# Intermediate biopsies during neoadjuvant chemotherapy for breast cancer to predict patient outcome

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## Background

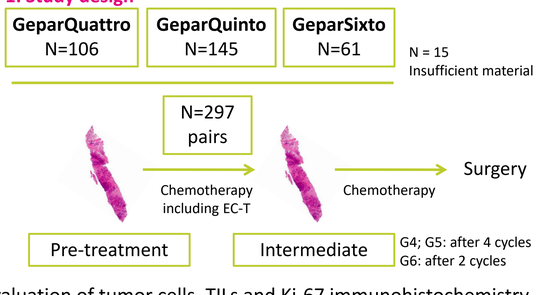
Patients with pathologic complete response (pCR) to neoadjuvant chemotherapy for invasive breast cancer have a better prognosis and are susceptible to a more limited surgical therapy. The prediction of pCR before treatment is challenging and it is unclear if biopsy procedures during neoadjuvant treatment might predict treatment outcome. This could offer opportunities for de-escalation of medical and surgical treatment beside serving as a platform for biomarker discovery.

## Patients and Methods

We evaluated the use of intermediate biopsies that were taken during neoadjuvant treatment from 297 patients with invasive breast cancer treated within three prospective randomized neoadjuvant trials (GeparQuattro[1], GeparQuinto[2] and GeparSixto[3]). We evaluated the presence and quantity of invasive breast cancer as well as the quantity of tumor-infiltrating lymphocytes (TILs) and the proliferation marker Ki-67 by immunohistochemistry (IHC) and compared the results to the matched pre-treatment samples. We explored the association of residual cancer in the intermediate biopsies (tu- vs tu+) and dynamics (Δ) in TILs and Ki-67 with pCR rates and disease-free survival (DFS) using logistic and Cox regression models with 95% confidence interval (CI), respectively. The proportion of intermediate biopsies overall, and by BC subtype and tumor stage were assessed using Fisher's exact- or Pearson $\chi^2$-test. Differences in DFS between subgroups of intermediate biopsies were analyzed by Kaplan-Maier curves and Cox proportional hazard models.

***Primary objective of the study:*** to evaluate if intermediate biopsies taken during neoadjuvant therapy are useful for the prediction of therapy response and survival after completion of treatment.

### Figure 1: Study design




EC-T, epirubicin plus cyclophosphamide followed by docetaxel

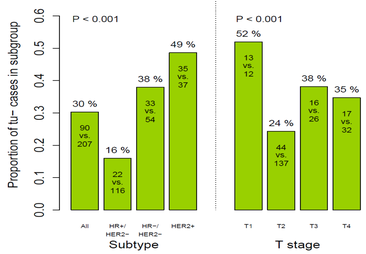
## Results

### Table 1: Baseline characteristics

| Parameter | Category | N (valid %) |
|---|---|---|
| **BC subtype** | HR-/HER2- | 87 (29.3%) |
| | HR+/HER2- | 138 (46.5%) |
| | HER2+ | 72 (24.2%) |
| **T stage** | T1 | 25 (8.4%) |
| | T2 | 181 (60.9%) |
| | T3 | 42 (14.1%) |
| | T4 | 49 (16.5%) |
| **N stage** | N0 | 125 (42.1%) |
| | N1-3 | 171 (57.6%) |
| | Missing | 1 (0.3%) |
| **Grading** | G1-2 | 156 (52.5%) |
| | G3 | 136 (45.8%) |
| | Missing | 5 (1.7%) |
| **Histology** | NST | 268 (90.2%) |
| | Lobular/other | 29 (9.7%) |
| **TILs** | TILs < 60 % | 79 (26.6%) |
| | TILs ≥60 % | 25 (8.4%) |
| | Missing | 193 (65.0%) |
| **Response** | No pCR | 235 (79.1%) |
| | pCR | 62 (20.9%) |

