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.

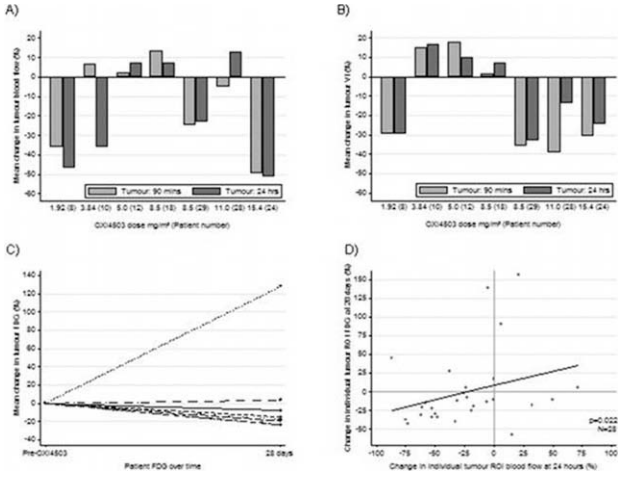

Figure 1.

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

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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.

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

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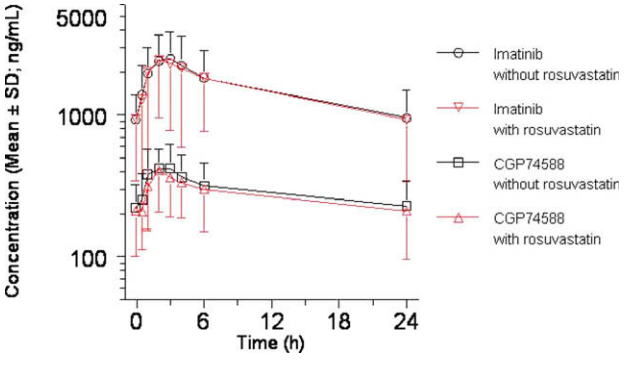
Background: The oral bioavailability of imatinib (Gleevec®) is about 90−95%. We previously reported that imatinib is a substrate of the intestinal uptake transporter, OATP1A2 (*SLCO1A2*) (Hu et al, *Clin Cancer Res* 2008). We hypothesized that the absorption of imatinib may be reduced by medication that 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.



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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

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