Circulating tumor cells in Metastatic (met) Breast Cancer (BC)

In **met BC**, we usually start our studies with patients who present with recurrence of a mammary carcinoma diagnosed years before or who exhibit progression of the disease under different ongoing treatments, and are about to undergo a new course of therapy.
In our **first published study**, we detected **CTCs** in **52%** of the patients (CTC characteristics: 86% *EpCAM*; 86% *MUC1*; 32% *HER2*; 35% *ER*; 12% *PR*) **before treatment start**. The **OS** rate of patients in whom no CTCs were found or in whom CTCs were **eliminated** during treatment **significantly differed** from those patients with **persistent CTCs** (**Figure 1; Tewes et al., 2009**).

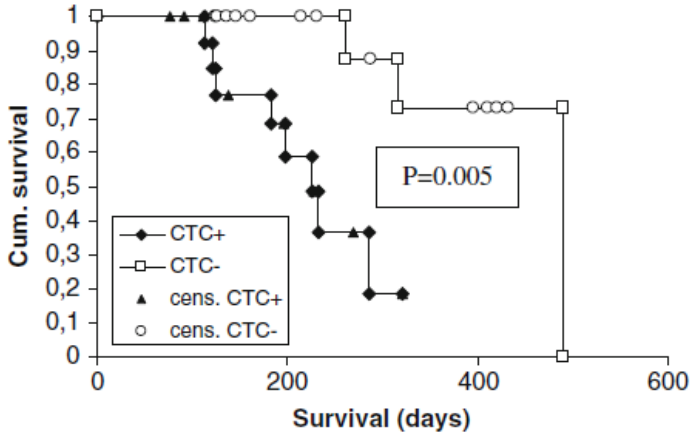

Figure 1: Kaplan–Meier analysis. 8/16 CTC+ patients died within 12 months in contrast to 3/16 patients in the CTC-negative group. The presence of CTC was a significant prognostic factor with respect to poor overall survival (P = 0.005) (censored patients: still alive and under observation) (***Tewes et al., 2009***).

As the groups of patients were clinically comparable, we analyzed whether the **persistent cells** were **stem cells** or cells with **EMT** character. We were able to show that ***ALDH1*** and at least one of the three **EMT markers** were frequently expressed in **CTC-positive patients** and these results correlated with the **response** to treatment (**Figures 2 and 3; Aktas et al., 2009**). This **paper** has been receiving **a lot of attention** regarding citations since we demonstrated for the **first time** that **stem cell like CTCs** were present in blood of met BC patients and, probably are **responsible for treatment failure**.

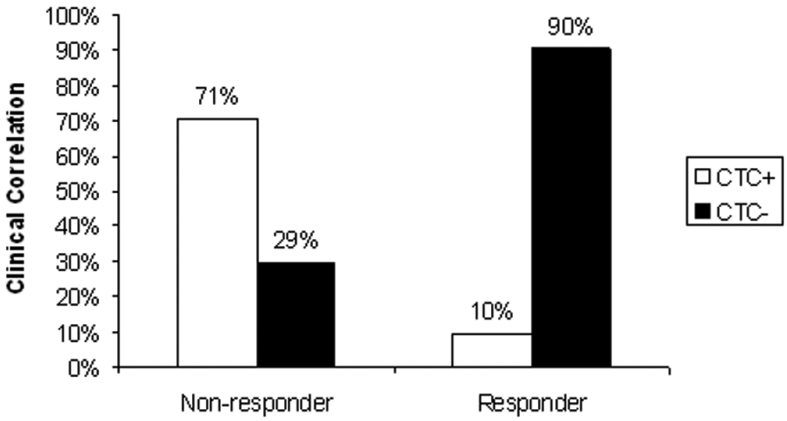

Figure 2: Correlation of CTCs and response to therapy. Patients are stratified into responders and non-responders (***Aktas et al., 2009***).

