CA4P at 30 mins and an increase of 15.6% with OXi4503 at 90 mins ($p = 0.012$), indicating potential advantage for combination therapy.
Conclusions: PET provided evidence of early anti-vascular mechanistic effects and anti-proliferative response following 1 cycle of OXi4503, even at low doses, and in a range of tumour types (now in phase 1b trial). Early changes in PET derived tumour perfusion may be useful bio-indicators of tumour response for VDAs.

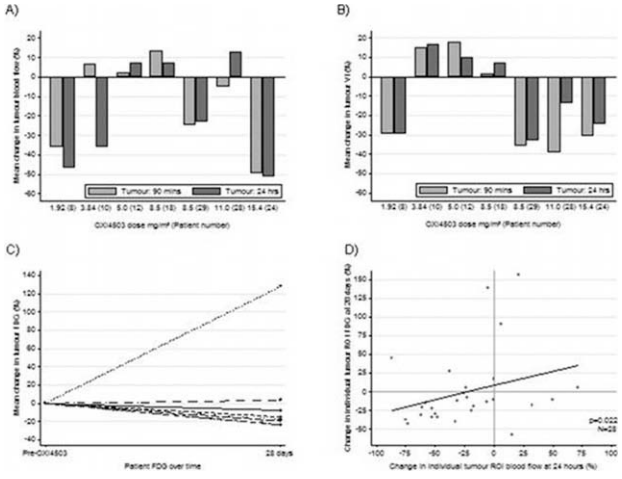


Figure 1.

381 POSTER

Preliminary results of a dose escalation study of the Fibroblast Growth Factor (FGF) "trap" FP-1039 (FGFR1:Fc) in patients with advanced malignancies

A. Tolcher[1], K. Papadopolous[1], A. Patniak[1], E. Heath[2], A. Weise[2], T. Prokop[2], S. Morrone[3], J. Zanghi[4], H.N. Keer[3], P. LoRusso[2].
[1]START, Clinical Trials, San Antonio, USA; [2]Karmanos Cancer Institute, Developmental Therapeutics, Detroit MI, USA; [3]Five Prime Therapeutics, Clinical Development, San Francisco CA, USA; [4]Five Prime Therapeutics, Preclinical Development, San Francisco CA, USA

