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.

**701** POSTER

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

H.M. Prince[1], D. George[2], A. Patnick[3], M. Mita[3], P. Atadja[4], M. Dugan[5], D. Butterfoss[5], K. Culver[5], H.S. Burris[6], J. Beck[7]. *[1]Peter MacCallum Cancer Centre, Haematology and Medical Oncology, Melbourne, Australia; [2]Duke University, Urologic Surgery, Durham, USA; [3]Institute for Drug Development, Cancer Therapy and Research, San Antonio, USA; [4]Novartis Institutes for Biomedical Research Inc, Oncology Clinical Development, Cambridge, USA; [5]Novartis Pharmaceuticals, Oncology Clinical Development, East Hanover, USA; [6]Sarah Cannon Cancer Center, Hematology/Oncology, Nashville, USA; [7]Johannes-Gutenberg-Universitat, Medical and Tumor Immunology, Mainz, Germany*

**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.

**702** POSTER

**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.

**Results:** There was 1 dose-limiting toxicity (DLT) (transient G4 thrombocytopenia) at the 20 mg/m$^2$ dose. Other G3/G4 toxicities include G3 transient thrombocytopenia, G3/G4 neutropenia (G3 – 5 pts, G4 – 5 pts), G3 anemia (5 pts), G3 hypophosphatemia (1 pt), G3 hypokalemia (1 pt), G3 nausea (1 pt), and G3 pruritus (1 pt). Of 2042 ECGs analyzed, 1 pt had an increase in QTcF from baseline of >60 ms and 1 pt had QTcF >500 ms at 20 mg/m$^2$. LBH589 plasma concentration peaked at the end of the 0.5 h infusion, then declined with a mean terminal half-life of 16 h. Median $C_{max}$ with 20 mg/m$^2$ was 1000 ng/mL. The $AUC_{0-inf}$ of LBH589 increased linearly with IV doses of 10−20 mg/m$^2$. No significant accumulation of LBH589 was seen. There was a dose-dependent ⩾2-fold increase in HA 7 days after one dose in 43%, 50%, and 60% of patients, respectively, at 10 mg/m$^2$, 15 mg/m$^2$, and 20 mg/m$^2$. One week after the second dose at 20 mg/m$^2$, 80% of patients had increased HA. One CTCL pt had a complete response; 1 PTCL pt had a partial response that has persisted for more than 7 months; 1 prostate cancer pt had a confirmed partial response in nodal disease and a >50% drop in PSA.
**Conclusions:** The maximum tolerated dose of LBH589 given IV weekly on a 3 of 4 week schedule is 20 mg/m$^2$. Preliminary evidence of antitumor activity was seen.

**703** POSTER

**A phase I and pharmacokinetic (PK) study of BIBW 2992, an oral irreversible dual EGFR/HER2 inhibitor**

R. Plummer[1], L. Vidal[2], R. Perrett[1], J. Spicer[3], P. Stopfer[4], M. Shahidi[5], G. Temple[5], A. Futreal[6], H. Calvert[1], J. de Bono[3]. *[1]Northern Institute for Cancer Research, Medical Oncology, Newcastle upon Tyne, United Kingdom; [2]Royal Marsden Hospital, Drug development Unit, Sutton, United Kingdom; [3]Royal Marsden Hospital, Drug Development Unit, Sutton, United Kingdom; [4]Boehringer Ingelheim, Oncology, Biberach, Germany; [5]Boehringer Ingelheim, Oncology, Bracknell, United Kingdom; [6]Wellcome Trust Sanger Institute, Oncology laboratory, Hinxton, United Kingdom*

**Background:** BIBW 2992 is a novel oral, potent and irreversible inhibitor of EGFR and HER2. A phase I pharmacokinetic study is reported including the effect of food on the pharmacokinetics of BIBW 2992.
**Materials:** Patients eligible for this trial had advanced solid malignancies. Oral daily BIBW 2992 dose was doubled in successive cohorts until toxicity > grade 2 occurred, when escalation of no more than 50% was allowed. Sequencing of tumour DNA for EGFR was performed in objective responders. An expanded cohort of patients at the 40 mg dose group (N = 16) was assessed for the effect of food on BIBW 2992 PK parameters. PK sampling was performed in all patients on days 1−2 and at steady state of the initial treatment course. Trough PK samples were taken during the initial and repeated treatment courses. For patients taking part on the food effect arm two single dose PK profiles were taken with a wash out time of two weeks in between.
**Results:** 47 evaluable patients have been treated (24 male); median age was 56 years (range 31−78). The BIBW 2992 dose was escalated from 10 to 50 mg. Three dose-limiting toxicities (DLT) were seen in cycle 1; one patient developed dyspnoea with interstitial changes at 30mg and fully recovered on discontinuation of BIBW 2992; two developed grade 3 acneiform rash at doses of 40 mg and 50 mg, which resolved on discontinuation and dose reduction. Other adverse events were mild (grade 1 or 2): nausea, diarrhoea, hand-foot syndrome and fatigue.
Three patients with NSCLC had confirmed durable Partial Response to treatment (duration of 26, 20 and 8+ months respectively). Two of them were found to have activating deletion mutations in the EGFR domain (exon 19). A further 8 patients with a variety of advanced malignancies remained on treatment with BIBW 2992 for more than 6 months. Updated clinical data will be presented at the meeting.
Generally, maximum plasma concentrations and exposure of BIBW 2992 increased with dose either after single dose or at steady state. There was no deviation from dose-proportional PK. BIBW 2992 exhibited a high apparent volume of distribution indicating a high tissue distribution of the drug. Data from the food effect arm will be presented as well.
**Conclusion:** The recommended phase II BIBW 2992 dose of 50mg daily is well tolerated. Partial Response or durable Stable Disease (>6 months) were seen in 23% of the patients. PK studies indicate that BIBW 2992 exposure increased with dose on day 1 and at steady state. Further clinical studies of BIBW 2992 in phase II is warranted.

