Germline mutation status of *BRCA*1/2 and other breast cancer predisposition genes as predictive and prognostic biomarker: Results of the GeparX study (GeparX-BRCA)

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Background

There is accumulating evidence that the RANK/RANKL signaling pathway plays a pivotal role in breast tumorigenesis, particularly in the development of *BRCA1*-mutated tumors. Studies using bone-modifying agents as adjuvant therapy showed reduced rates of bone metastases and improved breast cancer (BC) survival, as well as prevention of treatment-induced skeletal events.[1, 2, 3]

The GeparX (GBG88; NCT02682693) clinical trial[4] assessed the use of denosumab in patients with primary BC as an adjunct to neoadjuvant chemotherapy for its ability to enhance pathological complete response (pCR) rate and to improve outcome. In a 2x2 randomization a total of 780 patients were first randomized to receive or not receive denosumab 120 mg every 4 weeks (q4w) followed by the randomization to nab-paclitaxel 125 mg/m^2 weekly or days 1 and 8 every 3 weeks (d1,8 q22) for 4 cycles, both followed by 4 cycles of epirubicin/cyclophosphamide, 90/600 mg/m^2 q2w or q3w at investigator's discretion (**Figure 1**). Overall, the pCR (ypT0 ypN0) rate was 41% with denosumab vs 43% without; nab-paclitaxel at a dosage of 125 mg/m^2 weekly resulted in a significantly higher pCR rate of 45% vs 39% with a dosage of 125 mg/m^2 d1,8 q22.

Research question: Does the germline mutation status of *BRCA1/2* and other BC predisposition genes affect treatment outcome in the GeparX study?

Patients and Methods

Genetic germline analyses assessing pathogenic variants in *BRCA1/2* and 16 other BC predisposition genes were performed at the Center for Familial Breast and Ovarian Cancer, Cologne, Germany; 767 patients were included in this exploratory analysis (308 triple-negative BC [TNBC], 306 human epidermal growth factor-2 -negative [HER2-]/hormone receptor-positive [HR+] BC, 153 HER2-positive [HER2+] BC). Due to small patient numbers, the mutation prevalence of *BRCA*1/2 was summarized.

