and effect of antimetabolite treatment was assessed by urogenital and prostate weights, tumor grade and proliferation, and apoptotic markers. To study possible roles for FAS in prostate cancer, we examined the genetic alterations, which are associated with FAS protein expression and activity knockdown. We conducted a gene microarray analysis of prostate cancer cells with FAS knockdown by FAS gene specific siRNA in comparison to control treated cells.
Results: The anti-tumor efficacy of FAS inhibitors c75 and Orlistat was dose dependent and demonstrated a strong correlation to inhibition of akt phosphorylation and FAS pathway activity, reduced prostate and urogenital weights and decreased tumor grade compared to vehicle treated mice. Additional anti-tumor mechanistic studies demonstrated inhibition of tumor cell proliferation and induction of apoptosis. Our gene array data revealed that numerous genes are altered in expression including many proliferation and apoptotic genes with FAS knockdown that play significant roles in many pathways including cell growth, development, and cell signaling. These data suggest the upregulation of FAS expression plays a key role in tumorigenesis and provide insight into dysregulation of this gene in cancer.
Conclusions: These results indicate that the antitumor activity of FAS inhibitors may be mediated by direct effects on tumor cell growth or survival mechanisms.

403 POSTER

Cell death pathways as therapeutic targets for cancer

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Proper execution of cell death plays an essential role in tumor suppression. Apoptosis is a form of regulated cell death. Defects in this process are a hallmark of cancer and contribute to chemotherapy resistance. Our laboratory recently determined that the proapoptotic protein Bim determines tumor responsiveness to taxanes and that Bim inactivation by MAPK-mediated phosphorylation and degradation in proteasomes confers chemotherapy resistance. The same studies also revealed a mechanism by which addition of a proteasome inhibitor reactivates apoptosis and abrogates MAPK pathway-dependent resistance to taxanes enabling tumor regression. These preclinical studies are now being translated to a clinical trial of taxane and bortezomib combinatorial treatment for solid tumors with activated MAPK pathway, and set an example of rationally designed tumor genotype-specific chemotherapy.
An alternative to reactivation of apoptosis is to divert apoptosis-resistant tumor cells to an alternate pathway of cell death such as type II programmed cell death (autophagy). Beclin1 is a key regulator of autophagy and defective autophagy plays a role in mammary oncogenesis since beclin1 haploinsufficiency is common in human breast carcinomas. We have developed a novel mouse mammary epithelial model for studying the mechanisms regulating breast tumorigenesis and are applying this model to determine the role of autophagy in breast cancer progression and treatment responsiveness. Primary mouse mammary epithelial cells (MMECs) were isolated from beclin1 +/− and beclin1 +/+ mice, immortalized (iMMECs) by inactivation of the retinoblastoma and p53 pathways, and their response to metabolic stress, capacity for 3D-morphogenesis, and tumorigenicity were compared. Allelic loss of beclin1 in iMMECs increased susceptibility of iMMECs to metabolic stress, indicating that autophagy is indeed a survival, and not a cell death, mechanism in mammary epithelial cells. Furthermore, beclin1 +/− iMMECs were more tumorigenic than beclin1 +/+ iMMECs after orthotopic injection demonstrating that beclin1 haploinsufficiency promotes mammary tumorigenesis. Thus, autophagy may function as a tumor suppression mechanism by mitigating metabolic stress, thereby preventing the accumulation of damaged tumor cells that can promote tumor progression. These findings also suggest that autophagy inhibitors may be a means to drive apoptosis resistant tumor cells to cell death in response to metabolic stress.

404 POSTER

Pharmacodynamics (pd) of xl880, a novel spectrum selective kinase inhibitor (SSKI), administered orally to patients (pts) with advanced solid tumors (AST)

