and results on MCT, EGFR and COX-2 expressions were previously described.
Results: Importantly, both MCT1 and MCT4 were found to be more frequently expressed in CD147 positive cases than in CD147 negative cases and we observed that the co-expression of CD147 with MCT1 was significantly associated with lymph-node and/or distant metastases in adenocarcinomas. Interestingly, we found positive correlations between COX-2 and both MCT2 and MCT4 expressions, as well as between EGFR and lack of MCT2 expression. Moreover, EGFR also correlated with CD147 expression.
Conclusions: In sum, our results contribute to the understanding of the metabolic alterations in cervical cancer and also provide evidences for the regulation of MCTs in human cervical samples, which could be of value in the development of new therapeutic strategies.

Phase I

379 POSTER

A phase I study of XL184, a MET, VEGFR2, and RET kinase inhibitor, administered orally to patients (pts) with advanced malignancies, including a subgroup of pts with medullary thyroid cancer (MTC)

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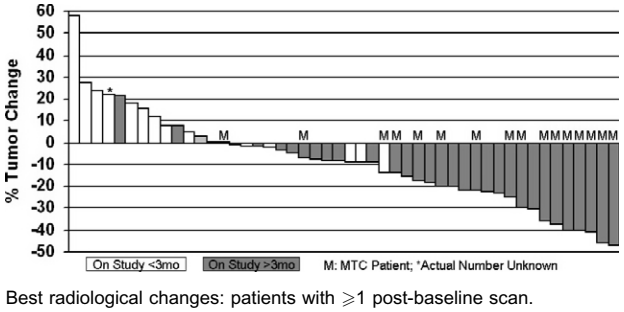
Background: XL184, a multi-kinase inhibitor, strongly inhibits proliferation in MTC cell lines harboring activated RET. Pharmacodynamic studies show substantial inhibition of RET & MET phosphorylation in the TT xenograft model of MTC.
Methods: XL184 was administered QD on Days 1–5 of 14 day cycles (5&9 schedule; cohorts (C) 1–9), or as continuous QD dosing (C10+). Initial mg/kg dosing using a suspension formulation changed to flat dosing using capsules. Response is assessed on day 28 & every 8 weeks (wks). Plasma markers reflecting anti-angiogenic therapy & RET status in blood & tumor samples are being analyzed.
Results: 70 pts (22 with MTC) have been treated across 13 dose levels: 0.08–11.52 mg/kg 5&9, (C1−9); 175 mg/d, 265 mg/d, 175 mg/d (capsules) & 250 mg/d (capsules). Eight DLTs include grade (Gr) 3 palmar/plantar erythema (PPE), & Gr 3 AST, Gr 3 ALT & Gr 3 lipase elevations at 11.52 mg/kg 5&9, Gr 2 & 3 mucositis at 265 mg/d resulting in dose reduction, & Gr3 AST elevation & G3 PPE at 250 mg/d using capsules. The capsule MTD is 175 mg QD. Frequent XL184-related AEs include diarrhea (25%), nausea (21%), fatigue (20%), mucosal inflammation (16%), anorexia & increased AST (13% each), hypertension & vomiting (11% each), increased ALT, hair color changes & PPE (10% each). Pharmacokinetic (PK) analysis suggests linear PK; the terminal half-life is ~100 hrs. XL184 resulted in statistically significant changes in pharmacodynamic biomarkers (PlGF, VEGF-A, sVEGFR2) in pts enrolled at the MTD & sMET, a potential biomarker of MET inhibition, was modulated.
Twenty-four pts have had SD $\geqslant$3 months including 9 pts with SD $\geqslant$ 6 months. One pt with neuroendocrine carcinoma had an unconfirmed partial response (PR). Eight of 16 MTC pts with measurable disease had a PR (50%, 5 confirmed) with all others experiencing prolonged SD; the overall disease control rate (PR + SD >3 months) is 100%. Three MTC pts have non-measurable disease & 3 are too early to evaluate. Three PRs in MTC pts were reported at the first radiographic evaluation. Most pts with MTC have had substantial reductions in plasma calcitonin & CEA. Best radiological changes are shown in the figure.



