Kinase activity as a sensor for efficacy of doxorubicin and/or bevacuzimab treatment of breast cancer

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Study Design
An established xenograft model for invasive breast cancer was used (fig.1). At t₀, mice received treatment as a bolus injection of doxorubicin and/or bevacuzimab or vehicle only (control). Three days after the injection, tumors were sampled, snap frozen and cryo-slices were homogenised in lysis buffer and cleared by centrifugation. Supernatants were subjected to protein tyrosine kinase activity profiling on the PamChip® microarray. For each of the 144 kinase targets (peptides) on the array, treatment-response was calculated as the log-transformed ratio of phosphorylation by lysate from treated over control mice. This creates a 144-point ‘response-signature’ for each treatment. The color-coded response signatures is shown in figure 2a as a heatmap where treatment-related upregulation of kinase activity is reflected by red and a decrease results in blue. As an example, fig2B shows significant kinase modulation by doxorubicin treatment.

Key Findings
• Systemic chemotherapy and/or antiangiogenic treatment reflected by significant alteration of kinase activity in local tumor tissue.
• Alteration of intracellular kinase activity in tumors is treatment-correlated and thus differential between treatments.

“Author Quote”
Studying kinase activity allows us to unravel the complexity of combination therapy in our animal models.

Background
Breast cancer is often treated with surgery and adjuvant chemotherapy (e.g., doxorubicin). Combination treatment with additional drugs, such as the angiogenesis antibody bevacuzimab, aiming for enhanced effectiveness, has been applied with varying degrees of success and is topic of extensive research. Kinases are a family of proteins which play an important role in the regulation of cell growth and may serve as a readout for treatment response. In this study, we apply chemo- and/or antiangiogenic treatment in a mouse model for breast cancer. After treatment, tumors analysed for tyrosine kinase activity using PamChip technology. The resulting activity profiles of tumors from different treatments were compared.

Conclusion
Kinases in cancer cells are affected by chemotherapy and antiangiogenic treatment. This can be visualised by PamChip® tyrosine kinase activity profiling, which thus provides a sensor for response characterisation.

Figure 1: Study design

Figure 2: Analysis: response profiles

References:
1. Bergamaschi et al. Mol.Oncol. 3 : p469
2. Lindholm et al (Manuscript in preparation)