was 63 days (33–336). The main side-effects of gefitinib were grade 1–2 skin rash, diarrhea and transaminitis. Data analyses on QoL are ongoing. Four patients underwent prostate biopsy. EGFR was overexpressed in 2 patients, cerbB2 was absent in all tissue samples. Serum HER2 ECD was assessed in 12 patients. Mean basal value was 10.1 ng/ml (6.5–14.4). After 2 months mean value was 11.7 (9.0–15.7). Serum EGFR was assessed in 14 patients. Mean basal value was 55.5 ng/ml (41.4–64.8). Mean value at 2 months was 52.8 ng/ml (47.5–58.3). Gefitinib has been associated with infrequent PSA responses and no objective response in patients with metastatic HRPC. Further evaluation of data from this study will clarify the effect on QoL and the correlation between serum EGFR and HER2 and clinical outcome.

386 POSTER

Effect of angio-sonography to monitor response during imatinib treatment in patients with metastatic gastrointestinal stromal tumor (GIST): a preliminary report

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GIST metastases are typically intra-abdominal and hypervascular. BR1 is a new blood pool ultrasound second-generation contrast agent, which consists of stabilized microbubbles, which allows angio-sonography through continuous real time examination during different vascular phases of contrast enhancement using low transmission power. We assessed angiosonography to monitor response during imatinib treatment (400 mg orally once daily) in patients with metastatic cKIT+ GIST. Ten consecutive patients with known advanced cKIT+ GIST were investigated with angio-sonography and CT. We also monitored the serum levels of vascular endothelial growth factor (VEGF). Angio-sonography showed an early reduction in tumor vascularization in all 10 cases. The tumor perfusion appeared reduced in the central part of the GIST metastases. With a median follow-up of 15 months (range 3–21), a reduction in tumor vascularization was continuously observed in all 10 patients, but in 2 progressive disease (PD) was documented after 12 and 21 months of imatinib treatment. CT documented tumor response according to standardized criteria in 6 patients (median time to response 4 months, range 1–9), stable disease (SD) in 2 lasting 18+ and 21+ months, and PD in 2 according to angio-sonography. Serum VEGF levels behaved in an heterogeneous manner, but an early reduction in serum VEGF levels was observed as early as 1 week in the 2 cases with higher pretreatment serum VEGF levels. In a single case receiving a strict angio-sonographic evaluation with angio-sonography at 1, 2, 4, 6, 8 weeks, a reduction in tumor vascularization was observed as early as 2 weeks but standardized tumor response based on CT was reported only after 9 months. A reduction in tumor vascularization observed before a reduction in tumor size coupled with the observation that the perfusion is mainly reduced in the central part of the treated tumors is in line with recently performed studies of monitoring antiangiogenic therapy with vascular functional imaging. Imatinib-mediated antiangiogenic properties have been demonstrated in experimental models and in vivo in CML and neuroblastoma. Imatinib could induce antiangiogenic effects in GIST. This effect could be easily monitored with angio-sonography. Large studies are warranted.

387 POSTER

A phase I study of AEE788, a novel multi-targeted inhibitor of ErbB and VEGF receptor family tyrosine kinases