Best radiological changes: patients with $\geqslant$1 post-baseline scan.

Conclusions: XL184 appears generally well tolerated & the daily dosing MTD using capsules has been defined. Antitumor activity has been observed in pts with various cancers and 50% of response-evaluable MTC pts achieved a PR while all 19 evaluated MTC pts derived clinical benefit. A Phase 3 study of XL184 in MTC is planned.

380 POSTER

Transcriptional and metabolic response associated with acute doxorubicin cardiotoxicity in perfused rat heart

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Background: Doxorubicin (DXR) belongs to the most efficient anticancer therapeutics. However, its application is limited by the risk of severe cardiotoxicity, molecular mechanisms of which are not yet completely understood. While fast selective down-regulation of the several cardiac specific genes have been implicated in development of DXR cardiotoxicity, general impact of the drug on heart gene profile is less characterized.
Material and Methods: Here we use a genome-wide DNA microarray approach to analyse the acute transcriptional response of the perfused Wistar rat heart to the low DXR dose. In addition, to better understand gene-function relationships, we focus on a group of genes involved in cardiac energy metabolism and analysed in more detail the corresponding phenotype: mitochondrial respiration in permeabilized cardiac fibers and levels of high energy phosphates.
Results: We show that perfusion of the rat hearts with 2 microM DXR during 2 hours induced moderate but significant hemodynamic dysfunction as well as distinct transcriptional reprogramming associated widespread downregulation of gene expression in DXR treated hearts. Selective upregulation of individual genes/gene sets was also observed; upregulation was however less sound both in term of fold changes and statistical power. For several genes our unbiased analysis converged with previous candidate oriented studies but we identified new potentially interesting DXR-responding genes/gene sets as well. Though in our model only minor changes were observed in general energy status (ATP, PCr level) and in the respiratory activities measured in permeabilized cardiac fibers, the upregulation of glycolytic and Krebs cycle genes seems to be a compensatory mechanism triggered by the onset dysfunction.
Conclusions: Doxorubicin rapidly induces widespread repression of gene expression in heart. Induction of some genes/gene sets escaping this repressing tendency can be, at least in a part, due to action of compensatory mechanism. Functional consequences of the transcriptomic changes can be of meaning both for cardiotoxic but and anticancer action of DXR.

381 POSTER

Detecting EGFR mutations in NSCLC by mutant specific antibodies

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Background: Patients of non-small cell lung cancer (NSCLC) carrying the somatic mutation of epidermal growth factor receptor (EGFR) have been shown to be hyperresponsive to the EGFR tyrosine kinase inhibitor Gefitinib and Erlotinib. The most common NSCLC associated EGFR mutations are the 15-bp nucleotide in-frame deletion in exon 19 (E746_A750del) and the point mutation replacing leucine with arginine at codon 858 in exon 21 (L858R), accounting for 85–90% EGFR mutations. The ability to detect mutated gene products in cancer cells can identify patients most likely benefit from such therapies, and make clinical trials more efficient and informative.
Methods: We generated rabbit monoclonal antibodies (RmAb) against EGFR with E746-A750 deletions and L858R point mutation. We tested the antibodies by western blot, Immunofluorescence (IF) and immunohistochemistry (IHC).
We used the antibodies staining 40 molecularly pre-typed NSCLC tumor samples by IHC. Then, we used IHC by a panel of four antibodies (two mutant antibodies, wtEGFR and pan-keratin antibodies) to screen 340 cases of NSCLC patient tumor samples without information of phenotypes.
Results: The western blot, IF and IHC were confirmed that the antibodies can specifically detect the mutant EGFR proteins. 40 molecular pre-typed

