A randomised phase III trial comparing two intense dose-dense approaches (ETC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto)

#118

Schneeweiss A[1], Möbus V[2], Tesch H[3], Hanusch C[4], Denkert C[5], Lübbe K[6], Huober J[7], Klare P[8], Kümmel S[9], Untch M[10], Kast K[11], Jackisch C[12], Thomalla J[13], Ingold Heppner B[5], Blohmer J U[5], Rezai M[14], Frank M[15], Nekljudova V[16], von Minckwitz G[16], Loibl S[16]

[1]Universitätsklinikum Heidelberg, Germany; [2]Klinikum Frankfurt-Höchst, Germany; [3]Praxis Bethanien, Frankfurt, Germany; [4]Klinikum zum Roten Kreuz, München, Germany; [5]Institut für Pathologie, Charité-Universitätsmedizin, Berlin, Germany; [6]Henriettenstiftung Hannover, Germany; [7]Universitäts-Frauenklinik, Ulm, Germany; [8]Praxisklinik Krebsheilkunde für Frauen Berlin, Germany; [9]Breast Unit Kliniken Essen-Mitte, Essen, Germany; [10]HELIOS Klinikum Berlin Buch, Germany; [11]Universitätsklinikum, Dresden, Germany; [12]Sana Klinikum Offenbach, Germany; [13]Praxisklinik für Hämatologie und Onkologie Koblenz, Germany; [14]Luisenkrankenhaus Düsseldorf, Germany; [15]Ortenau Klinikum, Germany; [16]German Breast Group Neu-Isenburg, Germany

Background

Two chemotherapy regimens are currently considered to be among the treatments with the highest efficacy in patients with high-risk early stage breast cancer: sequential treatment of intense dose-dense (idd) epirubicin (E), paclitaxel (T), and cyclophosphamide (ETC) mainly based on the AGO ETC adjuvant study[1], and weekly treatment of paclitaxel in combination with non-pegylated liposomal doxorubicin (NPLD) and with a dual HER2-blockade for HER2-positive disease or carboplatin (Cb) for triple negative breast cancer (TNBC) (PM(Cb)) based on the GeparSixto study.[2]

The aim of the GeparOcto study was to compare efficacy and safety of the ETC with PM(Cb) treatment regimen.

Materials and Methods

Trial design: GeparOcto (GBG 84; NCT02125344) was a multicentre, prospective, randomised, open-label phase III study. The study design is presented in Figure 1.

Statistical considerations: Sample size calculations assumed a pCR rate of 50% for ETC and 60% for PM(Cb), requiring 950 patients to show significant superiority (p<0.05) of PM(Cb) with 85% power. The significance level was set to a two-sided α=0.05. An amendment implemented conduction of a non-inferiority test in case the superiority test fails to detect a significant difference. The non-inferiority margin for pCR-rate difference was set to 5%.

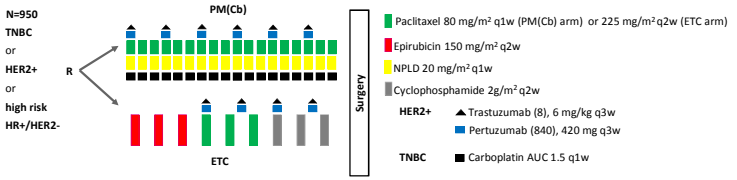
Objectives

Primary objective: pCR defined as ypT0/is ypN0

Secondary objectives:

- pCR defined as ypT0 ypN0
- pCR rates per arm separately for the stratified subpopulations (HER2+ HR+/- vs HER2- HR+ vs TNBC
- Toxicity and compliance
- Loco-regional invasive recurrence free (LRRFS), distant-disease-free (DDFS), invasive disease-free (IDFS), and overall survival (OS) in both arms and according to stratified subpopulations

