Correlation of ex vivo PamChip® kinase inhibition profiles of erlotinib with in vivo tumour efficacy in pancreatic PDTX models

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Study Design
Human Patient Derived Tumour Xenograft (PDTX) models have been considered fairly predictive of drug efficacy in humans. As a first step to investigate if in vivo erlotinib response could be predicted from ex vivo PamChip® kinase activity inhibition, 18 pancreatic PDTX protein lysates (Oncotest Germany; www.oncotest.de) were spiked ex vivo with erlotinib and inhibition profiles generated (Fig. 1a). In vivo efficacy studies were performed at Oncotest, for six select PDTX models that were differentially inhibited in the PamChip® assay by erlotinib (70 mg/kg/d) (Fig 1b). Median relative tumour volumes were compared to PamChip® inhibition profiles.

Key Findings
PamChip® inhibition ratios of erlotinib were used to rank the ex vivo sensitivity of different PDTX tumours and the in vivo efficacy of erlotinib was determined for the corresponding PDTX model. Inhibition of kinase activity ex vivo by erlotinib correlated with in vivo data: PAXF 546 and PAXF 1869 showed highest inhibition in the PamChip assay relating to the highest reduction in median relative tumour volume in vivo. Extent of tumour growth inhibition in vivo are similar to the ranking patterns ex vivo. PAXF 1876, which also expresses very high p-AKT (Oncotest historic data), is least inhibited ex vivo but responds to treatment at a later stage in vivo. Results are under further investigation, with insights into molecular mechanisms, development of resistance, and prediction models. The result requires further expansion of sample numbers to make a definitive conclusion.

“Author Quote”
“The innovative PamChip kinase activity profiling assay is a promising approach towards personalized targeted therapy for pancreatic cancer”.

Background
Targeted therapy with protein tyrosine kinase inhibitors (PTKIs) has emerged as a beneficial treatment option for various cancers. Since only very few patients respond to treatment it would be advantageous to develop technology for patient selection that could predict patient response to PTKIs. Erlotinib is the only PTKI approved by FDA (2005) to treat metastatic pancreatic cancer in combination with gemcitabine but there are no response prediction markers.

Conclusions
The ex vivo profiles correlated well with in vivo responses in tumour-bearing mice, for erlotinib. Extrapolating from the results on the PDTX efficacy study, PamChip® microarrays could be potentially useful to predict treatment outcome in patients treated with targeted drugs.