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Background: Combined blockade of multiple signal transduction pathways may result in improved antitumor effects. AEE788 is an orally active, reversible, small molecule multi-targeted kinase inhibitor with potent inhibitory activity against ErbB and VEGF receptor family of tyrosine kinases. In preclinical *in vitro* and *in vivo* studies, inhibition of both the ErbB and VEGF receptor pathways has been shown. AEE788 has an IC_{50} of less than 100 nM against EGFR, ErbB2, VEGFR2. This phase I study was to assess the safety, pharmacokinetics (PK), MTD/DLT dose levels, and optimal biological dose of AEE788.
Methods: Patients (pts) with advanced solid tumors were enrolled. Dose escalation approximated a modified Fibonacci series with 3–6 pts/cohort. Safety monitoring included additional cardiac assessment. No prior EGFR/ErbB2 or VEGF/VEGFR directed therapies were permitted. Pharmacodynamic markers were analyzed in pre- and post-treatment skin and tumor biopsies. A 24 hr PK profile was obtained on days 1, 15 and 28, with trough sampling on days 8 and 22.
Results: To date, 27 advanced cancer pts (15 male, 12 female), median age 55 (range 25–78), have been treated with AEE788 at doses of 25 (5), 50 (6), 100 (5), 150 (5) or 225 mg (6) per day. AEE788 was given on a continuous daily schedule. Tumor types treated were breast (5), colon (5), bladder (2), melanoma (2), liver (2), soft tissue sarcoma (2), and 9 other tumor types (1 each). No dose limiting toxicities have been reported. The most common adverse events (>10%) included diarrhea (41%), nausea (33%), fatigue (30%), skin rash (18%) anorexia (15%), cough (15%), vomiting (15%), anemia (11%), asthenia (11%), cancer pain (11%), constipation (11%), pruritus (11%) and pyrexia (11%). 6 pts had diarrhea suspected to be related to AEE788; (50 mg-1 pt grade (gr) 1; 150 mg-1 pt gr 1, 1 pt gr 2; and 225 mg-3 pts gr 1). 5 pts had drug-related skin rash (100 mg-1pt gr 1, 150 mg-1pt gr 1, 225 mg-2 pts gr 1, 1 pt gr 2). There were no study drug-related grade 3 or 4 adverse events or lab abnormalities. There was no QTc > 500 ms in over 1000 ECGs. Exposure to AEE788 increased overproportionately with dose, with estimated half-life of 24–30 hrs. The ratio of an active metabolite (AQM674) to parent (AEE788) was on average ~ 0.7 (range 0.2 to 2). Exposure to AEE788 and AQM674 was similar after 15 and 28 days of dosing (with the exception of the 25 mg dose), suggesting that PK equilibrium was reached on or before day 15. The best response was stable disease (SD). To date, 7 patients have received AEE788 for > 2 cycles. The median number of cycles of AEE788 was 1.6 (range 0.5–8.8).
Conclusion: AEE788 was well tolerated at daily doses up to 225 mg/day. The study is continuing, the MTD/DLT dose level has not yet been reached.

388 POSTER

The abrogation of rapamycin-induced AKT activity by the small molecule IGF-IR inhibitor, AEW541, and the enhanced antitumor activity of combined mTOR and IGF-IR inhibition

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mTOR (the mammalian target of rapamycin) is a serine/threonine kinase that senses nutrient availability and acts as a central regulator of cell growth. mTOR activates p70 S6 kinase (RSK) which increases translation of mRNA with 5′ polypyrimidine tracts and inhibits the translational repressor 4E-BP1. Small molecule inhibitors of mTOR (rapamycin, CCI-779, RAD001) have antitumor activity in pre-clinical cancer models and modest single agent activity in cancer patients. We hypothesized that resistance to mTOR inhibitors may be the result of adaptive induction of parallel survival pathways following mTOR inhibition. We observed that exposure of MDA-468 (breast) and DU-145 (prostate) cells to rapamycin (1nM) resulted in the induction of IRS-1, a key adapter protein in the IGF-1 signal transduction pathway. IRS-1 (insulin receptor substrates-1) mediates insulin and IGF-1 signaling by linking the IGF-1 and insulin receptor tyrosine kinases to multiple downstream signaling proteins, including p85, the regulatory subunit of PI3K, via interaction with the p85 SH2 domain. We found that rapamycin-stimulated IRS-1 induction was accompanied by increased AKT activity and phosphorylation of its downstream substrate GSK3β. Furthermore, inhibition of IGF-1R with AEW541, an inhibitor of IGF-1 receptor tyrosine kinase, abrogated the upregulation of p-Akt seen following mTOR inhibition. This combination of rapamycin and AEW541 also synergistically inhibited cell growth. The data suggest that IGF-1R inhibition sensitizes cancer cells to mTOR inhibition by counteracting the rapamycin-induced positive feedback upregulation of IGF-1 signalling molecules. This evidence provides a rationale for testing combined inhibition of IGF-1R and mTOR in cancer patients.

389 POSTER

CF101, an agonist to the A3 adenosine receptor enhances the chemotherapeutic effect of 5-fluorouracil in a colon carcinoma murine model

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Background: The molecular mechanism underlying chemo-resistance of tumor cells to cytotoxic drugs entails high levels of NF-kB and the upstream kinase PKB/Akt, acting as inhibitors of apoptosis. A3 adenosine receptor (A3AR) activation with the specific agonist CF101 has been shown to inhibit the development of colon carcinoma growth in vitro and in vivo. In addition CF101 protected mice against myelotoxic effects of chemotherapy via its capability to induce G-CSF production. In this study we examined the