Germline mutation status and therapy response in high-risk early breast cancer: Results of the GeparOcto study (NCT02125344)

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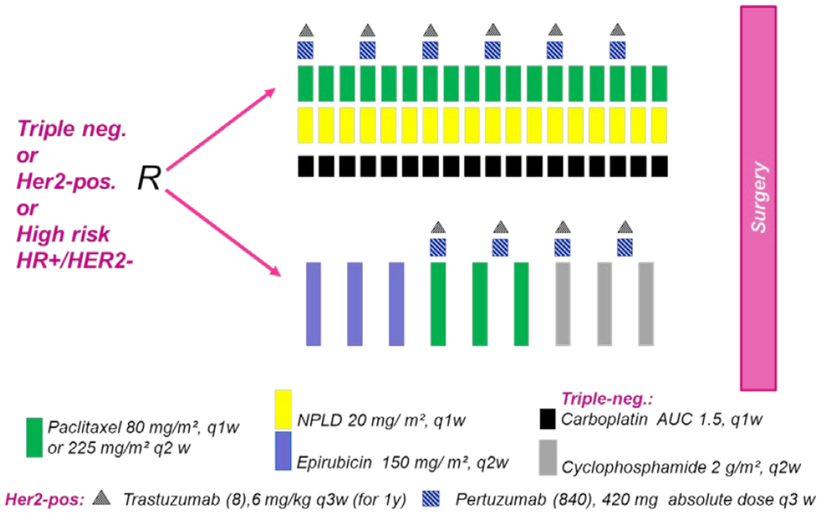
Background

GeparOcto compared the efficacy of two neoadjuvant treatment regimens in high-risk early breast cancer (BC): Sequential intense dose-dense epirubicin, paclitaxel, and cyclophosphamide (iddEPC) and weekly paclitaxel plus non-pegylated liposomal doxorubicin (PM), plus carboplatin (PMCb) in triple-negative BC (TNBC) (**Figure 1**). Overall, there was no difference in pathologic complete response (pCR, ypT0/is ypN0) rates [1]. Here, we analyzed pCR rates according to germline mutation status.

Figure 1. Study design. Patients with TNBC, high-risk HER2-/HR+ BC, or HER2+ BC were randomized to one of the two treatment arms, iddEPC or PM(Cb).



NPLD, non-pegylated liposomal doxorubicin; AUC, area under curve

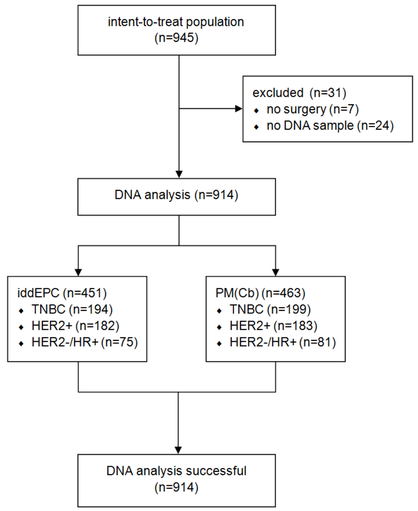
References

1. Schneeweiss et al. Eur J Cancer. 2019 Jan; 106:181-192.

Patients and Methods

Next generation sequencing (NGS)-based germline mutation analysis of *BRCA1, BRCA2,* and 16 further BC (candidate) predisposition genes (*ATM, BARD1, BRIP1, CDH1*, CHEK2, FANCM, MRE11A*, NBN, PALB2, PTEN*, RAD50, RAD51C, RAD51D*, STK11*, TP53, XRCC2*; *no mutation identified) was carried out in 914 patients: 393 patients with TNBC (iddEPC n=194, PMCb n=199), 156 patients with high-risk HER2-/HR+ BC (iddEPC n=75, PM n=81), and 365 patients with HER2+ BC (iddEPC n=182, PM n=183) (**Figure 2**).
Deleterious (International Agency for Research on Cancer (IARC) class 4/5) variants were validated by Sanger sequencing. Detection of copy number variations (CNV) was carried out using an in-house CNV detection tool and established open access tools. Validation of CNVs was performed by either Multiplex Ligation-dependent Probe Amplification (MLPA) or real-time polymerase chain reaction.

