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CNTO 95, A fully human monoclonal antibody to integrins alpha v β3 and alpha v β5 has direct anti-tumor and antiangiogenic activity

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Integrins alpha v β3 and alpha v β5 are implicated in tumor-induced angiogenesis, but their role in tumor growth has not been fully explored. These receptors are upregulated on angiogenic endothelial cells, and previous studies have demonstrated that inhibition of endothelial alpha v β;3 and alpha v β5 integrins can inhibit angiogenesis. These receptors may also directly contribute to tumor cell growth and invasion. We have developed a fully human antibody, CNTO 95, to integrins alpha v β3 and alpha v β5. Since CNTO 95 is a fully human antibody, it should be considerably less immunogenic in humans compared with chimeric or humanized antibodies. CNTO 95 bound to purified alpha v β3 and alpha v β5 with a K_D of ~200 pM. It did not bind to other integrin receptors such as alpha 5 β1 and alpha IIb β3. *In vitro* angiogenesis and anti-tumor assays demonstrated that CNTO 95 was a potent inhibitor of alpha v β3- and alpha v β5-mediated cell adhesion, invasion, and proliferation. In contrast, monospecific antibodies that blocked only alpha v β3 or alpha v β 5 were not as effective as CNTO 95. CNTO 95 inhibited human melanoma cell adhesion, migration and invasion at doses ranging from 7-20 nM. In a rat aortic ring sprouting assay CNTO 95 (~70 nM) completely inhibited sprouting. In order to determine if CNTO 95 had direct anti-tumor activity *in vivo*, we developed a human melanoma xenograft model in nude mice. In this model, CNTO 95 bound and inhibited alpha v β3 and alpha v β5 on the human tumors but did not inhibit mouse angiogenic integrins. CNTO 95 (10 mg/kg, 3x/week) inhibited growth of human melanoma tumors in nude mice by ~ 80% (P=0.0005). These data demonstrate that direct blockade of human tumor cells expressing alpha v β3 and alpha v β5 integrins by CNTO 95 can inhibit tumor growth independent of its antiangiogenic activity. These findings suggest that alpha v β3 or alpha v β5 in addition to participating in angiogenesis can also directly contribute to tumor growth. In conclusion, CNTO 95, a fully human monoclonal antibody to alpha v β3 and alpha v β5, has potent anti-tumor and antiangiogenic properties. CNTO 95 simultaneously inhibits angiogenesis and tumor growth and may offer substantial clinical advantage over agents that only have either antiangiogenic or anti-tumor properties.

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A phase I study of S-3304 a matrix metalloproteinase inhibitor in patients with solid tumors

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Background: S-3304 is a potent, orally active, non-cytotoxic inhibitor of matrix metalloproteinases (MMP) primarily MMP-2, -9 and -12. It prolonged survival in mice bearing B16-BL6 melanoma and the MA44 human lung carcinoma. It was well tolerated in healthy volunteers receiving 2400 mg b.i.d.
Objectives: To determine the maximum tolerated dose (MTD) dose limiting and other toxicities, the pharmacokinetic (PK) profile and the activity of S-3304 in inhibiting MMP in tumor from patients receiving the drug. Study Design: Patients (pts) with advanced solid tumors who have failed standard therapy or for whom no standard therapy exists are entered on study. All pts have a biopsy of accessible tumor. Following 28 days of twice daily oral administration of S-3304 (1 course), a second biopsy is performed. Tumor biopsies are evaluated by film in-situ zymography which has been shown to be useful in the evaluation of MMP inhibition *in vivo* in pre-clinical studies (Ikeda, M., et al. Clin Cancer Res 2000, 6:3290-6). Samples for PK are drawn on days 1 & 28. Treatment is continued until progressive disease or unacceptable toxicity.
Results and Discussion: A total of 19 patients completed at least 1 course, 6 at 800 mg b.i.d.; 6 at 1200 mg b.i.d. and 7 at 2400 mg b.i.d. Toxicities have been mild with grade I nausea and vomiting and grade I fatigue being the most common. A grade I rise in CPK has been noted in 2 pts. No clearly drug-related toxicity > grade II has been seen. Possibly drug related toxicities >grade II (each in 1 pt) include, grade III: - nausea, vomiting; grade II: - nausea, anorexia, myalgia, light headedness, proctitis and peripheral neuropathy. Steady-state conditions for the 12 patients on 800 mg b.i.d and 1600 mg b.i.d were reached by day 8 of the study with individual $C_{max,ss}$ ranging from 38 to 84 μg mL-1 and individual AUC_{ss} ranging from 177 to 592 μg mL^{-1}. h. Data for 2400 mg b.i.d. are pending. Film in-situ zymography of tumor biopsies demonstrated moderate-strong inhibition of MMP at both the 800 and 1600 mg b.i.d. dose levels at 28 days. Data for 2400 mg b.i.d. are pending. The study is continuing with recruitment at the final dose level of 3200 mg b.i.d.
Conclusion: S-3304 is a very well tolerated, oral MMP inhibitor which shows activity in tumor tissue from pts at doses which give minimal toxicity. Film in-situ zymography is an effective technique for monitoring MMP inhibition in patients with biopsiable tumor.

