Effect of antiangiogenic therapy on tumor growth, vasculature and kinase activity in basal- and luminal-like breast cancer xenografts

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Study Design
To determine factors of importance for antiangiogenic treatment response and/or resistance, two representative human basal- and luminal-like breast cancer xenografts were treated with bevacizumab, a VEGF inhibitor, and as chemotherapy doxorubicin, alone or in combination. In vivo growth inhibition, microvessel density and proliferating tumor vessels were analysed, while kinase activity was determined using the PamChip® Tyrosine kinase microarray system.

Key Findings
Both doxorubicin and bevacizumab inhibited basal-like tumor growth significantly with a superior effect when given in combination. Doxorubicin inhibited luminal-like tumor growth most effectively, and with no additional benefit of adding antiangiogenic therapy. The antiangiogenic treatment in the basal-like compared to the luminal-like tumors showed almost complete vasculature reduction at early time points (three days after treatment) and sustained inhibitory effects until the end of the experiment (day 18). In contrast, luminal-like tumors only showed significant effect on the vasculature at day 10 in the tumors having received both doxorubicin and bevacizumab. Kinase activity profiling on the PamChip® in both tumor models demonstrated that the most effective treatment in vivo was accompanied with increased phosphorylation of various relevant kinase substrates as VEGFR, EGFR, Annexin, and PLCγ.

“Author Quote”
“...densitometric measurements confirmed the results found in the PamChip measurements”

Background
The biological mechanisms responsible for treatment resistance of breast cancer are not fully understood. It may be that breast cancer is a clinically heterogeneous disease. A large clinical benefit in a small subpopulation of patients will then be diluted in large clinical trials with unselected patients, and therefore, one of the most important challenges is to identify possible responders to different types of targeted therapies among the unselected group of breast cancer patients. This study a search for factors identifying the patient population responding to antiangiogenic therapy was started.

Conclusion
Potential signaling pathways identified by kinase activity profiling may suggest candidate markers for selection of patients for antiangiogenic therapy, and for identifying targets to combat treatment related resistance.

Reference: