gene in 3/4 tests. In a cross validation of this gene in cell line and xenograft datasets, its overall predictive accuracy was 77% and 86% respectively.
Conclusions: UPB1 and CTPS2 are promising novel candidate determinants of 5-FU activity. On-going studies are incorporating gene combination analyses, and gene modulation and human tissue investigations.

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Genetic polymorphisms associated with adverse events in childhood acute lymphoblastic leukaemia treated with SHOP-2005 protocol

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Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer, and still the most important cause of cancer-related death in children. Although the introduction of treatment protocols has improved survival, interindividual differences in drug responses are an important cause of resistance to treatment and adverse drug reactions. Pharmacogenetic studies are providing a rational base for further treatment efficacy and reduction of complications.
The aim of the present study was to determine if there was a correlation between genetic polymorphisms and toxicity and/or outcome during therapy in paediatric ALL patients treated according to the SHOP-2005 protocol (high-dose methotrexate [MTX] and 6-mercaptopurine [6-MP]).
We analyzed 12 polymorphisms of 9 genes in 21 paediatric ALL patients: 3 genes of the MTX pathway (MTHFR, RFC1 and ABCB1), 1 gene of the 6-MP pathway (TPMT) and 5 genes involved in xenobiotic detoxification (CYP1A1, NQO1 and the GSTs GSTM1, GSTT1 and GSTP1). Then, data were analyzed by using the Fischer exact test.
Several associations were found, such as that of the MTHFR C677T and A1298C polymorphisms and minimal residual disease (predictor of relapse in ALL), and the association between the MTHFR A1298C polymorphism and vomiting, as well as that of the GSTM1 null genotype and diarrhoea. Moreover, when the genes involved in the MTX pathway and the GST genotypes were analyzed together, they predicted diarrhoea even better than GSTM1 alone.
Our results indicate that several polymorphisms of the MTX-related genes and GST genes may be useful as predictors of gastrointestinal toxicity and outcome of the SHOP-2005 treatment protocol.

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Influence of PXR haplotype variants on paclitaxel pharmacokinetics and pharmacodynamics in Asian cancer patients

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Background: Paclitaxel is primarily metabolized by CYP3A4 and CYP2C8 and transported by ABCB1, which are downstream targets of the pregnane X receptor (*PXR*) gene. The objective of this exploratory study was to investigate the influence of *PXR* genetic variants on the pharmacokinetics and pharmacodynamics of paclitaxel in Asian cancer patients.
Materials and Methods: A total of 25 Asian cancer patients receiving intravenous infusions of paclitaxel either as a weekly (80 mg/m^2, N = 11) or three weekly (170 mg/m^2, N = 14) dosage regimens were recruited. Pharmacogenetic and pharmacokinetic data were available for all the patients and pharmacodynamic data was available for 12 patients. Paclitaxel pharmacokinetic parameters were estimated using non-compartmental analysis (WinNonlin) and Mann-Whitney *U* test was used to assess genotypic-phenotypic correlations.
Results: Two main *PXR* haplotype groups were identified, *PXR*1B* and non-*PXR*1B* haplotype groups. The *PXR*1B* haplotype group was tagged by the IVS6−17C>T and 2654T>C SNPs. Patients harbouring the *PXR*1B* haplotypic constitution had significantly lower clearance [CL/dose ($mL \times h^{-1} \times mg^{-1}$), median: 94.0; range: 45.3–207.2] and significantly higher exposure levels of paclitaxel [$AUC_{0-\infty}$/dose ($hr \times \mu g \times mL^{-1}$): median: 52.8; range: 35.5–89.0] compared to patients belonging to the non-*PXR*1B* haplotype group [CL/dose ($mL \times h^{-1} \times mg^{-1}$), median: 229.50; range: 65.5–624.3, (P = 0.03) and $AUC_{0-\infty}$/dose ($hr \times \mu g \times mL^{-1}$): median: 27.2; range: 12.5–53.9, (P = 0.007), respectively]. Patients carrying the *PXR*1B* haplotype group also had significantly higher C_{max} levels of paclitaxel [C_{max}/dose ($\mu g \times mL^{-1}$): median: 17.6; range: 12.1–40.9] compared to patients belonging to the non-*PXR*1B* [C_{max}/dose ($\mu g \times mL^{-1}$): median: 11.03; range: 1.3–22.5, P = 0.03] haplotype group. Pharmacodynamic analysis revealed that patients carrying the *PXR*1B* haplotypic constitution had 2.1- and 1.7-fold lower absolute neutrophil counts and platelet counts when compared to the patients bearing the non-*PXR*1B* haplotypic constitution.
Conclusion: The *PXR*1B* haplotype group was found to be associated with significant alterations in the pharmacokinetics of paclitaxel and a non-significant trend towards decreased ANC counts and thrombocytopenia. This exploratory study suggests that *PXR* haplotype constitution may be important in influencing interindividual variations in the disposition of paclitaxel.