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Background: XL880 is a sub-nM inhibitor of the hepatocyte growth factor receptor (Met) and vascular endothelial growth factor (VEGF) family receptor tyrosine kinase (RTK), with low in vitro nM inhibition of PDGFRβ, KIT, FLT3, Tie-2 and Ron. It is the 1st orally bioavailable small molecule Met inhibitor to enter the clinic. An ongoing phase I study of XL880 in pts w/ASTs showed that XL880 is well tolerated up to 3.6 mg/kg, with definition of the maximum tolerated dose ongoing. Two dose limiting toxicities have been observed (1 grade 3 lipase and 1 grade 3 transaminase). Manageable hypertension and edema have been seen in pts treated at the highest doses for prolonged times. Two pts w/spontaneous papillary renal cell carcinoma (SPRC) have a PR (1 unconfirmed), 2 pts w/carcinoid and melanoma have had MRs and a pt w/medullary thyroid cancer showed tumor reduction by physical exam and decreased cortisol levels while receiving XL880.
Methods: Blood samples were collected from all pts. Tumor and normal (surrogate) tissues from selected pts were collected at baseline and following administration of XL880. Plasma samples were analyzed for ligands and soluble receptors via ELISA. Selected blood samples and tumor biopsies, including diagnostic (archival) paraffin embedded tumor sections, were analyzed for mutation of Met at known mutation hotspots. Tumor, skin, and hair follicles were processed for extensive IHC analyses.
Results: Staining of Met, phospho-Met (pMet), RON, pRON, pERK, and pAKT was detected in normal tissue, skin, and tumor tissue from a pt with melanoma who experienced a MR. Administration of XL880 decreased tumor staining of pMet, pRON, pERK, and pAKT, but staining for Met and RON was unchanged. Decreased tumor cell proliferation (Ki67 staining) and increased tumor cell apoptosis (TUNEL) were also observed. No hotspot mutations were observed in SPRC pts who exhibited PRs. However, when compared to adjacent normal renal tissue, staining for Met, pMet, RON, pRON and Ki67 was elevated in untreated tumor tissue. Additional pt tumors and tumor vasculature are under analysis.
Conclusions: In pts with solid tumors, administration of XL880 is associated with decreased activation of Met and RON, decreased activity of associated signaling pathways (AKT and ERK), decreased tumor cell proliferation, and increased tumor cell death. These data from clinical human samples are consistent with preclinical data demonstrating that XL880 exhibits potent anti-tumor activity by targeting MET. The responsiveness of SPRC pts to XL880 was not associated to mutational activation of Met. In the absence of clinical evidence of target inhibition with this novel SSKI, the tumor staining confirms activity against Met at doses at or below VEGF receptor and PDGFRβ inhibition.

405 POSTER

A phase I dose-escalation study of the safety and pharmacokinetics of a XL184, a VEGFR and Met kinase inhibitor, administered orally to subjects with advanced malignancies

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Background: XL184 is an orally available small molecule inhibitor of multiple receptor tyrosine kinases involved in tumor cell growth and angiogenesis. The primary targets of XL184 are Met, VEGFR2/KDR, and additional targets include KIT, FLT3, and Tie-2. The purpose of this study is to define the maximum tolerated dose (MTD) and pharmacokinetics (PK) of XL184. In addition, exploratory pharmacodynamic (PD) assays are being evaluated using blood plasma samples.
Methods: Patients (pts) with advanced solid malignancies are enrolled in successive cohorts to receive XL184 orally as a single dose on day 1 with pharmacokinetic (PK) sampling, followed on day 4 by 5 consecutive daily doses with additional PK sampling and observation until day 21. In subsequent cycles, pts receive daily dosing for 5 days every 14 days. Tumor response is assessed every 8 weeks by RECIST criteria. PD blood samples were collected from all pts and plasma samples will be analyzed for ligands and soluble receptors via ELISA.
Results: To date, a total of 12 pts (carcinoid [3], mesothelioma [1], gastric [1], pancreatic cancer [1], breast cancer [1], parotid carcinoma [1], cholangiocarcinoma [1], T-cell lymphoma [1], angiosarcoma [1] and gastro/esophageal carcinoma [1]) have been treated across 3 dose levels: 0.08, 0.16, and 0.32 mg/kg. Currently, the maximum tolerated dose is not yet defined and dose escalation continues. Of 12 treated pts, 3 have had stable disease greater than 3 months (ongoing stability at 7, 6 and 4 months), including one patient with carcinoid carcinoma with liver metastases who has had approximately 20% reduction in tumor size (treated at 0.08 mg/kg). There have been no drug-related AEs or SAEs to date. Preliminary PK analysis (0.08–0.32 mg/kg) indicates that systemic drug exposure (area under the plasma concentration-time curve; AUC) and peak plasma levels (Cmax) tend to increase with increasing XL184 dose. Average Cmax values were 34.2±20.7, 70.0±51.6, and 189.3±49.6 ng/mL following the fifth dose at 0.08, 0.16 and 0.32 mg/kg, respectively. The terminal half-life was approximately 90 hours after 5 days of dosing, with levels as high as