Germline mutation status and therapy response in patients with homologous recombination deficient, HER2-negative early breast cancer: Results of the GeparOLA study (NCT02789332)

Jan Hauke[1], Corinna Ernst[1], Peter A. Fasching[2], Christian Jackisch[3], Fenja Seither[4], Peter Klare[5], Kerstin Rhiem[1], Sabine Schmatloch[6], Jens Huober[7], Andrea Stefek[8], Sabine Seiler[4], Christoph Uleer[9], Gabriele Doering[10], Andreas Schneeweiß[11], Carsten Denkert[12], Michael Untch[13], Jens-Uwe Blohmer[14], Rita K. Schmutzler[1], Sibylle Loibl[4], Eric Hahnen[1]

[1] Center for Familial Breast and Ovarian Cancer and Center for Integrated Oncology (CIO), Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany; [2]University Hospital Erlangen, Erlangen, Germany; [3]Sana Klinikum Offenbach GmbH, Offenbach, Germany; [4]German Breast Group (GBG), Neu-Isenburg, Germany; [5]MediOnko-Institut GbR Berlin, Berlin, Germany; [6]Elisabeth Krankenhaus Kassel, Kassel, Germany; [7]Ulm University Medical Center, Ulm, Germany; [8]Johanniter-Krankenhaus Genthin-Stendal, Stendal, Germany; [9]Gemeinschaftspraxis Hildesheim, Hildesheim, Germany; [10]Hämato-Onkologie im Medicum Bremen, Bremen, Germany; [11] National Center for Tumor Diseases,University of Heidelberg, Heidelberg, Germany; [12]Institut für Pathologie, Philipps-Universität Marburg und Universitätsklinikum Marburg; [13]Department of Gynecology and Obstetrics, Helios Klinikum Berlin-Buch, Berlin, Germany; [14]Charité, Department of Gynecology, Berlin, Germany.

P86

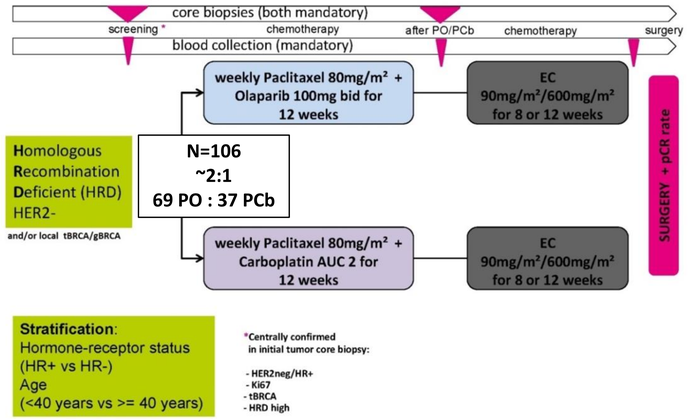
Background

The phase II GeparOla study randomized patients with homologous recombination deficient (HRD), HER2-negative early breast cancer to receive neoadjuvant treatment with paclitaxel plus either olaparib (PO) or carboplatin (PCb) prior to epirubicin /cyclophosphamide (EC). We determined pathological complete response (pCR, ypT0/is ypN0) according to treatment arm and germline mutation status

Patients and Methods

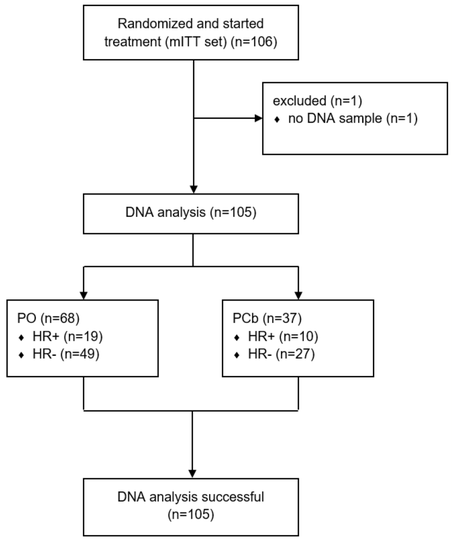
Overall 105 patients (68 in PO and 37 in PCb arm) were analyzed by next generation sequencing (NGS)-based germline mutation analysis for mutations in *BRCA1/2* and 16 other cancer predisposition genes [1] (*ATM, BARD1, BRIP1, CDH1, CHEK2, FANCM, MRE11A, NBN, PALB2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53, XRCC2*) (Fig. 2). Bioinformatic analyses were carried out using VARBANK 2.0 as previously described [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 [3]. Validation of CNVs was performed by either Multiplex Ligation-dependent Probe Amplification (MLPA) or real-time polymerase chain reaction. The definition of mutation status contains pathogenic mutations on the genes *BRCA1/2* regardless of mutations in 16 non *BRCA1/2* genes. The pCR rates were compared using a two-sided continuity corrected $\chi 2$-test.