Figure 1. Main study design



Results

Figure 2. Consort statement

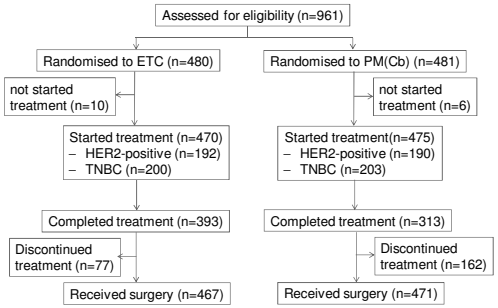


Table 1. Baseline characteristics

Parameter	Category	ETC (n=470) N (%)	PM(Cb) (n=475) N (%)
Age, years	Median (range)	48.0 (23.0-76.0)	48.0 (21.0-76.0)
cT	cT1-3	453 (96.4)	456 (96.0)
	cT4a-c	8 (1.7)	5 (1.1)
	cT4d	9 (1.9)	14 (2.9)
cN	positive	214 (45.9)	217 (46.6)
ER/PgR	ER and/or PgR positive	207 (44.0)	219 (46.1)
HER2	positive	192 (40.9)	190 (40.0)
Tumor grading	G1	8 (1.7)	10 (2.1)
	G2	158 (33.6)	144 (30.3)
	G3	304 (64.7)	321 (67.6)
Histological tumor type	ductal/ductal-lobular invasive	382 (81.3)	392 (82.5)
	other	88 (18.7)	83 (17.5)

Table 2. Most common SAEs

SAEs	ETC N	PM(Cb) N
Leukopenia	26	3
Neutropenia	40	0
Febrile neutropenia	43	10
Diarrhoea	3	21
Nausea	6	0
Fatigue	1	4
General physical health deterioration	13	3
Pneumonitis*	2	15
Pneumonia	3	31

*AE of special interest (AESI)

Overall 175 (37.2%) patients in the ETC and 173 (36.4%) in the PM(Cb) arm had at least one SAE. Nine (1.9%) patients in the ETC and 24 (5.1%) in the PM(Cb) arm had at least one AE of special interest. Two deaths in the PM(Cb) arm were reported during study treatment (one due to pneumonia and one due to multiple septic cerebral embolism).

Figure 3. pCR (ypT0/is ypN0) rates by treatment arms (A) and by subtypes (B)

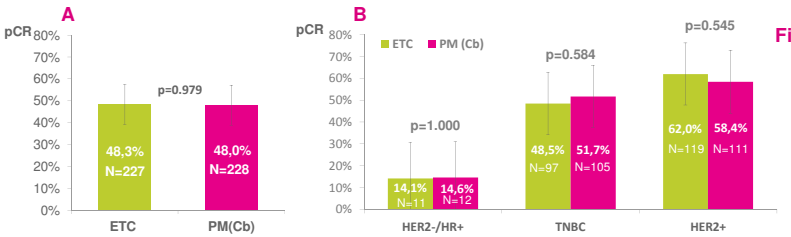
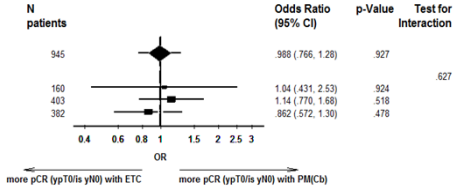


Figure 4. pCR (ypT0/is ypN0): odd ration (OR) overall and in subtypes



Conclusions

In high-risk early stage breast cancer patients, pCR (ypT0/is ypN0) rates of idd ETC compared to weekly PM(Cb) were not significantly different. Non-inferiority of PM(Cb) could not be shown. No significant difference was observed for pCR rates between the two treatment arms according to biological subtypes. PM(Cb) was associated with a higher rate of pneumonia and pneumonitis than ETC. PM(Cb) appeared to be less feasible for high-risk early stage breast cancer patients.

References

1. Moebus V, Jackisch C, Lueck HJ, et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. J Clin Oncol. 2010;28:2874-80.
2. von Minckwitz G, Schneeweiss A, Loibl S, 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;15:747-56.

Presented at ASCO Annual Meeting 2017, Chicago, Illinois, USA, June 2-6, 2017

Financial and Drug Supply was provided by Roche, Amgen, Teva, Vifor