mg/day group, in IDEAL 1 and 2, respectively. In pts who were symptomatic at entry, a symptom improvement (SI) (*/=2 point increase, */=4 weeks) was observed in 40% and 37% of pts receiving 250 and 500 mg/day, respectively, in IDEAL 1, and in 43% and 34% of all pts, respectively, in IDEAL 2. A positive association was observed between SI and both radiologic response and survival in both trials. Overall, quality of life (QoL) was improved in 24% and 22% of pts receiving 250 and 500 mg/day, respectively, in IDEAL 1, and in 34% and 23% of pts, respectively, in IDEAL 2. Most drug-related adverse events (AEs) were mild grade 1/2 diarrhea and skin disorders. Drug-related AEs were more frequent in the higher dose group. Withdrawal due to drug-related AEs was 2% and 9% for pts receiving ZD1839 250 and 500 mg/day, respectively, in IDEAL 1, and 1% and 5%, respectively, in IDEAL 2. In conclusion, in pretreated pts with advanced NSCLC, oral ZD1839 250 mg/day resulted in clinically significant antitumor activity, had an acceptable tolerability profile and provided improvement in disease-related symptoms and QoL. 'Iressa' is a trademark of the AstraZeneca group of companies

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ABX-EGF, a fully human anti-epidermal growth factor receptor (EGFr) monoclonal antibody: phase II clinical trial in renal cell cancer (RCC)

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EGRr is a transmembrane glycoprotein that promotes cell growth in a variety ofnormal and transformed tissues. ABX-EGF is a high-affinity, fully human IgG2monoclonal antibody to EGFr generated in Xenomouse mice. Part 1 of a two-partphase 2 trial consisting of 8 weekly infusions of ABX-EGF was performed inpatients (pts) with RCC who failed or were unable to receive IL-2/IFN-alfa.Stable or responding pts were eligible for extended weekly treatment at theassigned dose for 8 additional months or until disease progression. In Part 1,88 pts received at least one dose of ABX-EGF at the following dose levels: 1.0mg/kg (22 pts), 1.5 mg/kg (22 pts), 2.0 mg/kg (23 pts), and 2.5 mg/kg (21 pts).Overexpression of EGFr was documented in 95% of pts enrolled. Eleven percent of the pts had received no prior biotherapy or chemotherapy, whereas 56% and 33%were more heavily-pretreated, having received 1?2 and at least 3 prior regimens,respectively. All pts have completed one 8-week cycle of ABX-EGF and areevaluable for response. Three pts (1 each at 1, 1.5 & 2.5 mg/kg) had partialresponses. Two patients (1 each at 1.0 & 2.5 mg/kg) had minor responses. Fiftypercent of pts had stable disease as their best response. A transient acneiformskin rash, which is a potential pharmacodynamic surrogate of EGFr blockade, wasobserved in 70%, 91%, 95% and 100% of pts treated with at least 3 doses ofABX-EGF at 1.0, 1.5, 2.0 and 2.5 mg/kg, respectively. Other >/= grade 2 adverseevents in over 2% of pts included asthenia, pain, abdominal pain, back pain,constipation, cough and dyspnea. An analysis of peak and trough serum ABX-EGFconcentrations indicates low intrapatient variability and consistent drugexposure in individual pts throughout the 8-week treatment period in all dosinggroups which is consistent with the lack of human anti-human antibody (HAHA)formation in pts tested to date. The inter-patient variability in ABX-EGFexposure was extremely low and trough concentrations at ABX-EGF doses of atleast 2 mg/kg consistently exceeded IC90 values determined for human tumorsxenograft models. The relationship between the incidence of skin rash and dosewas well described by a sigmoidal model, which predicted a 90% incidence of skinrash at an ABX-EGF dose of 1.5 mg/kg (ED90) in agreement with the results ofphase 1 studies. In conclusion, ABX-EGF is well tolerated and preliminaryevidence of antitumor activity was observed in heavily-pretreated RCC pts.