NSCLC tumor samples were 100% matching the data of DNA sequencing. In those 340 cases of unknown phenotype tumor samples, 28 cases were stained positive by L858R antibody and 24 cases were stained positive by exon 19 deletion antibody. The positive rate by both antibodies is 15.3%. The DNA of all positive samples and all staining negative adenocarcinoma samples were sent to do DNA sequencing, which showed the sensitivity of the IHC with the antibodies is 92.5% and the specificity is 95.8%. Some tumor samples carrying the mutations with low percentage of cancer cells were missed by direct sequencing, but detected by IHC with mutant EGFR antibodies.
Conclusions: The IHC combined mutant EGFR specific antibodies and wtEGFR antibody can be used to detect the EGFR mutations and measure the expression level of total EGFR protein in tumors. In addition, this assay enables us to examine paraffin blocks from small biopsy samples, which are difficult to extract enough high quality DNA for sequencing. The assay has the potential to be used to screen lung cancer patients for the treatment with EGFR kinase inhibitors in a clinical setting.

382 POSTER

Comparison of phase I trial (P1T) abstract quality between the EORTC-NCI-AACR and ASCO meetings

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Background: Conference abstracts of P1T communicate important information on anti-cancer drug development. Based on an electronic survey of 27 experts in oncology developmental therapeutics, our group recently reported a scoring system which assessed the quality of P1T abstract reporting (Strevel et al. Clin Cancer Res 14:1782–1787, 2008). For instance, the top three items deemed absolutely essential in phase I abstract reporting were description of dose-limiting toxicity, recommended dose, and grade 3 or greater toxicity at least possibly attributable to the study drug.
Methods: A scoring system for evaluating the quality of P1T abstracts based on a survey of experts was previously developed. This system was applied to all P1T abstracts presented at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics from 2003 to 2007. The results were compared to quality scores of 1,683 P1T abstracts published in the ASCO Annual Proceedings from 1997 to 2006, previously reviewed and reported by Strevel et al.
Results: 304 EORTC-NCI-AACR P1T abstracts were reviewed. Characteristics of these abstracts are as follows: oral proffered paper vs poster presentations = 2.3% vs 97.7%; governmental or academic vs industry funding = 18.4% vs 81.6%; US vs Europe vs international vs others = 58% vs 27% vs 10% vs 5%; multi-centre vs single-centre trials = 71% vs 29%. The mean quality score for the 229 EORTC-NCI-AACR P1T abstracts was 69.6%, as compared to 64.5% for the 713 ASCO P1T abstracts published in the same overlapping time period from 2003 to 2006. A strong correlation was observed between the two conferences in whether the abstracts contained the information of interest (Spearman correlation coefficient = 0.78). Multivariate analysis of combined conference abstracts indicates that predictors of increased quality score include a more recent year of presentation ($p < 0.001$), combination therapy trials ($p < 0.001$), non-North American trial centers ($p < 0.001$), and industry-sponsor trials ($p = 0.05$).
Conclusions: P1T abstracts presented at the EORTC-NCI-AACR have slightly higher quality scores than those presented at ASCO. This is likely due to higher character limits (2,500 vs 2,000), allowance for updating previously presented data, and the more sub-specialized anti-cancer drug development focus of the EORTC-NCI-AACR conference. There remains room in both conferences for improving abstract quality, which may be achieved by adopting P1T reporting guidelines.

383 POSTER

A phase 1 study of XL281, a potent and selective inhibitor of RAF kinases, administered orally to patients (pts) with advanced solid tumors