Figure 1: Study design



Results

Figure 2: Flow diagram



- The *gBRCA1/2* mutation prevalence was 56.2% (59/105) overall, 72.4% (21/29) in HR+ and 50.0% (38/76) in HR- breast cancer.
- Nine of the 46 *BRCA1/2* wild type patients carried mutations in additional genes analyzed.
- Overall pCR rates were significantly higher in patients with *gBRCA1/2* mutations than in patients without. This could also be observed in subgroup of HR+ BC (Fig. 3).
- A trend towards a significant difference between gBRCA1/2 carriers vs non-carriers could be seen in the PCb but not in the PO arm (Fig. 4)
- Differences in pCR rates between PO and PCb arm were not significant for patients with *gBRCA1/2* mutations (61.0% vs 66.7%, p=0.901) or patients without mutation (48.1% vs 31.6%, p=0.412).
- Regardless of the treatment arm, pCR rates were higher in patients with HR- than in patients with HR+ breast cancer .

Figure 3: *gBRCA1/2* mutation status and pCR rates overall and in subgroups by hormone receptor status

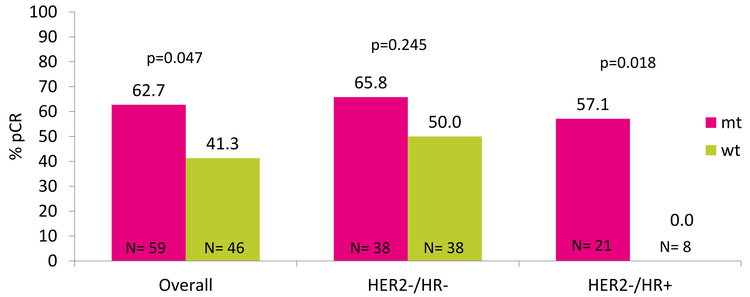
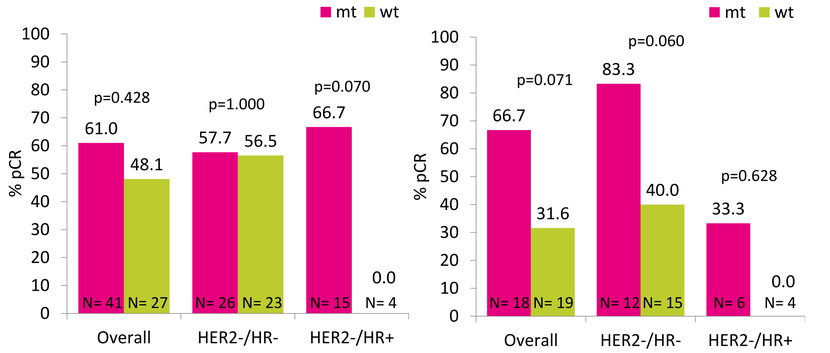


Figure 4: *gBRCA1/2* mutation status and pCR rates overall and in subgroups of HR- and HR+ breast cancer per treatment arm



Conclusions

Even in patients with HRD tumors, germline *BRCA1/2* mutation status predicts therapy outcome. For patients without *gBRCA1/2* mutations, numerically higher pCR rates were observed in the PO arm vs the PCb arm. Overall results should be interpreted with caution due to limited sample size but may guide future clinical trials.

References

1. Easton DF, Pharoah PD, Antoniou AC, et al. Gene-Panel Sequencing and the Prediction of Breast-Cancer Risk. N Engl J Med. 2015.
2. Hahnen E, Lederer B, Hauke J, et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncology.
3. Plagnol V, Curtis J, Epstein M, et al. A robust model for read count data in exome sequencing experiments and implications for copy number variant calling. Bioinformatics. 2012.

Conflicts of interest

The first author has no conflicts of interest to declare.

Presented at: ESMO Virtual Congress, 19-21 September 2020.

The trial was financially supported by AstraZeneca. Support for research and genetic analyses was provided by the Köln Fortune Program, Faculty of Medicine, University of Cologne, Germany.