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Transcriptome analysis method for in vivo mechanism of action study: IMC-D11 anti-FGFR3 +/− cisplatin in bladder cancer models

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Background: IMC-D11, a fully human IgG1 against the human fibroblast growth factor 3 (FGFR3), enhances the anti-tumor effects of cisplatin (CDDP) when given as a combination therapy in the RT112, RT4 and BFTC-905 bladder cancer xenograft models. The molecular mechanisms in support of this combination however have not been fully elucidated. To this end, we took a systems approach to gain further insights into the molecular networks underlying the synergistic/additive effects between IMC-D11 and CDDP in vivo.
Materials and Methods: Total RNA from RT112, RT4 and BFTC-905 derived tumors treated with IMC-D11, CDDP or the combination (n = 3 tumors per group) were subjected to a global gene expression profiling using Affymetrix Human Genome U133A array.
Results: The raw data were normalized, filtered and statistically analyzed, and the lists of genes significantly regulated by IMC-D11, CDDP or the combination treatment as compared to control groups were determined. Two levels of comprehensive bioinformatics analysis of these data were performed; at the gene level and at the pathway/network level. Combination treatment with IMC-D11 and CDDP uniquely altered the expression of many genes. In RT112 for example, DOK3, FOXP3 and hprt (1200 kb deletion mutant) were significantly upregulated only with combination treatment. However, none of the genes regulated by the combination treatment were found common to three models. We therefore further examined whether these differentially expressed genes are associated with common functions, networks, or processes using Gene Ontology (GO) annotation. The results indicate that the main GO classes found enriched in the combination group in the three models were related to the processes of cell cycle/proliferation, cell death/apoptosis, DNA replication and repair.
Conclusions: Results from these analyses, and others being performed, provide not only a molecular framework for further investigation on the mechanism by which IMC-D11 and CDDP exert their anti-tumor effects, but also crucial information that may potentially be utilized for optimizing therapeutic strategies against bladder cancer.

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In Mdm2 SNP309 cancer cells the small molecules nutlin-3 and MI-63 facilitate recruitment of RNA polymerase II to p53 target genes

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Background: Mdm2 inhibits p53 transactivation in part by forming a p53-Mdm2 complex on chromatin. A homozygous single nucleotide polymorphism (T to G) in the mdm2 gene at position 309 (SNP309) results in increased Mdm2 expression and increases susceptibility to cancer. In human cancer cells overexpressing Mdm2 due to homozygous G/G SNP309, the p53-Mdm2 chromatin complex is highly stable and is not disrupted following DNA damage.
Materials and Methods: To determine how the p53 response phenotype was influenced in cells with variable mdm2 genotypes using differential activation of the p53 pathway we compared targeted p53-Mdm2 complex disruption by the small molecule inhibitors Nutlin-3 and the MI-63 in wild-type p53 human cancer cell lines with variable SNP309 genotypes and wild type p53 to etoposide DNA damage treatment. The ability of the small molecule inhibitors to facilitate increased transcription factor recruitment to the chromatin was compared to the recruitment facilitated by treatment