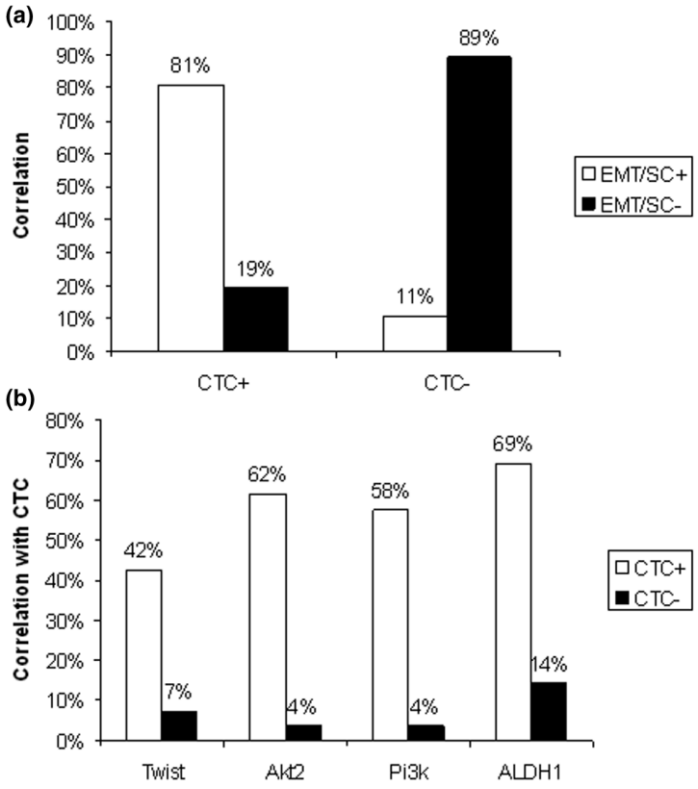

Figure 3: Corrrelation of CTCs, EMT markers, and/or *ALDH1*. (a) The identification of EMT markers was considered positive if at least one marker (*Twist*, *AKT2* or *PI3K*) was detected in the sample. **(b)** Detailed analysis for the correlation of CTC and *ALDH1* as well as the EMT markers (***Aktas et al., 2009***).

We frequently documented a **discordant receptor expression** of ER, PR and HER2 on **CTCs** as compared to the **primary tumor** and /or **metastases** (**Aktas et al., 2011; 2016; Figure 4**).

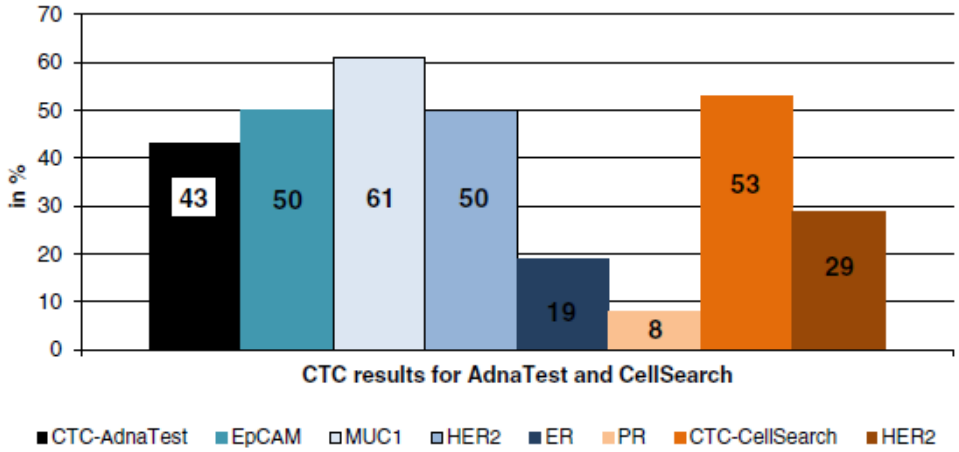

Figure 4: Results for CTCs obtained by the AdnaTest Breast Cancer and the CellSearch Assay (Aktas et al., 2016).

The phosphatidylinositol 3-kinase (**PI3KCA)-AKT** serine/threonine kinase (AKT) **signaling pathway** has been identified as one of the most important and most frequently mutated pathways involved in the process of EMT and survival of stem cell-like CTCs (slCTCs). We compared this pathway in **CTCs/CTCs in EMT** and the corresponding tumor tissues of 90 met BC patients (**Bredemeier et al., 2017**).
slCTCs were identified in **23%** and **CTCs in EMT** in **56%** of the patients. **pAKT** and **ALDH1** positivity in **tumor tissue** was identified in **47** and **9%** of cases, respectively, and a **PTEN loss** was observed in **18%** of patients. A **significant association** was detected between **pAKT**

expression in cancerous **tissue** and AKT2 expression in **CTCs** (P=0.037). ***PI3KCA* mutations** were detected in **32%** of the patients, most frequently on exons 21 (55%) and 10 (45%). Patients with ***PI3KCA* mutations in tumor tissue** had a significantly **longer OS** than patients with wild-type *PI3KCA* expression (**P=0.007; Figure 5**). Similar results were obtained for patients with aberrant PI3KCA signaling in CTCs and/or aberrant signaling in cancerous tissue (**P=0.009; Figure 6**).