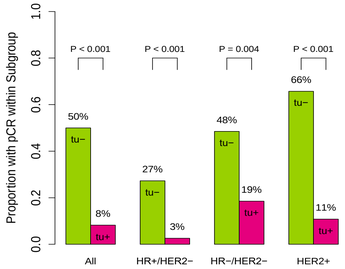
NST, no special type

### Figure 2: Intermediate biopsies and tumor characteristics



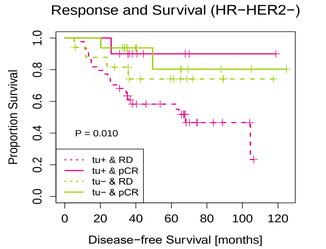

90 (30%) intermediate biopsies were negative for residual cancer (tu-). This was more frequently observed in HER2+, HR-/HER2- and low-stage tumors. There was no significant association with nuclear grade, nodal status or TILs.

### Figure 3: Patients with positive intermediate biopsies had a low probability of pCR




Overall, pCR rate was 50% in patients without residual cancer (tu-) and 8% in patients with residual cancer (tu+) in the intermediate biopsy after completion of treatment.

### Figure 4: Intermediate biopsies are not independently predictive for survival

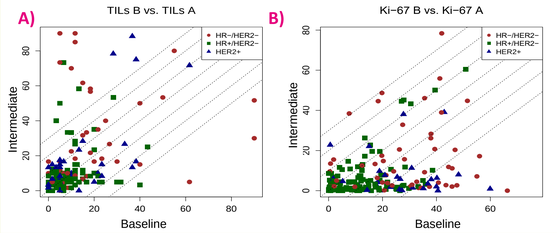



| Parameter | HR (95% CI) | P |
|---|---|---|
| tu- vs. tu+ | 0.54 (0.22-1.37) | 0.19 |
| pCR vs. no pCR | 0.28 (0.08-0.96) | 0.04 |

tu+, residual cancer; tu-,without residual cancer

In univariate analysis the presence of tumor cells in intermediate biopsies was predictive for DFS in HR-/HER2- but not in the other subtypes. It was not predictive in HR-/HER2- in a bivariate Cox regression analysis adjusted for pCR (table).

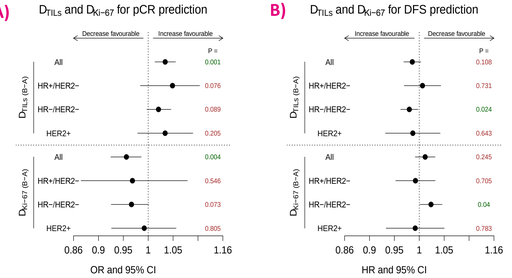
### Figure 5: Distribution of TILs and Ki-67 by BC subtype




TILs increased in a subset of patients after onset of treatment (Fig. 5A).
We observed a decrease in proliferation in most patients (Ki-67 IHC) (Fig. 5B).

Abbreviation: A, baseline; B, intermediate

### Figure 6: Dynamic changes of TILs and Ki-67 to predict patient outcome




An increase in TILs or a decrease in Ki-67 was associated with a higher probability of pCR in the overall study cohort (Fig. 6A; univariate logistic regression).
An increase in TILs or a decrease in Ki-67 was associated with a longer DFS in HR-/HER2- breast cancer. but not within the other subtypes (Fig. 6B).

## Conclusions

- **Intermediate biopsies can identify patients that are unlikely to respond to treatment.** However, it is not suitable for pCR prediction as the probability in patients with negative biopsies is 50%.
- **Intermediate biopsies might be useful for translational biomarker discovery** to study mechanisms of therapy resistance.
- **Intermediate biopsies might be used to tailor therapy concepts** for patients at high risk for non-pCR within clinical trials.
- **Further studies are needed** to evaluate if a standardized biopsy procedure during neoadjuvant treatment can improve diagnostic sensitivity and can be used to adapt the planned treatment strategy.

## References

1. von Minckwitz G, et al. Ann Oncol 2014;25:81-9, 2. von Minckwitz G, et al. Ann Oncol 2014;25:2363-72
3. von Minckwitz G, et al. Lancet Oncol 2014;15:747-56

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