of human cancer cells with the DNA damaging drug etoposide using chromatin immunoprecipitation.
Results: Strikingly, Mdm2-overexpressing G/G and G/T SNP309 cells showed a substantial increase in the RNA Polymerase II recruitment to p53 target genes when treated with the small molecule inhibitors while less increase in RNA Polymerase II recruitment to p53 target genes occurred after etoposide treatment. Importantly, all the treatments resulted in equally high levels of nuclear p53 but the small molecule inhibitors resulted in more nuclear Mdm2 protein accumulation.
Conclusions: Categorizing the mechanisms by which the small molecule inhibitors facilitate more efficacy for activation of wild type p53 on chromatin in Mdm2 G/G or G/T SNP309 cells could set the stage for a molecular predictive biomarker to be associated with potential tumor response to small molecule based therapy.
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Predicting a metastatic treatment response in advanced colorectal cancer patients by gene expression profiling

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Background: Roughly one half of patients with colorectal cancer develop liver metastases during the course of their disease. In this metastatic setting, administration of chemotherapy likely to induce a maximal response in the first course of treatment is critical to enhance overall treatment success. A major clinical challenge is to identify a subset of patients who could benefit from chemotherapy. The aim of this study was to identify a pattern of gene expression able to predict response to FOLFIRI in CRC patients using liver metastases gene expression profiles.
Methods: Metastasis mRNA samples from 19 chemonaive CRC patients with synchronous and unresectable liver metastases were profiled using the Affymetrix HG U133 GeneChip. We defined responder and non-responder patients according to the WHO criteria. We used ROC analysis and multiple testing procedures to select informative genes.
Results: We determined an 11-gene signature that clearly separate responder and non-responder patients. Then, using an SVM-learning algorithm, we defined a predictor classifier and its performance was evaluated by the leave-one-out cross validation. All the 8 responders (100% specificity) and the 11 non-responders (100% sensitivity) were correctly classified, for an overall accuracy of 100%.
Conclusion: Our results show gene expression signature that makes a useful contribution to improving the response to metastatic treatment in CRC. Indeed, in metastatic setting, the time is an important factor and to make the good first-line treatment choice could be decisive.

Phase II

203 POSTER

Neratinib (HKI-272), an irreversible pan-ErbB receptor tyrosine kinase inhibitor: preliminary results of a phase 2 trial in patients with advanced non-small cell lung cancer

