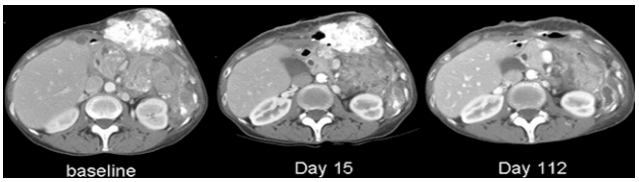

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The Pan-HER inhibitor BMS-599626: biological effects, pharmacokinetic profile, and early clinical evaluation of a phase I trial

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Background: BMS-599626 is an orally bioavailable inhibitor of HER1 (EGFR), HER2 (ErbB2) and to a lesser extent HER4.
Methods: This is a phase I dose escalation study of BMS-599626 administered by daily oral dosing. Patients: ⩾18 yrs with metastatic solid tumors, refractory to standard therapies and whose tumors expressed HER1 or HER2 by IHC (FISH for breast). A large translational ancillary study included skin biopsies, optional tumor sampling (both baseline and Day 8) and analysis of biomarkers of HER1 and HER2. Dosing was initiated at 100 mg/d and escalated in subsequent cohorts based on a modified Fibonacci scheme.
Clinical results: Between May 2004 and April 2005, 19 patients have been treated (8M/11F), median age 50 (range 35–79). 18 patients harboured HER1-positive and 9 patients HER2-positive tumors. A total of 48 cycles have been given, and 6/19 patients are still on study. BMS-599626 doses in mg/d (no. pts/cohort) were: 100 (3), 200 (3), 320 (3), 480 (3), and 660 (6). Adverse events at least possibly related to BMS-599626 included anemia (1), aptyalism (1), diarrhea (6), abdominal pain upper (1), nausea (1), vomiting (1), anorexia (3), hirsutism (1), constipation (2), asthenia (3), mucositis (1), rhinitis (1), muscle cramp (1), dyspnea (1), hyperhydrosis (1), dermatitis acneiform (3), dry skin (2), pruritus (1) and rash (4). During dosing escalation, mild to moderate toxicity was observed up to 480 mg/d. Dose-limiting toxicities (DLT) were observed in 3 of 6 patients at 660 mg/d. One patient experienced grade (G) 3 QTc interval prolongation, the 2 other patients reported hepatic toxicities with G3 or G4 ALAT increased (2), G3 ASAT increased (2) and G3 alkaline phosphatase increased (1). Because the maximum tolerated dose (MTD) was exceeded, a new dose cohort of 600 mg/d is currently enrolling.
Biological and pharmacokinetic results: Preliminary immunohistochemistry data on skin (34 samples) and fresh tumor biopsies (2 samples) suggest that Ki67, a marker of cell proliferation, is a viable pharmacodynamic marker of the study. During treatment with BMS-599626, Ki-67 decreased in 15 of 17 paired skin samples. Evaluation of pAKT, pERK, pSTAT3, and p27 is currently being performed and will be correlated with Ki-67. Plasma pharmacokinetics (PK) data for doses up to 480 mg indicate that BMS-599626 was rapidly absorbed, with a mean T max between 3 and 4 hours (range 0.5–24) and T half of approximately 20 hours. PK on day 8 and day 29 revealed similar findings, suggesting no significant accumulation in exposure over time.
Conclusions: To date, 19 patients have been treated with BMS-599626 in the study and the MTD has been exceeded at 660 mg. Proof of concept of the biological effect of the pan-HER inhibitor has been achieved through modulation of Ki-67 in paired skin-biopsies and through induction of skin rash. Additional clinical, pharmacological and translational data will be presented.

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The multitargeted kinase inhibitor sunitinib malate (SU11248): soluble protein biomarkers of pharmacodynamic activity in patients with metastatic renal cell cancer

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Background: Metastatic renal cell carcinoma (RCC) is a disease both highly resistant to systemic therapy and with a vascular phenotype. In a phase II study of patients with RCC, significant clinical responses have been observed with sunitinib malate (a multitargeted tyrosine kinase inhibitor which specifically blocks VEGFR, PDGFR, KIT, RET and FLT3, and has antiangiogenic and antitumour activity). To characterise potential biomarkers of sunitinib pharmacological activity, plasma levels of 4 soluble proteins identified as candidate biomarkers (VEGF, soluble VEGFR-2 [sVEGFR-2], placenta growth factor [PlGF], and soluble KIT [sKIT]) were analysed serially.
Materials and methods: The RCC patients (n = 63) received sunitinib 50 mg/day for 28 days followed by a 14-day period without treatment in each cycle. Plasma samples for biomarker analysis were obtained pre-dose on Days 1 and 28. The biomarkers were measured via validated ELISAs.
Results: At the end of the first cycle, levels of VEGF and PlGF increased >3-fold (relative to baseline) in 24/54 and 22/55 cases, respectively, and levels of sVEGFR-2 decreased ⩾30% in 50/55 cases and ⩾20% in all cases (mean changes were all $P < 0.001$). For each of these markers, levels tended to return to near baseline at the end of the 14-day period without treatment, and some dependence of changes in levels on drug exposure (as measured by trough plasma levels) was suggested. Mean levels of sKIT also decreased over the course of the study ($P < 0.001$); a cyclical pattern was not observed for this marker, and no strong correlation with drug exposure was apparent. When mean marker level changes were correlated with tumour response, larger proportional changes in VEGF and sVEGFR-2 levels were observed in patients exhibiting objective responses compared with those exhibiting stable disease or rapid progression.
Conclusions: Results indicate that a panel of circulating proteins has utility as biomarkers of pharmacological (VEGF, sVEGFR-2 and PlGF) and clinical activity (VEGF and sVEGFR-2) of sunitinib in RCC.

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SB-497115, a novel, oral platelet growth factor, increases platelet counts in healthy subjects

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Introduction: The major risk of chemotherapy-induced thrombocytopenia (CIT) is hemorrhage secondary to decreased platelet counts. Furthermore, the presence of significant thrombocytopenia can limit the benefits of chemotherapy by preventing appropriate administration of drugs at optimal doses and schedules. SB-497115 is novel, since it represents the first in a class of orally bioavailable, small molecule thrombopoietin receptor agonists that induce differentiation and proliferation of megakaryocytes and have been shown to increase platelet counts in preclinical and clinical studies.
Methods: In a randomized, single blind, placebo-controlled, parallel group, phase I study in 72 healthy male subjects, SB-497115 was administered as oral capsules once daily for 1 day and, after a 1 week washout, for 10 days at doses of 5 to 75 mg.
Results: SB-497115 was shown to be orally bioavailable in humans with a pharmacokinetic profile suitable for a once daily oral medication. When administered at oral doses of 30 mg to 75 mg for 10 days a dose dependent increase in the platelet count was observed, the maximum platelet count was observed on days 14 to 16 following initiation of dosing. At the 75 mg dose, SB-497115 increased the mean platelet count by 117,000/μL, with a maximum increase of 163,000/μL in one subject. SB-497115 was well tolerated in the study, the most common adverse event (AE) was headache. There were no serious AEs, no significant changes in laboratory or cardiovascular safety parameters and there was no observed relationship between the incidence or severity of adverse events and dose. Most AEs were mild in intensity and self-limiting. Platelet function was not affected by SB-497115, when administered at up to 75 mg for 10 days, as measured by platelet activation and aggregation.
Conclusion: On the basis of this safety, pharmacokinetic and pharmacodynamic data the oral platelet growth factor, SB-497115, is being tested in studies involving cancer patients receiving thrombocytopenic chemotherapies.