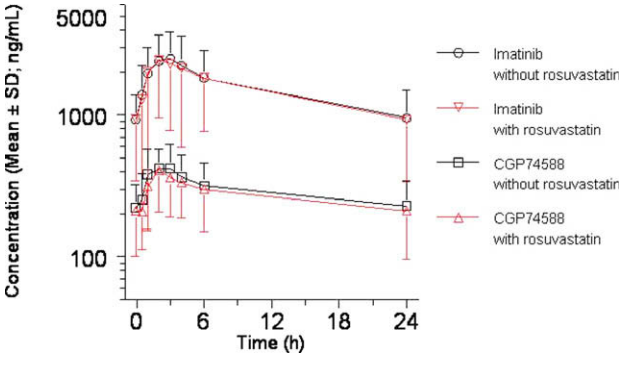
Background: The human FGF axis has been implicated in tumor growth promotion, angiogenesis, and tumor stem cell maintenance. FP-1039 acts as a ligand "trap" that sequesters multiple FGF family ligands, neutralizing their ability to bind to and activate multiple FGF receptors. FP-1039 targets multiple FGFs linked to multiple cancers, but does not target members of the keratinocyte growth factor subfamily (FGF-7, -10, -22: ligands of the putative tumor suppressor, FGFR2b) or the hormonal FGFs (FGF-19, -21, -23, involved in bile acid, glucose and phosphate regulation, respectively). FP-1039 has anti-tumor activity in multiple xenograft models, both as a single agent and in combination with other anticancer agents. We report preliminary results of a first-in-human study of FP-1039 as a single agent in patients with advanced solid malignancies.
Methods: Subjects received 4 once-weekly iv doses of FP-1039 by 30 min infusion, followed by a 2 week observation period. In the absence of unacceptable toxicity or progressive disease, patients were eligible to receive additional weekly doses of FP-1039. Plasma samples were taken for PK, pharmacodynamic biomarker, and immunogenicity studies.
Results: 24 subjects have received FP-1039 at doses from 0.5−4.0 mg/kg. While 2 DLTs were observed in the initial 1 mg/kg dosing cohort, no consistent pattern related to drug exposure could be discerned and confounding factors were present. Therefore, dose escalation continued beyond 1 mg/kg, and FP-1039 has been well tolerated to date without observations of drug-related weight loss, hypertension, or soft tissue calcification. PK analysis revealed a linear, dose-dependent increase in drug exposure in the plasma compartment. Mean terminal half-lives ranged from 63 to 102 hours, and appeared to be similar on Day 1 and Day 22. There was accumulation after 4 weekly doses of FP-1039. Free plasma FGF2 levels were assessed prior to initial dosing and at subsequent timepoints. All subjects had elevated FGF2 levels prior to FP-1039 treatment compared to normal individuals, and a decrease in free FGF2 following FP-1039 treatment. 15 subjects completed the treatment period, 7 did not due to adverse events or rapidly progressive disease, and 2 are pending. By RECIST criteria, 8 subjects had stable disease. In a subject with progressive prostate cancer after castration and docetaxel, a reduction in FDG PET SUV on 2- and 6-week scans and a 20% decrease in tumor size by CT scan were demonstrated.
Conclusions: FP-1039 appears to be well tolerated at doses of 0.5−4 mg/kg, and exploration of higher doses is in progress. Preliminary PK and target engagement data (reduction in FGF2) support a weekly or longer dosing interval. The adverse event profile observed to date suggests FP-1039 may be incorporated into multi-drug regimens containing chemotherapy and/or biologic therapies. Preliminary single agent activity is promising. These data suggest that phase Ib combination studies and a phase II single agent study of FP-1039 are warranted.

382 POSTER

Influence of rosuvastatin on the pharmacokinetics of imatinib: a cross-over study

K. Eechoute[1], R.M. Franke[2], W.J. Loos[1], P. de Bruijn[1], J. Verweij[1], A. Sparreboom[2], R.H.J. Mathijssen[1]. *[1]Erasmus University Medical Center, Medical Oncology, Rotterdam, The Netherlands; [2]St. Jude Children's Research Hospital, Pharmaceutical Sciences, Memphis, USA*

Background: The oral bioavailability of imatinib (Gleevec®) is about 90−95%. We previously reported that imatinib is a substrate of the intestinal uptake transporter, OATP1A2 (*SLCO1A2*) (Hu et al, *Clin Cancer Res* 2008). We hypothesized that the absorption of imatinib may be reduced by medication that blocks OATP1A2 function, such as rosuvastatin (Crestor®), a frequently used HMG-CoA reductase inhibitor in Europe.
Material and Methods: Serial blood samples were obtained from 12 patients with gastrointestinal stromal tumors (11 male, 1 female; age, 38−70 years old) receiving imatinib monotherapy (400 mg per day) before and after concomitant dosing of rosuvastatin for 14 days (20 mg a day; intake 20 min prior to imatinib). Plasma concentrations of imatinib and its active metabolite CGP74588 were determined by LC-MS/MS. Pharmacokinetic (PK) parameters were estimated by non-compartmental analysis using WinNonLin.
Results: The systemic exposure (AUC) to imatinib and CGP74588 did not differ between the first and second PK-measurement (37.6 *v* 37.0 and 7.18 *v* 6.62 μg × h/mL, respectively), as shown in Figure 1. There was a trend ($P = .065$; paired t-test) towards a lower AUC ratio of CGP74588/imatinib during rosuvastatin co-treatment (0.197 v 0.187), suggesting a lower metabolic conversion and/or an altered hepatobiliary excretion. In general, treatment-related toxicity did not alter as a result of rosuvastatin co-administration, except for grade 2 edema and diarrhea in 1 patient, and grade 1 muscle cramps in 2 patients.
Conclusion: The combination of imatinib and rosuvastatin does not lead to a substantially reduced systemic exposure to the anti-cancer drug at steady-state, suggesting that the intestinal absorption of imatinib is unaltered. Although rosuvastatin may inhibit formation of the active metabolite CGP74588, this is unlikely to have a negative influence on anti-cancer activity.



