G3/4, 5.3%) and rash (G1/2, 44.7%; G3/4, 0%). The recommended phase II dose is being explored in expanded cohorts enriched for molecular variations of HER family receptors in multiple tumor types, as well as wild-type KRAS in refractory non-small cell lung cancer (NSCLC). Updated PK/PD results are presented, with preliminary efficacy data for the NCSCL cohort.

Materials and Methods: PK data were collected on day 14 of cycle 1. PD measures included assessments of skin rash, diarrhea, HER-related signaling pathways by immunohistochemistry analyses of serial skin biopsies, and tumor functional (FDG-PET) imaging. PK/PD relationships were assessed by Spearman Correlation analysis. Tumor response was evaluated in patients with NSCLC.

Results: C_{max} and AUC increased with dose and no evidence of dose- or time-dependent PK was seen; the average terminal half-life was ~85 hours. Significant positive correlations were noted between diarrhea severity and PK parameters or dose ($p \leqslant 0.0001$), and between rash severity and dose ($p = 0.0009$). Significant negative associations ($p < 0.05$) were seen between the skin biomarkers, Ki67 and pMAPK, and C_{max} or dose. Ki67 changes also negatively correlated with diarrhea severity ($p = 0.0296$) and positively correlated with changes in pMAPK ($p = 0.0048$). Forty-three patients with NSCLC were enrolled. Four patients achieved a partial response, and disease was controlled in 50% of patients.

Conclusions: At the recommended phase II dose, 45 mg/day, the mean steady-state trough concentration approached the predicted human efficacious concentration. PK/PD analysis in skin suggests that PF-00299804 mechanistically inhibits the EGFR-MAPK signalling pathway, decreases the Ki67 proliferation marker and produces rash/diarrhea in a dose- or exposure-dependent manner. Updated efficacy results and tumor functional imaging data will be presented at the meeting.

565 POSTER

Activity of the anti-IGF-IR antibody CP-751,871 in combination with docetaxel as first-line treatment for castration resistant prostate cancer in a randomized Phase II trial

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Background: CP-751,871 is a fully human IgG2 monoclonal antibody against the insulin like growth factor 1 receptor (IGF-IR). Inhibition of the IGF-IR is a promising novel therapy for prostate cancer. Elevated serum IGF-1 is associated to increased prostate cancer risk; up-regulation of the IGF-IR has been documented in prostate cancer refractory to hormonal therapy (HRPC); and IGF-IR blockade is active in animal models of HRPC.

Methods: We are conducting a phase 2 trial to determine the activity of the combination of docetaxel 75 mg/m^2 q3 weeks (D), prednisone 5 mg p.o. BID (P), and CP-751,871 20 mg/kg q3 weeks (I) in metastatic, chemotherapy-naive HRPC patients (pts) with performance status 0−1. A total of 200 pts will be randomized 1:1 to receive DPI or DP alone. Pts progressing on DP alone are eligible to receive DPI. Pts receiving DPI with response (PR) or stable disease are eligible to receive I or PI upon D discontinuation for up to 12 mos. The primary endpoint is PSA response according to PSAWG criteria.

Results: Ninety seven men with metastatic, HRPC have been enrolled. Median age was 70 yrs; PS 0 (13%), PS 1 (76%), PS 2 (11%). DPI was well tolerated. All causality grade 3, 4 toxicity included (DPI, DP): hyperglycemia (22%, 7%), fatigue (4%, 15%), and neutropenia (41%, 48%). PSA response data are available for 42 patients: 45% of patients responded to DPI and 32% to DP.

Conclusions: DPI is well tolerated and appears active in HRPC. Accrual continues to further assess the clinical activity of this combination treatment.

