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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202 POSTER

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.

204 POSTER

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

completed the 1st treatment course have received additional courses; none have discontinued therapy due to progressive disease.
Conclusions: Outpatient therapy with rIL-21 plus sorafenib is well tolerated with appropriate dose modification and associated with anti-tumor activity as a 2nd or 3rd-line therapy for mRCC. Updated results from all available subjects in Phase 2, including 6 months of follow-up for the first 15 subjects, will be available at the meeting.

205 POSTER

A phase II study of oral enzastaurin HCl in patients with metastatic colorectal cancer

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Background: About 50% of all colorectal cancer (CRC) patients (pts) ultimately die of metastatic disease signifying a need for improved treatment. Enzastaurin, a protein kinase C-β/AKT inhibitor with antiangiogenic and proapoptotic properties, has shown activity in hematological and solid tumors. We evaluated enzastaurin monotherapy using a Phase 2 Window study in chemonaive pts with asymptomatic metastatic CRC (mCRC) for whom standard chemotherapy could be safely delayed. The main objective of this single-arm, open-label study was to estimate the 6-month progression-free survival (PFS); secondary objectives included evaluation of safety and efficacy, time-to-event measures, and carcinoembryonic antigen (CEA) levels.
Materials and Methods: Patients with asymptomatic mCRC with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with at least one measurable lesion received a 400 mg TID loading dose of enzastaurin on Day 1 of Cycle 1, followed by 500 mg once daily for the remaining cycle (1 cycle = 28 days), and all subsequent cycles. Patients were considered eligible only if they were not candidates for chemotherapy-induced tumor reduction that could potentially lead to total tumor resection. Plasma samples for pharmacokinetic characterization were collected on Day 2, Cycle 1 (day after loading dose); Day 1, Cycle 2; and Day 1, Cycle 3 (both steady-state).
Results: A total of 28 pts (16 male, 12 female; median age 69 yrs) enrolled and received treatment. Six (21%, 95% CI = 13−44%) pts reached a 6 month PFS. No pt had a clinical response, 12 (43%) achieved stable disease. Overall survival was censored at 82%. The survival rate at 20 months = 77% (CI 47%-92%) and median PFS was 2 months (95% CI = 1.8–4.5 months). Correlation between CEA level changes and enzastaurin activity was not apparent. Four of 28 pts received the planned 6 cycles of therapy. Of the 2 discontinuations, one (cerebral hemorrhage leading to death) was possibly related to study drug. There were 4 dose omissions but no dose reductions. Eight pts had Grade (Gr) 3 toxicities and 1 pt had a Gr 4 upper respiratory infection. The Gr 3 toxicities included nausea, transaminase elevation (possibly related to study drug), edema, etc, but no prevalence of any specific toxicity was evident. Alterations in QTc intervals observed on electrocardiogram assessments were not deemed medically significant even when conducted at Cmax level. Slit-lamp exams did not indicate cateractogenesis or changes in existing cataracts with enzastaurin treatment. Pharmacokinetics of enzastaurin and its active metabolite in mCRC pts were comparable to those seen in previous studies in other tumor types.
Conclusions: Enzastaurin is well tolerated but exhibits modest activity as monotherapy in chemonaive pts with mCRC. Further studies of enzastaurin in combination with other agents in mCRC are warranted.

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Phase II study of sunitinib in patients (pts) with progressive metastatic adenoid cystic carcinoma (ACC)