383 POSTER

First-in-human study of PF-04691502, a small molecule oral dual inhibitor of PI3K and mTOR in patients with advanced cancer: Preliminary report on safety and pharmacokinetics

C.D. Britten[1], A.A. Adjei[2], R. Millham[3], B. Houk[4], Z.A. Wainberg[1], T. Guthrie[5], G. Dy[2], P.M. LoRusso[5]. *[1]David Geffen School of Medicine at UCLA, Medicine, Los Angeles, USA; [2]Roswell Park Cancer Institute, Medicine, Buffalo, USA; [3]Pfizer Oncology, Clinical Development and Medical Affairs, New London, USA; [4]Pfizer Oncology, Clinical Development and Medical Affairs, La Jolla, USA; [5]Karmanos Cancer Institute, Medical Oncology, Detroit, USA*

Background: The PI3K/mTOR pathway regulates cell growth, proliferation, glucose metabolism and survival. The significance of the pathway has

been implicated in many cancers by mutational activation of PI3Kα, loss of function of PTEN and/or activation of upstream receptor tyrosine kinases. PF-04691502 is an orally available dual-specificity inhibitor of PI3K and mTOR which has shown potent and selective activity in *in vitro* (biochemical, cell) and xenograft models.
Methods: PF-04691502 is administered to adult patients with advanced solid tumors orally once daily (QD) continuously, starting with a dose of 2 mg QD. Assessments include safety (NCI CTC AE v4.0), pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity. Dose escalation occurs in 100% increments in 3-patient cohorts until a Dose Limiting Toxicity (DLT) or two grade 2 non-tumor related adverse events (AEs) are observed in the first cycle, at which point dose escalation is changed to no more than 40% increments until the DLT rate reaches or exceeds 33%. PD assessments include blood glucose and insulin. Antitumor activity is assessed per RECIST v1.1.
Results: As of 17 May 2010, a total of 8 patients have been dosed at 2, 4, and 8 mg QD. Tumor types have included NSCLC (2), breast, gastric, melanoma, ovarian, CRC and sarcoma (one each). PF-04691502 has been well tolerated with the most common treatment-related AEs being nausea, fatigue, headache and vomiting. Treatment-related AEs have been mostly mild to moderate (grade 1−2). One patient has experienced DLT (grade 3 fatigue) at the 8 mg QD dose level. Preliminary PK data indicate that PF-04691502 is eliminated with a half life of approximately 11−15 hours, with low clearance and a relatively high volume of distribution. At steady state, plasma concentrations exceed that estimated to be required for 50% suppression of phosphorylation of Akt, based on preclinical predictions. Minor changes in blood glucose and insulin have intermittently been observed. No objective tumor response has been observed. Dose evaluation continues.
Conclusions: Daily oral administration of PF-04691502 appears safe and tolerable across multiple dose levels. Nausea, fatigue and headache are the most frequently reported treatment-related AEs, those with only mild to moderate severity. To date one DLT (grade 3 fatigue) has been reported in a patient receiving 8 mg QD. Updated data for safety, PK, PD and antitumor activity will be presented.