566 POSTER

Pyrazolo[3,4-d]pyrimidines as dual kinase inhibitors of both insulin-like growth factor receptor (IGF-IR) and members of the epidermal growth factor receptor family (EGFR and ErbB-2)

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As kinase targeted therapies for cancer have reached the clinic, selective agents have generally failed to yield durable clinical responses. However, the use of these agents in combination with other classes of therapeutics (antibodies, receptor tyrosine kinase inhibitors, cytotoxics) has yielded improved clinical results. For some combination therapies, the rationale is to not only target the desired oncogenic protein (kinase), but also to target known resistance mechanisms.

For the epidermal growth factor (ErbB) family of receptor tyrosine kinases (RTKs), the clinical effectiveness of trastuzumab is significantly diminished by overexpression of the insulin-like growth factor receptor (IGF-IR) and its corresponding ligands. Additionally, cellular systems expressing both RTKs have shown decreased sensitivity to not only trastuzumab, but also, gefitinib. In vitro, we have previously demonstrated that inhibition of both the insulin-like growth factor receptor-I (IGF-IR) and the ErbB-family of RTKs results in a synergistic reduction in cancer cell proliferation, and increased induction of apoptosis.

A therapeutic strategy that simultaneously targeted inhibition of both members of the ErbB-family and the IGF-family would be potentially superior to either selective approach. High throughput screening of Abbott's compound collection indicated that pyrazolo[3,4-d]pyrimidines possess activity versus either IGF-IR or ErbB-1 (EGFR). Therefore, appropriate functionalization of the pyrazolo[3,4-d]pyrimidine scaffold might afford analogs with dual IGF-IR and ErbB-family in vitro and in vivo activity. The structure–activity relationships that were discovered during our lead optimization program will be presented. The result of these efforts led to the synthesis and characterization of A-947864, a pyrazolo[3,4-d]pyrimidine with dual IGF-IR and ErbB-family enzymatic and cellular activity.

567 POSTER

GSK1120212 is a novel Mek inhibitor demonstrating sustained inhibition of ERK phosphorylation and selective inhibition of B-Raf and *RAS* mutant cells in preclinical models

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GSK1120212 is an orally available, potent and selective allosteric inhibitor of the Mek1/2 enzymes. In biochemical assays it inhibits Mek1 activation by B-Raf ($IC50 = 0.4 \pm 0.1$ nM) and the phospho-Mek1 kinase activity ($IC50 = 10 \pm 2$ nM). Consistent with an allosteric mode of inhibition, GSK1120212 is highly selective with $IC50 > 10\ \mu M$ against more than 200 different kinases tested. Antiproliferative activity of GSK1120212 was measured in tumor cell lines and demonstrated potent inhibition of growth ($gIC50 < 50$ nM) in cell lines harboring an activating *RAS* or *BRAF* mutation, but was less active against tumor cell lines having wild-type *RAS* and *BRAF*. GSK1120212 demonstrated minimal activity against human normal non proliferating cells. In vivo studies using daily dosing for 14 days at 3 mg/kg demonstrated a sustained inhibition of phospho-Erk1/2 in A375PF11 (melanoma cell line; B-Raf V600E) xenograft with reduction of KI67 and increase of p27Kip1 levels correlating with inhibition of tumor growth. In a Colo205 (CRC cell line; B-Raf V600E) xenograft tumor model we demonstrated that efficacy of GSK1120212 increased with BID versus QD treatment at 1 mg/kg over a 14 day experiment. In this same model we demonstrated that long term efficacy with improved tolerability was observed with alternating weekly drug treatment at 1 mg/kg QD. Additional in vivo efficacy with GSK1120212 was also demonstrated in *RAS* mutant (HCT116; CRC cell line) xenograft models. The favorable properties of this compound make it a suitable candidate for further development for the treatment of cancer.

568 POSTER

Selective inhibition of Met kinase activity impairs metastatic cancer cell motility and survival

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The Met receptor tyrosine kinase is highly expressed in cancer cells in a significant fraction of solid tumors, whereas the Met ligand, HGF, is produced by stromal cells in the tumor microenvironment. The combined