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Background: A high level of c-kit expression, usually of wild-type, has been identified in >90% of ACC. However, imatinib has been found to be inactive in that population likely because its activity is dependent on specific c-kit mutations (Hotte et al, J Clin Oncol 2005). VEGF overexpression has been correlated with worse clinical outcome in ACC (Zhang et al, Clin Cancer Res 2005). Sunitinib, which inhibits multiple receptor tyrosine kinases including VEGFR and unmutated c-kit, is of interest for evaluation in ACC.
Methods: This is a two-stage, single-arm phase II clinical trial of sunitinib in adult pts with unresectable or metastatic ACC measurable by RECIST criteria, progressive disease is not mandatory at study entry. All patients were treated with a starting dose of sunitinib 37.5 mg PO on a daily and continuous schedule, in 4-week cycles. The primary endpoint is objective response rate, assessed radiologically every 8 wks. One or more objective responses must be observed out of 12 pts in the first stage for the study to enrol to a total of 37 pts.
Results: Since February 2007, 12 pts, including 8 males, with a median age of 61 (range, 50−70) were entered onto stage 1. Nine pts had no prior systemic treatments and 11 had prior radiation. Pts had a median of 5 target sites (range, 2−9) and lung lesions were most common. A total of 56 cycles and a median of 5 cycles (range, 2−8) have been administered. All pts but one had a best response of SD and 2 pts remain on study. No PR observed; PFS was nine months (mo) (95%CI 7.3 – NR) and 6-month progression free rate was 91%. Median time to failure was 7.3 mo (95%CI 6.6 mo – NR). This compares favourably to other phase 2 trials conducted by our group (Table). Four pts came off study because of toxicity. The most frequent adverse events (AE) of all grades and at least possibly related to sunitinib were (# of pts): fatigue (9), lymphopenia (9), mucositis (8), leucopenia (7), dyspepsia (7), hypophosphatemia (7), diarrhea (6), neutropenia (6), hand foot syndrome (6). Grade 3 AE of possible attribution were infrequently encountered (# of pts) and most common were: lymphopenia (4), fatigue (4) and neutropenia (3).
Conclusions: Sunitinb is associated with the expected toxicities but is reasonably well tolerated and may favourably affect rate of progression of disease. Decision regarding proceeding to second stage is pending.

Table 1

	lapatinib (mo)	imatinib (mo)	sunitinib (mo)
Median TTP	3.5 (31-NA)	2.3 (1.8-NA)	9 (7.3-NA)
3-mo PFS	70% (53−93%)	37% (19−74%)	–
6-mo PFS	35% (19−64%)	20% (6−62%)	91% (75–100%)

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Phase II study of gefitinib in combination with cisplatin and concurrent radiotherapy in patients with stage III/IV squamous cell head and neck cancer and to analyse the effect of gefitinib on tumour gene expression

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Background: Gefitinib has shown modest activity in squamous cell head and neck cancer (SCHNC) and is synergistic with radiation and cisplatin in exerting anti-tumour effects. This study aims to determine the feasibility and toxicity of adding gefitinib to cisplatin and concurrent radiotherapy in patients with locally advanced SCHNC.
Methods: Patients with accessible primary tumour site for repeat biopsies and who have stage III/IV unresectable SCHNC or who were deemed unsuitable for curative resection were eligible. Baseline biopsy of the tumour at the primary site was done and the patient was started on gefitinib at 500 mg/day as induction for 3 weeks. Two weeks after the start of gefitinib, a second tumour biopsy was done. A repeat CT/MR of the head/neck was done after the induction phase for response evaluation. Radiotherapy of 70 Gy in standard fractionation was started after induction phase with cisplatin at 80 mg/m^2 given on weeks 1, 4 and 7 of the radiation concurrently. Gefitinib was maintained at 500 mg/day during the radiotherapy phase and continued for 4 months as consolidation upon completion of radiotherapy. A repeat CT/MR was done 8 weeks after completion of radiation for evaluation and 3−4 monthly thereafter for the first 2 years. The paired tumour samples were analysed for changes in gene expression after gefitinib using the Affymetrix Gene Chip Human Genome U133 set.
Results: 31 patients were recruited; one patient declined further treatment after 1 week of induction gefitinib. Patient characteristics are as follows: median age 55 yrs (44−77), male 77%, eversmoker 68%. Tumour characteristics: oral cavity 36%, oropharynx 45%, others 19%; T1−2 19%, T3−4 81%, N0−1 32%, N2−3 68%. Three pts responded during induction phase (10%) with 2 complete responses (CR); at the first evaluation after completion of chemoradiotherapy, 74% had a major response (PR/CR). The 2-yr progression-free (PFS) and overall survival rate (OS) was 45%