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Session Title: Epithelial-Mesenchymal Transition in Cancer Progression and Metastasis
Presentation Title: Stem cell and epithelial-mesenchymal transition markers are frequently expressed in metastatic breast cancer patients with circulating tumor cells.
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Background: We recently demonstrated in a monitoring study that the persistence of circulating tumor cells (CTC) in metastatic breast cancer patients significantly correlated with shorter overall survival. The persistence of CTC might be associated with stem cell like tumor cells which have been suggested to be the active source of metastatic spread in primary tumors. Furthermore, these cells also may undergo phenotypic changes, known as epithelial-mesenchymal transition (EMT), which allows them to travel to the site of metastasis formation without getting affected by conventional treatment. In this study, we evaluated 145 blood samples of 42 metastatic breast cancer patients during a follow-up of palliative chemo-, antibody - or hormonal therapy for the expression of stem cell and EMT markers and correlated these findings with the presence of CTC and response to therapy.

Materials and Methods: 5 ml blood was analyzed for CTC with the *AdnaTest BreastCancer* (AdnaGen AG) for the detection of EpCAM, MUC-1 and HER-2 transcripts. The recovered c-DNA was additionally multiplex tested for three EMT markers [Twist1, Akt2, PI3K α (TAP)] and separately for the tumor stem-cell markers ALDH1 and BMI. The identification of EMT markers was considered positive if at least one marker was detected in the sample. Healthy donor samples were used to determine assay specificity.

Results: Applying an amplicon cut-off value of 0.2 ng/ μ l for Akt2, 0.15 ng/ μ l for Twist1, 0.25 ng/ μ l for PI3K α and 0.15 ng/ μ l for ALDH1 and BMI, 97% of 30 healthy donor samples investigated were negative for TAP, 95% for ALDH1 and 90% for BMI transcripts. CTC were detected in 40/145 (28%) cancer samples. In the CTC (+) group 68% were positive for at least one of the TAP markers, 57% for ALDH1 and 63% for BMI, respectively. In the CTC (-) group the percentages were 15%, 17% and 42%, respectively. The expression of ALDH1, BMI and TAP was further correlated with response during therapy. In non-responders, TAP, ALDH1 and BMI expression was found in 44%, 42% and 100% of patients, in patients with stable disease the percentages were 25%, 29% and 57% and in partial responders the rates were 25%, 16% and 36%, respectively. **Conclusion:** Whereas the role of BMI further has to be evaluated, the strong correlation between the expression of ALDH1 and EMT markers and the presence of CTC indicate that a major proportion of CTC found in the blood of metastatic breast cancer patients shows EMT and tumor stem cell characteristics. Furthermore, these markers may serve as an indicator for therapy resistant tumor cell populations and, therefore, for an inferior prognosis. Especially EMT markers might help to identify non-responders in the group of CTC (-) patients.