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Background: Neratinib (HKI-272) is a potent irreversible tyrosine kinase inhibitor (TKI) that inhibits both ErbB1 (EGFR) and ErbB2 (HER2). In a phase 1 study, 6 patients (pts) with advanced non-small cell lung cancer (NSCLC) and prior gefitinib or erlotinib treatment had stable disease (SD) ⩾24 wks. In this 3-arm phase 2 trial, pts with stage III-B/IV/recurrent NSCLC were evaluated to further characterize the safety and efficacy of neratinib.
Methods: EGFR mutations were analyzed by direct sequencing. Pts were enrolled and assigned to arm A or B if they had disease progression following ⩾12 wks of erlotinib or gefitinib and either EGFR mutation (arm A) or EGFR wild-type tumors (arm B). Pts were enrolled in arm C if they had no prior EGFR TKI treatment, adenocarcinoma, ⩽20 pack-year smoking history, and were current non-smokers. The primary endpoint was objective response rate.
Results: Accrual is complete and we report preliminary data for 165 pts (median age 60 yrs, 30% male, 58% with 0−2 and 43% with ⩾3 prior chemotherapy regimens).
Pts initially received 320 mg daily of neratinib but the protocol was amended to 240 mg because of reported gastrointestinal adverse events (AEs). Neratinib-related AEs any grade, in >15% of pts were diarrhea (89%), nausea (50%), fatigue (29%), anorexia (28%), vomiting (27%), abdominal pain (24%), and rash (16%). Diarrhea was the only ⩾grade 3 AE that occurred in ⩾5% of pts (320-mg dose: 38%, 240-mg dose: 22%). Reasons for discontinuation of the study included disease progression (78%), AEs (4%), and symptomatic deterioration (4%). 12/165 (7%) of pts had T790M mutations. Of the 28 pts in arm C, 9 pts had EGFR mutations; 5 pts had no EGFR mutations (14 pts were unknown). In arm A, 2 pts had partial response (PR) and 43 had SD, 14 with SD ⩾24 wks. In arm B, 1 pt had complete response (CR) and 22 had SD, 4 with SD ⩾24 wks. In arm C, 1 pt had PR and 11 had SD, 6 with SD ⩾24 wks. The objective response rate was 2% (4/165). None of the responders had T790M mutations.
Clinical benefit rates (CR+PR+SD ⩾24 wks) for pts in the 3 arms were 18% (arm A), 10% (arm B), and 25% (arm C). Median progression-free survival (PFS) was 8.9 wks (arm A), 8.0 wks (arm B), and 7.4 wks (arm C).
Conclusions: Neratinib is reasonably tolerated and diarrhea was the most common ⩾grade 3 AE. 18 (11%) of NSCLC pts with prior erlotinib/gefitinib treatment had SD ⩾24 wks. Exploratory analyses are ongoing to correlate outcome with clinical and molecular parameters.

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Recombinant IL-21 in combination with sorafenib as second or third-line therapy for metastatic renal cell carcinoma (mRCC): Interim results from a Phase 2 study

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Background: Despite the positive impact of tyrosine kinase inhibitors (TKIs) and mTor inhibitors on the outcome for mRCC, complete responses are rare and long-term survival remains poor. Recombinant IL-21 (rIL-21), a cytokine that enhances CD8+ T cell and NK cell activity, has single-agent anti-tumor activity as shown in Phase 1 studies. The combination of rIL-21 plus the TKI sorafenib was tested in a Phase 1 study in the outpatient setting. We now report interim results of a Phase 2 study to evaluate the safety, pharmacokinetics, and anti-tumor efficacy of rIL-21 plus sorafenib using the maximum tolerated dose determined in Phase 1.
Methods: 30 patients with mRCC will be enrolled from 14 sites in the United States and Canada to receive 2nd or 3rd-line therapy with sorafenib 400 mg BID plus 30 μg/kg rIL-21 IV on days 1−5 and 15−19 of each 6-week treatment course. Tumor response per RECIST criteria will be assessed by the investigator and by independent radiologic review.
Results: As of May 19, 2008, 18 patients were treated; the first 15 are summarized here. Median age was 59 (range 47−75), male:female ratio was 11:4, and ECOG performance status was 0 (n = 6) or 1 (n = 9). Patients had received 1 (n = 10) or 2 (n = 5) previous lines of therapy, which included sunitinib (n = 11), temsirolimus (n = 3), IL-2 (n = 3), pazopanib (n = 1), everolimus + avastin (n = 1), and vinblastine + interferon (n = 1). Most adverse events (AEs) were Grade 1 or 2, and consistent with the known toxicity of rIL-21 and sorafenib. Common AEs (>20% of subjects) included rash, diarrhea, hand-foot syndrome, flu-like illness, fever, chills, and pruritus. Grade 3 AEs occurred in 7 subjects and were hand-foot syndrome (n = 3), neutropenia (n = 2), thrombocytopenia (n = 2), rash (n = 1), elevated liver function tests (n = 1), metabolic acidosis (n = 1), coagulopathy (n = 1), and acute renal failure (n = 1). All 9 subjects for whom tumor assessment is available had stable disease, with tumor shrinkage of 0−27% as measured by the investigator. 7 of 10 subjects who have