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A phase I study of the oral vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor PTK787/ZK 222584 on a twice daily schedule in patients with advanced cancer

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PTK787/ZK 222584 (PTK/ZK) is an oral inhibitor of VEGF-mediated KDR/flk-1 and flt-1 receptor tyrosine kinases. Patients (pts) with histologically confirmed and measurable advanced malignancy were recruited onto this phase I dose-escalating study. PTK/ZK was dosed on a twice daily schedule to exploit the theoretical advantage of maintaining constant drug levels above a threshold known to interfere with VEGF receptor signalling. Cohorts of pts (3 evaluable at each dose) were treated with total daily doses of 300 mg, 500 mg, 1000 mg, 1500 mg and 2000 mg. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) was performed prior to PTK/ZK administration, on day 2 and after every 28 day cycle. The transfer constant Ki was calculated and tumour volumes measured for assessment by SWOG criteria. Full pharmacokinetic (PK) profiles were obtained on day 1 and day 28. 23 pts have been entered on to the study and 5 are ongoing. Tumour types treated include breast (1 pt), colorectal (15 pts), sarcoma (2 pts), gastric (2 pts), renal (2 pts) and carcinoid (1 pt). All were heavily pretreated. To date the range of cycles completed is 1-13 (median 3 cycles). 6 pts did not complete 1 cycle and were replaced, and 1 pt is too early for evaluation. DCE-MRI demonstrates reduction in Ki at all doses in a dose-dependent manner. In the 13 pts with evaluable disease, 4 had minor responses and 6 had stable disease (5/10 lasting * 6 months). Treatment has been well-tolerated. Transient grade 3 elevation in transaminases has been seen in 4 pts, and grade 3 hypertension in 2 pts, both with pre-existing hypertension. In addition transient grade 2 and 3 light-headedness and ataxia has been documented in 6 pts at total daily doses *1000 mg. Grade 3 nausea and vomiting has been seen in 4 pts, and grade 3 lethargy in 7 pts. PTK/ZK appears to reduce tumour perfusion/vascular permeability; moreover impressive stabilisation of disease and minor response * 6 months has been seen in 26% pts. Full PK and further MRI data will be presented demonstrating how these pharmacodynamic endpoints are guiding dose optimisation in future studies.

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Prognostic and predictive value of vascular endothelial growth factor (VEGF) in patients with non small cell lung cancer (NSCLC)

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VEGF is a regulator of angiogenesis and its production is stimulated by hypoxia. The circulating levels of VEGF could reflect the overall angiogenetic activity. The aim of our study was to investigate the prognostic value of VEGF on survival and response to chemotherapy in patients (pts) with NSCLC. 109 consecutive untreated NSCLC pts were enrolled in this prospective follow-up study from 4/1997 to 11/2001. Exclusion criteria were intra-vascular coagulation, recent transfusions (< 6 months), renal insufficiency, erythropoietin or anti-coagulant treatment. VEGF was measured in serum at baseline and at 2 hours after blood draw using a quantitative immunoassay kit for human VEGF 165 (Quantikine, R&D Systems, Minneapo-