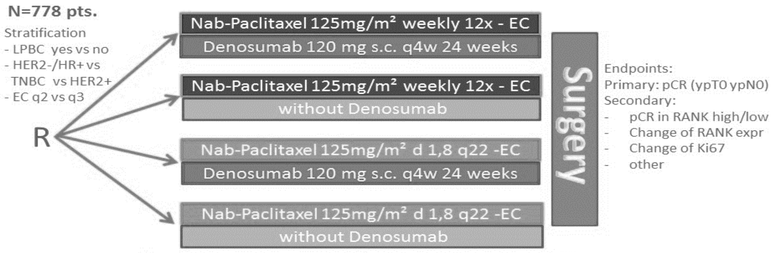


Figure 1: GeparX study design

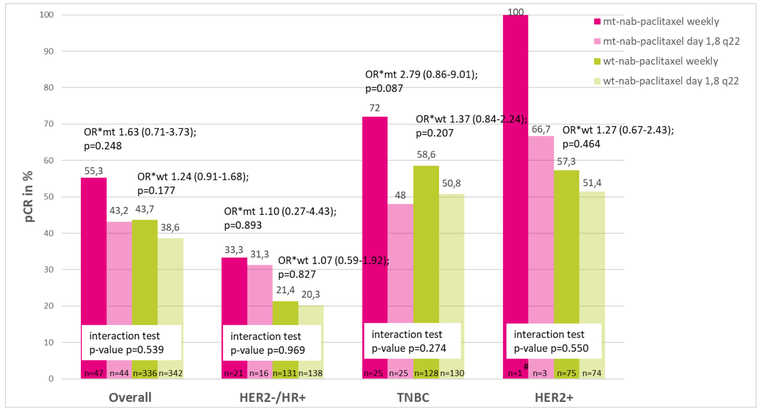
Results

Germline *BRCA1/2* mutations were present in 91/767 patients (11.9%), with a higher mutation prevalence in TNBC (50/308, 16.2%) and HER2-/HR+ BC (37/306, 12.1%), and a low mutation prevalence in HER2+ BC (4/153, 2.6%). Overall, the pCR rate (ypT0 ypN0) was elevated in *BRCA1/2* mutation carriers vs non-carriers (49.5% vs 41.1%; **Table 1**). Highest pCR rates were observed in TNBC in *BRCA1/2* mutation carriers vs non-carriers (60% vs. 54.7%) disregarding HER2+ due to low prevalence of *BRCA*1/2 mutations. Regarding treatment arms, both *BRCA1/2* mutation carriers and non-carriers numerically benefitted most from nab-paclitaxel at a dosage of 125 mg/m^2 weekly vs 125 mg/m^2 d1,8 q22 (55.3% vs 43.2% for *BRCA*1/2 mutation carriers, respectively; OR 1.63, 95% CI 0.71-3.73; 43.7% vs 38.6% for non-carriers, respectively; OR 1.24, 95% CI 0.91-1.68; interaction test p-value 0.539, **Figure 2**). No beneficial effect was observed for denosumab vs no denosumab (51.1% vs 47.8% for *BRCA*1/2 mutation carriers, respectively; OR 1.14, 95% CI 0.50-2.60; 40.3% vs 41.9% for non-carriers, respectively; OR 0.94, 95% CI 0.69-1.27, **Figure 3**). Of the 617 *BRCA1/2*-negative patients, 59 patients carried mutations in other BC predisposition genes which did not predict therapy response compared to patients without any mutation.

Table 1: pCR rates (ypT0 ypN0) by primary mutation definition (*BRCA1* and *BRCA2*)

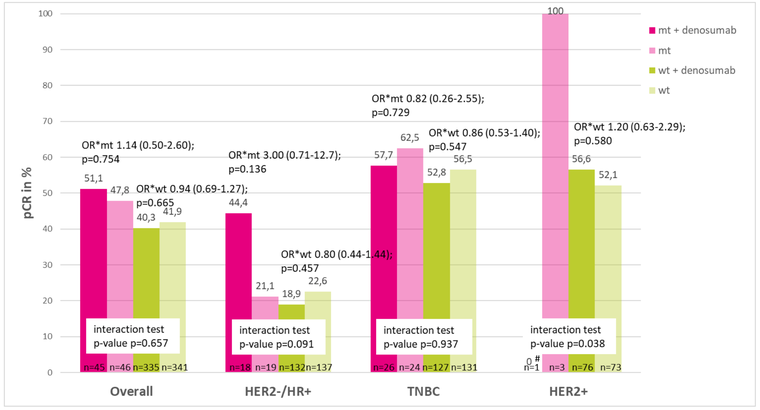
	***BRCA*1/2 mt N of N (%;[95% CI])**	***BRCA*1/2 wt N of N (%;[95% CI])**	**p-value (Fisher exact test) and OR**
all patients	45 of 91 (49.5% [38.8, 60.1])	278 of 678 (41.1% [37.4, 44.9])	p=0.142, OR 1.40; 95% CI 0.90-2.17
HER2-/HR+	12 of 37 (32.4% [18.0, 49.8])	56 of 269 (20.8% [16.1, 26.2])	p=0.138, OR 1.83; 95% CI 0.86-3.88
HER2+	3 of 4 (75.0% [19.4, 99.4])	81 of 149 (54.4% [46.0, 62.5])	p=0.627, OR 2.52; 95% CI 0.25-25.62
TNBC	30 of 50 (60.0% [45.2, 73.6])	141 of 258 (54.7% [48.4, 60.8])	p=0.536, OR 1.24; 95% CI 0.67-2.32

mt, mutant; wt, wildtype; OR, Odds ratio; CI, confidence intervall



mt, mutant; wt, wildtype; OR, Odds ratio; # only descriptive analysis (too few events)

Figure 2: pCR rates (ypT0 ypN0), by chemotherapy arm (weekly vs day 1,8 q22) and primary mutation definition (*BRCA1* and *BRCA2*)



mt, mutant; wt, wildtype; OR, Odds ratio; # only descriptive analysis (too few events)

Figure 3: pCR rates (ypT0 ypN0), by denosumab arm and primary mutation definition (*BRCA1* and *BRCA2*)

Conclusions

Irrespective of the treatment arm, higher pCR rates were observed in *BRCA1/2* mutations carriers vs non-carriers. Both *BRCA1/2* mutation carriers and non-carriers numerically benefitted most from weekly nab-paclitaxel. Absolute smaller differences were observed for denosumab in either group.

References

1. Link et al.: RANK expression as an independent predictor for response to neoadjuvant chemotherapy in luminal-like breast cancer - a translational insight from the GeparX trial. Clin Cancer Res. 2023 Sep 19. doi: 10.1158/1078-0432.CCR-23-1801.
2. Gerber et al.: Pathological Response in the Breast and Axillary Lymph Nodes after Neoadjuvant Systemic Treatment in Patients with Initially Node-Positive Breast Cancer Correlates with Disease Free Survival: An Exploratory Analysis of the GeparOcto Trial. Cancers (Basel) 2022. 14(3).
3. Schneeweiss et al.: Survival analysis of the randomised phase III GeparOcto trial comparing neoadjuvant chemotherapy of intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for patients with high-risk early breast cancer. 2022. Eur J Cancer 160: 100-111.
4. 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 Oncology 2022 Jul 1;8(7):1010-1018.

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