384 POSTER

Phase 1/2 trial of CF102, a selective A3 adenosine receptor (A3AR) agonist, in patients with hepatocellular carcinoma (HCC)

S. Stemmer[1], M.H. Silverman[2], W.D. Kerns[2], S. Bar Yehuda[2], S. Fishman[2], Z. Harpaz[2], M. Farbstein[2], O. Binyaminov[3], G. Medalia[3], P. Fishman[4]. *[1]Institute Of Oncology Davidoff Center Rabin Medical Center Sackler School Of, Rabin Medical Center, Peta Tikva, Israel; [2]can-fite Biopharma, Clinical Studies, Peta Tikva, Israel; [3]institute Of Oncology Davidoff Center Rabin Medical Center Sackler School Of Medicine Tel Aviv University, Davidoff Center, Peta Tikva, Israel; [4]can-fite Biopharma, Ceo, Peta Tikva, Israel*

Background: CF102, a novel, orally-active, A_3AR agonist which induces tumor cell apoptosis in HCC experimental animal models, is under evaluation in this trial for the treatment of HCC patients with incurable disease.
Methods: The objectives of this trial are to evaluate the safety and pharmacokinetic (PK) behavior of CF102 in HCC patients. Utilizing a "3 + 3" design, successive cohorts of patients with advanced HCC were enrolled at CF 102 doses of 1, 5, or 25 mg twice daily, given orally in continuous cycles of 28 days each. Progression to a higher-dose cohort was based on first cycle toxicity. Standard safety and PK assessments were performed; α-fetoprotein (AFP) levels were obtained each cycle, and tumor imaging was obtained every other cycle.
Results: 9 patients (5 males), median age 75 (63−90) years, Child–Pugh Class A or B, have been administered CF102 across 3 cohorts, 3 at each dose level. No dose-limiting toxicities specifically attributed to CF102 have been observed at any dose level. Through 3 cohorts, with a maximum exposure of 8 cycles, adverse events reported in at least 2 subjects were: anorexia (5 subjects); abdominal pain, asthenia (4 each); diarrhea (3); and leg edema/swelling, fatigue, fever, nausea, back pain, chest pain, leg pain (2 each). All events classified as drug-related were either grade 1 or 2. No drug-related abnormalities of hematologic, renal, or hepatic function have been observed on laboratory testing. CF101 has shown good oral bioavailability and linear PK behavior after single doses and at steady state. To date, one patient, at the lowest dose level, has shown stable disease for 6 cycles accompanied by complete clinical regression of biopsy-proven skin metastases and a sustained fall in AFP. Furthermore, another patient infected with hepatitis C virus experienced a 1.4 $\log_{10}$ drop in viral titer during dosing with CF102.
Conclusions: Daily oral CF102 is safe and well tolerated at doses up to 25 mg twice daily, and shows linear PK in patients with HCC. CF102 has shown preliminary evidence of clinical activity in HCC patients based on clinical observations of stable disease and AFP reduction. The observation of a decrease in hepatitis C viral load is consistent with CF102's known preclinical anti-viral activity. A_3AR agonist treatment appears to hold promise as a novel therapeutic strategy in the treatment of advanced HCC and related liver diseases, and enrollment in the dose-confirmation phase of this trial continues.

385 POSTER

A first in human phase 1 study of the safety and pharmacokinetics of a novel Cdc7 inhibitor NMS-1116354, administered orally to patients with solid tumors

K. Papadopoulos[1], S. Crippa[2], A. Hanssen[1], A. Montagnoli[3], F. Fiorentini[4], A.W. Tolcher[1], M. Martignoni[2], A. Isacchi[5], B. Laffranchi[2], A. Patnaik[1]. *[1]South Texas Accelerated Research Therapeutics (START), Clinical Research, San Antonio TX, USA; [2]Milano International Oncology/NMS Group, Clinical Development, Nerviano, Italy; [3]Nerviano Medical Sciences (NMS), Cell Biology, Nerviano, Italy; [4]Accelera, DMPK & ART, Nerviano, Italy; [5]Nerviano Medical Sciences (NMS), Biotechnology, Nerviano, Italy*