**704** POSTER

**A phase I dose escalation and pharmacokinetic study of BIBF 1120, a novel tyrosine kinase inhibitor against VEGFR, PDGFR and FGFR, in combination with docetaxel in advanced chemonaive hormone refractory prostate cancer patients (HRPC)**

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**Background:** BIBF 1120 is an oral potent kinase inhibitor targeting multiple tyrosine receptors such as VEGFR, PDGFR, FGFR involved in tumor angiogenesis. Objectives were to determine the maximum tolerated dose (MTD), to evaluate safety, and to characterize the pharmacokinetic (PK) profile of BIBF 1120 in combination with docetaxel and prednisone to chemonaive patients with advanced HRPC.
**Methods:** Twice daily escalating doses of BIBF 1120 were given (2×100 mg, n = 3; 2×150 mg, n = 3; 2×200 mg, n = 3; and 2×250 mg, n = 12) on the days without chemotherapy. Docetaxel (75 mg/m$^2$) was given every three weeks along with prednisone (2×5 mg per day). A 3 + 3 dose escalation design was followed. Hematological toxicity of ⩾CTCAE grade 3 was not considered as dose limiting toxicity (DLT) during the first cycle. Twelve patients were treated on the MTD level.
**Results:** A total of 21 patients (median age 68 years, range 58−79) received up to 6 courses of BIBF 1120 in combination with docetaxel. The MTD of BIBF 1120 was established at 2×250 mg BIBF 1120. BIBF 1120 related toxicity observed so far in 15 patients was of mild to moderate intensity (CTCAE grade 1, 2) with non-hematological toxicity consisting of diarrhoea (53%), asthenia (53%), nausea (33%), abdominal pain (20%), and vomiting (13%). With respect to DLT, a reversible CTCAE grade 3 drug-related ALT increase has been observed in one patient at 2×250 mg during the first cycle. During subsequent cycles, further DLTs of CTCAE grade 3 have been observed in another patient at 2×250 mg of BIBF 1120 (combined AST- and ALT elevation) and in three patients at 2×200 mg (diarrhoea, AST- and ALT elevations). In preliminary analyses, there was no increase of docetaxel related hematological toxicity associated with the addition of BIBF 1120. At 2×250 mg BIBF 1120, eight of twelve patients showed a confirmed decline of PSA ⩾ 50%, which may indicate antitumour activity. Thus far, PK of docetaxel and BIBF 1120 was analyzed from 6 patients (n = 3, 2×100 mg, n = 3, 2×150 mg BIBF 1120). The interim PK analysis suggests no significant change in the docetaxel plasma concentrations before and after 3 weeks of continuous daily treatment with BIBF 1120.
**Conclusions:** BIBF 1120 can be given safely front line at a dose of 250 mg twice daily together with docetaxel in patients with advanced HRPC. First signs of efficacy have been observed.

**705** POSTER

**Evaluation of thyroid function in an open-label Phase I study of AZD2171 with gefitinib**

E.E. Voest[1], H. van Cruijsen[2], C.M.L. van Herpen[3], P.O. Witteveen[1], K. Hoekman[2], M. Langenberg[1], C.J. Punt[2], J. Robertson[4], O. Saunders[4], G. Giaccone[2]. *[1]University Medical Center Utrecht, Department of Medical Oncology, Utrecht, The Netherlands; [2]VU University Medical Center, Department of Medical Oncology, Amsterdam, The Netherlands; [3]Radboud University Nijmegen Medical Centre, Department of Medical Oncology, Nijmegen, The Netherlands; [4]AstraZeneca, Macclesfield, Cheshire, United Kingdom*

**Introduction:** AZD2171 is an oral, highly potent and selective tyrosine kinase inhibitor of VEGFR-1, -2 and -3. Given that several modulating effects of VEGF on the thyroid gland have been described, thyroid function changes were evaluated in patients receiving AZD2171 with gefitinib as part of an ongoing Phase I study.
**Methods:** Patients received once-daily, oral AZD2171 (20–45 mg) and gefitinib (250 or 500 mg) (van Cruijsen et al. Proc Am Soc Clin Oncol 2006:abst 3017). The normal range of thyroid-stimulating hormone (TSH) used in this study was 0.3−5 mU/L; an increase from normal baseline to >5 mU/L was considered abnormal. Depending upon the centre, thyroxine (T4) was measured as either total (normal range 50–150 mmol/L) or free (normal range 8–22 pmol/L). Assessments were weekly for the first month of treatment and then fortnightly until withdrawal.