hMMP9 as predictive factor for response and progression free survival in breast cancer patients treated with bevacizumab and pegylated liposomal doxorubicin (PLD)

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Background: The anti-angiogenic drug, bevacizumab (Bv), is currently used in the treatment of different malignancies including breast cancer. Many angiogenesis-associated molecules are found in the circulation of cancer patients. Until now, there are no prognostic or predictive factors identified in breast cancer patients treated with Bv. We present here the first results of the prospective monitoring of 6 angiogenesis-related molecules in the peripheral blood of breast cancer patients treated with a combination of Bv and PLD in the phase II trial, SAKK 24/06.

Methods: Patients were treated with PLD (20 mg/m^2) and Bv (10 mg/kg) on days 1 and 15 of each 4-week cycle for a maximum of 6 cycles, followed by Bv monotherapy maintenance (10 mg/m^2 q2 weeks) until progression or severe toxicity. Plasma and serum samples were collected at baseline, after 2 months of therapy, then every 3 months and at treatment discontinuation. Enzyme-linked immunosorbent assays (Quantikine, R&D Systems and Reliatech) were used to measure the expression levels of human vascular endothelial growth factor (hVEGF), placental growth factor (hPlGF), matrix metalloproteinase 9 (hMMP9) and soluble VEGF receptors hsVEGFR-1, hsVEGFR-2 and hsVEGFR-3. The log-transformed data (to reduce the skewness) for each marker was analyzed using an analysis of variance (ANOVA) model to determine if there was a difference between the mean of the subgroups of interest (where $\alpha = 0.05$). The untransformed data was also analyzed in the same manner as a “sensitivity” check.

Results: 132 blood samples were collected in 41 out of 43 enrolled patients. Baseline levels of the molecules were compared to disease status according to RECIST. There was a statistically significant difference in the mean of the log-transformed levels of hMMP9 between responders [CR+PR] versus the mean in

patients with PD (p-value=0.0004, log fold change=0.7536), and between patients with disease control [CR+PR+SD] and those with PD (p-value=<0.0001, log fold change=0.81559), with the log-transformed level of hMMP9 being higher for the responder group. The mean of the log-transformed levels of hsVEGFR-1 was statistically significantly different between patients with disease control [CR+PR+SD] and those with PD (p-value=0.0068, log fold change=-0.6089), where the log-transformed level of hsVEGFR-1 was lower for the responder group. The log-transformed level of hMMP9 at baseline was identified as a significant prognostic factor in terms of progression free survival (PFS): p-value=0.0417, hazard ratio (HR)=0.574 with a corresponding 95% confidence interval (0.336 - 0.979)). No strong correlation was shown either between the log-transformed levels of hsVEGF, hPlGF, hsVEGFR-2 or hsVEGFR-3 and clinical response or the occurrence of severe toxicity, or between the levels of the different molecules.

Conclusions: Our results suggest that baseline plasma level of the matrix metalloproteinase, hMMP9, could predict tumor response and PFS in patients treated with a combination of Bv and PLD. These data justify further investigation in breast cancer patients treated with anti-angiogenic therapy.