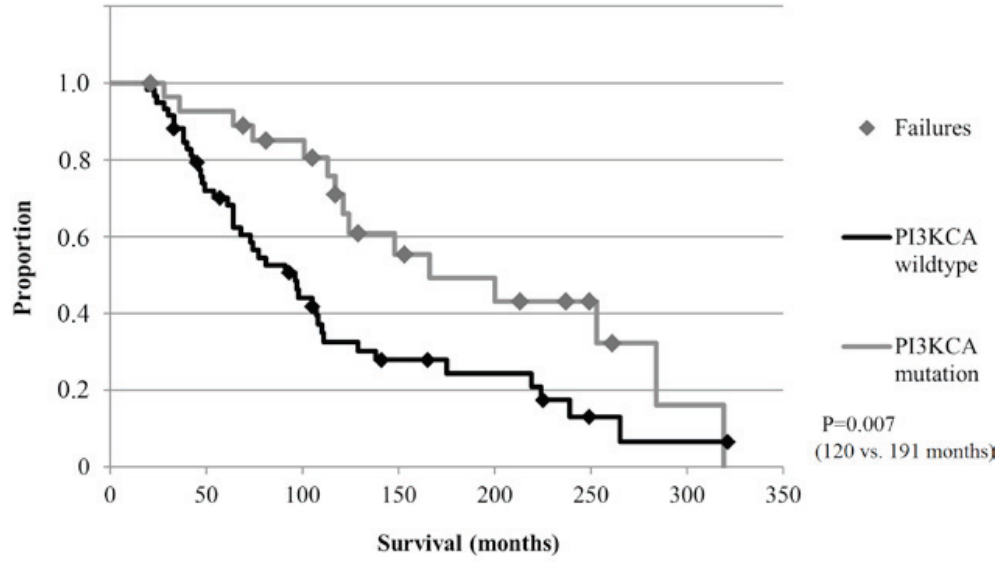

Figure 5: Overall Survival of patients harboring *PI3KCA* mutations in the tumor tissue (n=90 pts). Patients harboring a *PI3KCA* mutation had a significantly longer OS compared with patients with wild-type *PI3KCA* in their tumor tissue (120 months vs. 191 months; P=0.007). *PI3KCA*, phosphatidylinositol 3-kinase; OS, overall survival (***Bredemeier et al., 2017***).

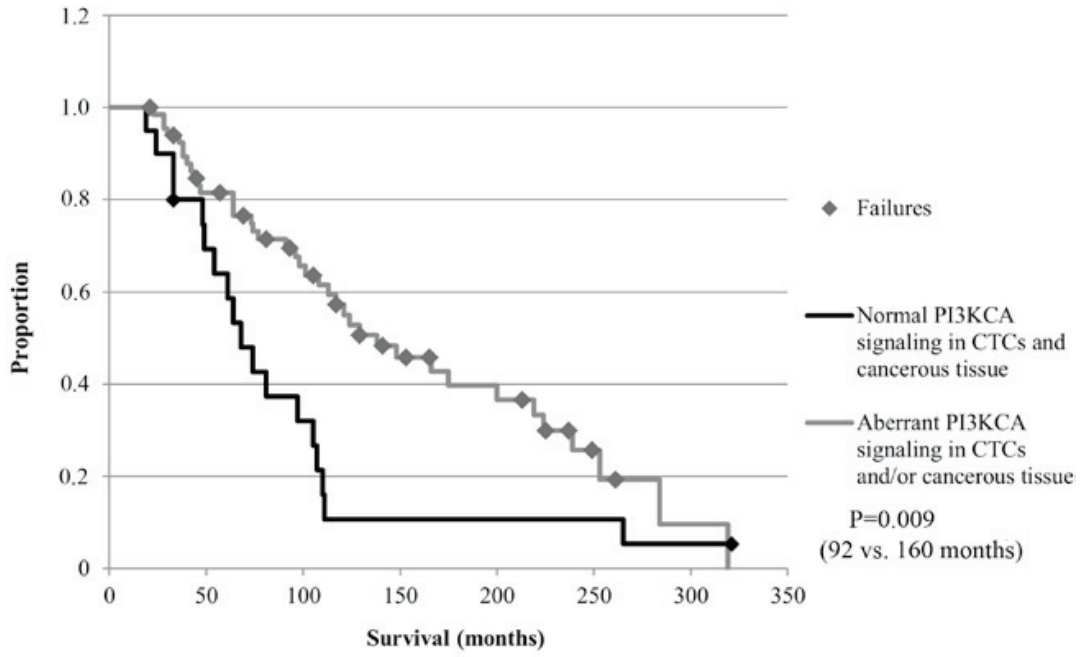

Figure 6: Overall Survival of patients with aberrant *PI3KCA* signaling in CTCs and/or tumor tissue (n=90 patients). Patients with aberrant *PI3KCA* signaling in CTCs and/or tumor tissue had a significantly longer OS compared with patients with normal *PI3KCA* signaling (92 months vs. 160 months; P=0.009). *PI3KCA*, phosphatidylinositol 3-kinase; CTCs, circulating tumor cells; OS, overall survival (***Bredemeier et al., 2017***).

References

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