Figure 2. Flow diagram.



Results

The *gBRCA1/2* mutation prevalence was 17.6% (69/393) in TNBC, 14.1% (22/156) in high-risk HER2-/HR+ BC, and 1.4% (5/365) in HER2+ BC.
Overall and in subgroups of TNBC and high-risk HER2-/HR+ BC, patients with *gBRCA1/2* mutations achieved higher pCR rates than *gBRCA1/2* wildtype patients with a higher benefit in the PM(Cb) arm. In the HER2+ BC subgroup, the *gBRCA1/2* mutation prevalence was too low to obtain meaningful results (**Figure 3&4**).
Of the *gBRCA1/2* wildtype patients, 9.3% (76/818) carried germline mutations in non-*BRCA1/2* predisposition genes. In this subgroup, pCR rates were similar to those observed in patients without any mutation.

Figure 3. *gBRCA1/2* mutation status and pCR rates overall and in subgroups of TNBC, high-risk HER2-/HR+, and HER2+ BC.

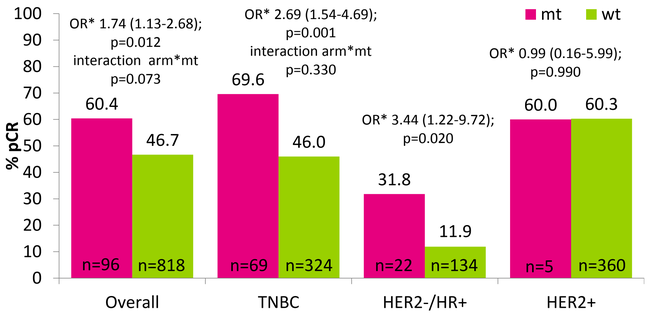
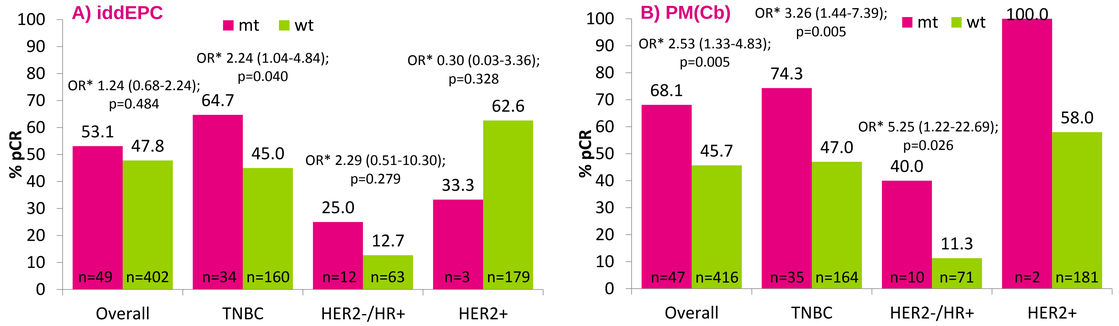


Figure 4. *gBRCA1/2* mutation status and pCR rates overall and in subgroups of TNBC, high-risk HER2-/HR+, and HER2+ BC per treatment arm A) iddEPC (n=451) and B) PM(Cb) (n=463).



mt, mutant; wt, wildtype; OR, odds ratio; *univariate logistic regression

Conclusions

Patients with *gBRCA1/2* mutations showed most benefit from neoadjuvant treatment with highest pCR rates achieved in the *gBRCA1/2* TNBC / PMCb group. The role of carboplatin for neoadjuvant treatment of *gBRCA1/2* TNBC should be further explored. Mutations in further BC predisposition genes are unlikely to predict therapy response.

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