# Predicting response and survival after neoadjuvant systemic treatment with on-treatment biopsies

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## Background

Early prediction of response to neoadjuvant systemic treatment (NST) in breast cancer (BC) may guide treatment tailoring even before NST completion. Patients (pts) could avoid ineffective treatments and be assigned to non-cross-resistant therapies. Here, we analyzed core needle on-treatment biopsies (OTB) taken after 2-4 cycles of NST for residual invasive cancer, Ki67, stromal tumor-infiltrating lymphocytes (sTILs), and their ability to predict treatment outcome.

## Patients and Methods

Patients with available and evaluable OTBs (n=449) of neoadjuvant clinical trials GeparSixto (n=47), GeparSepto (n=194), GeparNuevo (n=99), GeparX (n=47), and GeparOLA (n=62) were included. OTBs were retrospectively evaluated for the following parameters: presence of tumorbed, presence of residual cancer defined as cellularity of viable invasive cancer cells >0 (OTB+) vs 0 (OTB-), stromal TILs, and Ki67. Histological findings of OTB were compared with post-treatment response (pCR defined as ypT0/is ypN0) and time-to-event outcomes. Baseline pre- and post-treatment data were taken from the GBG data bank.

Categorical variables were descriptively summarized, and the Cochran-Mantel-Haenszel test stratified by study was used for comparison. Odds ratio (OR) together with its 95% confidence interval (CI) for categorical outcome was calculated using uni- and multivariate generalized logistic regression models with study as random effect, for subgroup analysis due to small pCR rates logistic regression stratified by study was used. Time-to-event (TTE) outcomes were compared using stratified log-rank test. Uni- and multivariate Cox frailty models with study as random effect were used for calculation of hazard ratio (HR) together with its 95% CI.

## Results

At baseline, most BC were cT2 (55%), cN0 (69.6%), of no special type (88%), and G3 (66.1%). TNBC (n=257, 57.2%) was the most prevalent subtype, followed by HR+/HER2- (n=108, 24.1%), and HRany/HER2+ (n=84, 18.7%). In 79.1% (355/449), a tumorbed in OTBs was identified. The remaining OTBs had unspecific (10%) or uncertain changes (6.2%) or no signs of tumorbed (4.7%). **Figure 1** shows the distribution of OTB by intrinsic type, Ki67, and sTILs (both median cutoff). Pts with OTB+ were identified in 60% (213/355), and only 20.2% (43/213) had a pCR after completion of NST. In contrast, 73.9% (105/142; p<0.001) of pts with OTB- (40%, 142/355) had a pCR. **Figure 2** illustrates the distribution of OTB+ vs OTB- by pCR status. In univariate logistic regression analysis, pts with OTB+ had a lower pCR rate (OR 0.091, 95% CI 0.055-0.152; p<0.001). In multivariate analysis adjusting for other established prognostic factors like nodal stage, intrinsic type, and grading, the presence of OTB+ still showed a significant decrease in the odds for pCR (OR 0.112, 95% CI 0.064-0.198; p<0.001). When analyzed according to subtype, the pCR rate at surgery for pts with OTB+ was 48% for HRany/HER2+ (12/25; p=0.016), 21.6% for TNBC (24/111; p<0.001), and 9.1% for HR+/HER2- (7/77; p=0.001). Significantly lower chances for pCR in pts with OTB+ were consistent in all subtypes (HRany/HER2+ OR 0.24, 95% CI 0.07-0.80; p=0.02; HR+/HER2- OR 0.13, 95% CI 0.03-0.52; p=0.004; TNBC OR 0.09, 95% CI 0.05-0.18; p<0.001, $p_{interaction}$=0.468).

**Figure 1** OTB+ vs OTB- by tumor characteristics at baseline (each p<0.001)

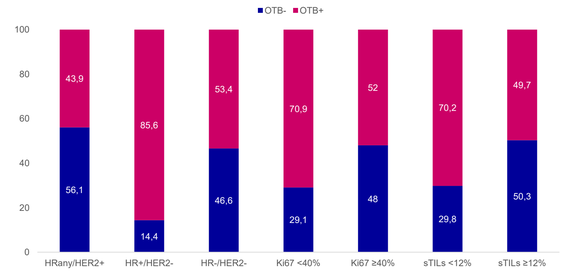
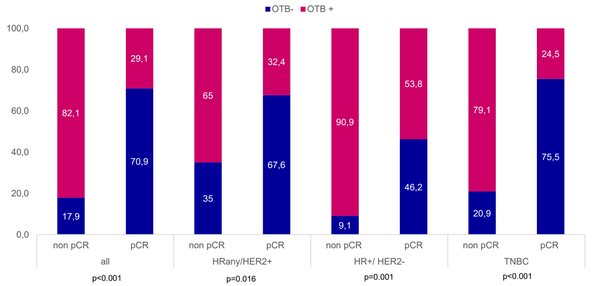
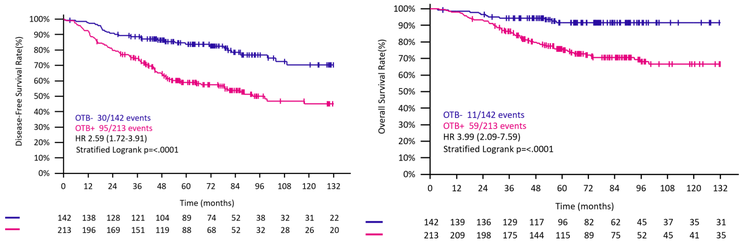