Background: NMS-1116354 is a potent oral inhibitor of the serine-threonine kinase Cdc7. Cdc7 promotes DNA replication and is often upregulated in cancer. In vitro, NMS-1116354 inhibits initiation of DNA replication resulting in cell cycle arrest and apoptotic tumor cell death and causes tumor growth inhibition or regression in multiple human xenograft tumor models.
Methods: Patients with advanced solid malignancies are enrolled in successive cohorts using a 3+3 design to receive NMS-1116354 orally once daily for 7 days followed by a 7 day rest period (2-week cycle). Dose-limiting toxicities (DLTs) are determined during the first cycle and are defined as grade 4 (g4) neutropenia for >7 days, febrile neutropenia, neutropenic infection, g4 thrombocytopenia (PLT), g3 PLT for >7 days or with bleeding, any g3/4 non-hematologic toxicities representing a shift of 2 grades from baseline, failure to administer 70% of NMS-1116354 in cycle 1, >2 week-delay in starting cycle 2. Pharmacokinetics on days 1 and 7 in cycle 1, pharmacodynamic modulation of Mcm2 phosphorylation and gene expression in skin biopsies and Mcl-1 level in leukocytes in cycle 1 are evaluated. Tumor response by RECIST is assessed every 8 weeks.
Results: To date, 13 patients with metastatic cancer (4 males; median age: 62 [39−73]; median ECOG PS: 1 [0−1]) were treated in 4 dose levels (3, 6, 12 and 24 mg/m^2/day) and received a total of 50+ cycles (median 3, range 1−8). Primary tumor types were: colon (3), lung (2), breast (2), prostate, sarcoma, pancreas, carcinoid, thyroid and ovarian (1, each). All toxicities reported so far were of grade 1−2 in severity or representing a shift of 1 grade from baseline, allowing for continuing dose escalation as per the accelerated dose titration design. Potential drug-related AEs were fatigue (3 pts), anorexia, constipation, dry mouth and nausea (1 pt each). No cycle 1 DLTs observed. Current PK data suggest Cmax and AUC increase with the dose. Preliminary signs of pharmacodynamic modulation, such as Mcl-1 down-regulation in leukocytes, were observed in surrogate tissues. Two patients with colon cancer remained stable for 8 cycles (16 weeks).
Conclusions: In this Phase 1 study, NMS-1116354 is well tolerated. The MTD has not yet been established and dose escalation is ongoing, with 48 mg/m^2/day being tested.

386 POSTER

Phase I study of the vascular disrupting agent (VDA) ombrabulin (Ob) in combination with taxanes (T) and platinum salts (PS) in patients (pts) with advanced solid tumors

J.C. Soria[1], R. Bahleda[1], B. Besse[1], C. Sessa[2], R.g. Calderone[2], L. Gianni[3], G. Del Conte[3], A. Perotti[3], B. Daglish[4], C. Oprea[4]. *[1]Institut Gustave Roussy, Medecine, Villejuif, France; [2]Iinstituto Oncologico Svizzera Italiana, Medecine, Belinzona, Italy; [3]Iirccs Instituto Nazionale Dei Tumori, Medecine, Milano, Italy; [4]Sanofi Aventis, Medecine, Villejuif, France*

Background: Ob is a tubulin binding VDA, derivative of Combretastatin A4. In preclinical studies synergy between Ob and T or PS has been observed.
Methods: Study objectives were to determine the recommended dose (RD), Dose-Limiting Toxicities (DLTs), safety and pharmacokinetics (PK), preliminary anti-tumor activity, potential predictive biomarkers of the combination of Ob with T (docetaxel D or paclitaxel P) and PS (cisplatin C or carboplatin Cb respectively) once every 3 weeks in pts who received a maximum of one previous line of chemotherapy (CT) for advanced disease.
Results: Forty-three pts (M/F 14/29), median age 51 (range 24−74), including 25 chemonaive pts (58%) were treated in 4 cohorts: I (Ob/C75 mg/m^2 day (d)1, D60 or 75 mg/m^2 d2 − 13 pts), II (Ob d1, C75/D75 d2 − 12 pts), III (Ob d1, CbAUC5/P175 d2 − 11 pts) and IV (Ob d1, CbAUC6/P200 d2 − 7 pts). Granulocyte growth factors were systematically administered as primary prophylaxis in cohort I and II. Dose levels (DLs) tested for Ob were: 15.5, 20, 25, 30, 35 mg/m^2.