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Background: Mutations in K-RAS or B-RAF are found in a large proportion of human tumors, and lead to RAF/MEK/ERK pathway activation. Preclinical models containing K-RAS or B-RAF mutations are sensitive to RAF kinase inhibitors. XL281 is a potent and selective inhibitor of wild type and mutant RAF kinases, and shows anti-tumor activity in multiple xenograft models.
Methods: Pts with advanced solid tumors are enrolled in successive cohorts and receive XL281 orally once daily on a 28-day cycle. Tumor response is assessed every 2 cycles. Pharmacokinetic (PK) samples from plasma and pharmacodynamic (PD) samples from hair, buccal mucosa, peripheral blood mononuclear cells (PBMC) and optional tumor biopsies are collected for biomarker analyses and B-RAF and K-RAS genotyping.
Results: Of twenty-one pts enrolled in 6 cohorts, dosed at10, 20, 40, 60, 100 or 150 mg daily; 16 pts are evaluable to date. Tumor types include colorectal (CRC) (n = 5), papillary thyroid (PTC) (5), ovarian (1), prostate (1), carcinoid (2) and melanoma (2). No dose-limiting toxicities were observed; the most frequent treatment-related adverse events are grade 1or 2 nausea, vomiting, diarrhea and fatigue. Three CRC pts have stable disease (SD) for 20 weeks, with one showing a ~20% reduction in target lesions. Five PTC pts, 2 with a confirmed B-Raf V600E mutation, have SD (36+, 32+, 20+, 8+, 8+ wks, respectively). Three pts (1 prostate, 1 carcinoid, 1 melanoma) have SD (19, 24+, and 22+ wks, respectively). XL281 is rapidly absorbed (median tmax = 2 hrs), has a median t1/2 of ~8 hrs, and shows minimal accumulation after repeat dosing. XL281 exposure generally increases with increasing dose and appears dose proportional. Administration of XL281 modulates RAF target activity as assessed by reduction in the stimulation of phosphorylated ERK in PBMCs post-treatment.
Conclusions: XL281 is generally well tolerated, with early signs of clinical activity. In 15 evaluable pts, 11 have SD of which 9 pts exceeded 16 weeks on study. Reduced pERK is observed in PBMCs, indicative of target modulation. The MTD has not yet been defined and dose escalation continues.

384 POSTER

Effect of selection of QTc formula on eligibility of patients for phase I cancer clinical trials

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Background: The corrected QT interval (QTc) is often utilized as an eligibility criterion in Phase I cancer clinical trials. Numerous formulae have been utilized in the conduct of these trials to calculate the QTc to correct for values based on the ventricular rate, characterized by the RR interval. The primary objective of this pilot study was to ascertain if selection of a particular formula (e.g. Bazzett) could affect the eligibility rate for patients enrolling on Phase I trials. Secondary objectives were to determine the proportion of patients who were on medications that could potentially prolong QTc, the proportion of concomitant medications that could potentially prolong QTc and if factors such as underlying cardiovascular disease, electrolyte imbalances (e.g. hypokalemia) or age were correlated with QTc prolongation.
Materials and Methods: A retrospective chart review was conducted in the setting of a Phase I clinic and 130 patient charts were reviewed. Absolute QT values were obtained from screening ECGs. Concomitant medications and co-morbidities of interest (underlying cardiovascular disease, history of arrythmias) were tabulated. QTc values for each patient were calculated using seven different formulae (Bazzett [B], Fridericia [F], Framingham [FR], Hodges [H], Mayeda [M], Van de Water [V] and Wohlfart [W]). Generally used values (>470 ms in females and >450 ms in males) were used for purposes of QTc prolongation. Concomitant medication potential for QTc prolongation was ascertained using a publicly available database, AzCert (www.qtdrugs.org). Statistical significance of the association between QTc and factors of interest were calculated using Fisher's exact test.
Results: Ineligibility rates ranged from 3.1% to 17.7% (FR:3.1%, V:3.1%, H:3.1%, W:3.1%, F:3.9%, B:10.8% and M:17.7%). We also found that a consistent ineligibility rate (3.1%) could be achieved by using formulae appropriate QTc thresholds as opposed to generally used values. The proportion of patients taking medications with potential to prolong QTc was 51% while the proportion of concomitant medications with the potential to prolong QTc was 12%. No correlation was found between QTc prolongation and age, gender, underlying cardiovascular conditions, primary site or electrolyte imbalances ($p > 0.05$ in all cases).
Conclusions: Uniform criteria and guidelines for selection of QTc formulae need to be developed. Formulae specific QTc thresholds also need to be specified.