**Figure 2** OTB+ vs OTB- by pCR status, overall and by intrinsic type



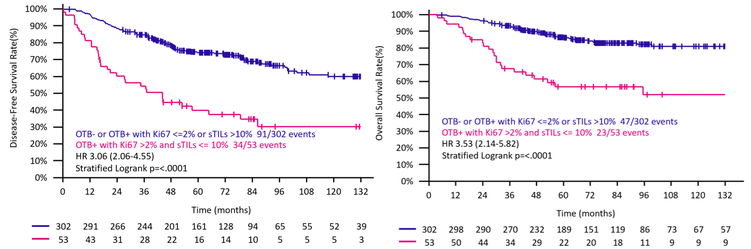

OTB+ was linked to worse DFS and OS (DFS: HR 2.59, 95% CI 1.72-3.91; OS: HR 3.99, 95% CI 2.09-7.59; log-rank p<0.001, respectively, **(Figure 3)**, remaining significant in multivariate analysis (DFS: HR 2.38, 95% CI 1.53-3.70; OS: HR 3.80, 95% CI 1.93-7.48; p<0.001, respectively). In subgroup analysis, the overall results for DFS were confirmed for all intrinsic subtypes (HRany/HER2+ HR 2.77, 95% CI 0.92-8.4; log-rank p=0.067; HR+/HER2- HR 3.82, 95% CI 0.92-15.9; log-rank p=0.065; TNBC HR 2.19, 95% CI 1.33-3.60; log-rank p=0.003, $p_{interaction}$=0.774). For OS, a statistically significant improvement could only be demonstrated for TNBC (HR 4.17, 95% CI 1.92-9.07; log-rank p<0.001), probably limited in other subtypes by paucity of OS events.

**Figure 3** Kaplan Meier curves for DFS and OS in pts with OTB+ vs OTB-




Change of Ki67 and sTILs after NST has a prognostic impact. To further investigate the prognosis of pts with OTB+, we combined OTB- and OTB+ with Ki67 ≤2% or sTILs >10% and compared this group with OTB+ Ki67 >2% and sTILs ≤10%. Median cutoff for Ki67 and sTILs as assessed on OTB were used. Pts with OTB- or OTB+ Ki67 ≤2%/sTILs >10% (n=302/355) had a statistically significant better DFS as compared to pts with OTB+ Ki67 >2%/ sTILs ≤10% (n=53/355) (HR 3.06, 95% CI 2.06-4.55; log-rank p<0.001) with 30% vs 64% of pts having a DFS event. Similar results were found for OS (HR 3.53, 95% CI 2.14-5.82; log-rank p<0.001), **Figure 4**.

**Figure 4** Kaplan Meier curves for DFS and OS in pts with OTB- or OTB+ Ki67 ≤2%/sTILs >10% vs OTB+ Ki67 >2%/sTILs ≤10%




## Conclusions

Our findings suggest that on-treatment biopsies are suitable to monitor neoadjuvant therapy response. Residual invasive cancer cells in OTBs have a prognostic impact, even if detected early during treatment. Therefore, OTB should be evaluated prospectively as biomarker to guide response-adapted treatment in neoadjuvant clinical trials.

## References

Hirmas et al. Shifting the paradigm: The transformative role of neoadjuvant therapy in early breast cancer. Cancers (Basel) 2024
Sinn et al. On-treatment biopsies to predict response to neoadjuvant chemotherapy for breast cancer. Breast Cancer Research 2024
von Minckwitz et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014
Untch et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG69): a randomized, phase 3 trial. Lancet Oncol 2016
Fasching et al. Neoadjuvant paclitaxel/Olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study). Ann Oncol 2020
Loibl et al. Neoadjuvant durvalumab improves survival in early triple-negative breast cancer independent of pathological complete response. Ann Oncol 2022
Blohmer et al. Effect of denosumab added to 2 different nab-paclitaxel regimens as neoadjuvant therapy in patients with primary breast cancer the GeparX 2 × 2 randomized clinical trial. JAMA Oncol 2022

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