in HA was seen in the 15 mg cohort, but HA increased in 50% of pts for 72 h postdose in the 20 mg and 30 mg cohorts. After dosing, LBH589 was rapidly absorbed in plasma (T_{max} 1.5 h) then decreased with a mean terminal half-life of 16 h. At doses between 15−30 mg, C_{max} and AUC increased linearly with an estimated bioavailability of 49%. Two CTCL pts had complete response and 4 CTCL pts attained partial response; stable disease was attained in 7 pts with CTCL, RCC, melanoma, mesothelioma, or parotic gland cancer; 15 pts progressed on treatment; 4 pts were not evaluable.
Conclusions: In the 20 mg oral MWF weekly cohort, LBH589 produced a sustained effect on HA in 50% of patients. No clinically significant effect on QtcF was seen. Objective evidence of tumor response was seen in CTCL patients.

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Phase I pharmacokinetic and pharmacodynamic study of once-weekly IV LBH589

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Background: LBH589 is a highly potent deacetylase inhibitor. We tested the safety and tolerability of IV LBH589 once weekly for 3 of 4 weeks in patients with advanced solid tumors or lymphoma.
Material and Methods: LBH589 was given IV on days 1, 8, and 15 of a 28-day cycle. Histone acetylation (HA) was studied using Western blots on total cell lysates from peripheral blood lymphocytes (PBLs). Plasma pharmacokinetic (PK) profiles, derived from plasma concentration time curves, were analyzed on days 1 and 8. Noncompartmental analysis was used to determine PK parameters. Thirty-five patients (pts) were treated at 3 dose levels (10 mg/m^2, 15 mg/m^2, and 20 mg/m^2) for cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), mesothelioma, and prostate, colon, or other malignancies.