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

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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