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Phase II study of OSI-774 in patients with metastatic colorectal cancer

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Epidermal Growth Factor Receptor overexpression is seen in upto 75% of colorectal cancers, and has been implicated in the development and propagation of the malignancy. OSI-774 is a potent epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) which is being evaluated in a phase II study to assess the activity in patients with metastatic colorectal cancer. Primary endpoints are response or disease stabilization, with a multinomial stopping rule and secondary endpoints are the assessment of molecular changes with therapy. The study is currently ongoing. Sixteen evaluable patients with metastatic colorectal cancer have been treated with OSI-774 at a dose of 150 mg PO daily continuously on a four weekly cycle. Paired biopsies of the tumors and skin have been obtained in 15 patients. Radiologic evaluation was done every 8 weeks and skin and tumor biopsies were performed prior to treatment and on day 8. Eleven (69%) were male and the median age was 59 years with a range from 43-76 years. Eight (50%) of patients had an ECOG status of 1 and 8 (50%) had an ECOG status of 0. Apart from adjuvant chemotherapy, patients had only received chemotherapy for metastatic disease with one line irinotecan/5FU in combination or sequentially. The most common sites of disease were liver in 13 (81%), lymph nodes in 10 (63%) and lung in 7 (44%). Thirteen patients were evaluable for efficacy and toxicity. There are 3 (23%) patients with stable disease (2 confirmed and one pending confirmation) who remain on study (5, 4 and 3 cycles to date). Ten patients have progressed. The two most common toxicities observed were diarrhea [grade 1: 4pts (31%), grade 2: 1pt (8%) grade 3: 1pt (8%)] and rash [grade 1: 4pts (31%), grade 2: 5pts (38%) grade 3: 1pt (8%)]. There were no grade 4 toxicities related to this drug. There were 4 grade 3 toxicities assessed to be possibly or probably related to this drug including diarrhea, rash, elevation in INR and elevation in ALP. Treating patients with flamazine cream and minocycline antibiotic improved rash from OSI-774 in 70% of patients with a grade 2 or greater rash. Conclusion: Patients are being evaluated and correlative studies are ongoing.

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The use of predicting factors and surrogate markers in breast cancer biopsies treated with targeted erbB tyrosine kinase inhibitor

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Over-expression of erbB receptors is associated with aggressive breast cancers. Therapeutic strategies targeting these oncoproteins are in clinical trials. One approach is the use of a monoclonal antibody to erbB2, Herceptin. Studies performed *in vitro* have attributed the therapeutic potential of Herceptin to enhance intracellular degradation resulting in a functional inhibition of erbB2. Another effective approach is the use of tyrosine kinase inhibitors (TKIs) that block the nucleotide-binding site of the erbB kinases, specifically erbB1 and erbB2. An alternative way to enhance degradation and inhibit activity of erbB proteins involves targeting the heat shock protein 90 (Hsp90) using benzoquinone ansamycins such as geldanamycin (GA). Hsp90 forms complexes with erbB2 proteins and stabilizes them. GA blocks ATP binding to Hsp90 resulting in poly-ubiquitination and destruction of the erbB2. However, GA's broad effect is of concern. In contrast, the TKI group of drugs is highly selective to erbB receptors blocking only the nucleotide-binding site of tyrosine kinase proteins. Consequent to blocking kinase activity, most downstream signaling pathways are inhibited leading to growth arrest. In this work, we used cancer tissue biopsies from patients before and after TKI treatment to understand the mechanism and the factors associated with response or non-response to TKI treatment. Breast cancer biopsies from patients, before and after TKI treatment, were immunostained for erbB1 and erbB2. Their phosphorylated forms and phosphorylated ERK (pERK) (a downstream signal) were used as a surrogate marker of response (antibodies were purchased from Cell Signaling and Ventana). Levels of staining were quantitated by microscope based image analysis. Patients with high levels of EGFR, HER-2 and pERK responded to TKI. Their response was confirmed by using surrogate biomarkers as