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

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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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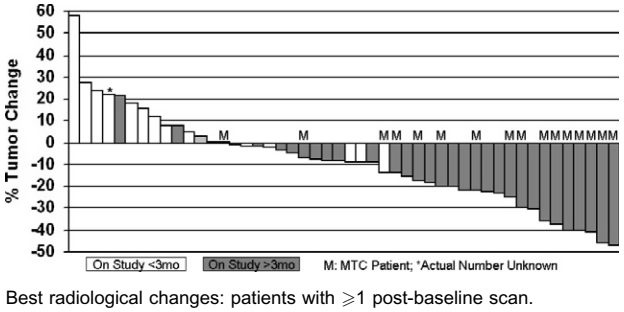
Background: XL184, a multi-kinase inhibitor, strongly inhibits proliferation in MTC cell lines harboring activated RET. Pharmacodynamic studies show substantial inhibition of RET & MET phosphorylation in the TT xenograft model of MTC.
Methods: XL184 was administered QD on Days 1–5 of 14 day cycles (5&9 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.

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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.

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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