CLINICAL STUDY REPORT

A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/ carboplatin followed by epirubicin/ cyclophosphamide as neoadjuvant chemotherapy in patients with HER2-negative early breast cancer and Homologous Recombination Deficiency (HRD patients with deleterious *BRCA*1/2 tumor or germline mutation and/or HRD score high)

(GeparOLA)

EudraCT No.: 2015-003509-41

Investigational Products:	Olaparib / Carboplatin
Indication:	Neoadjuvant treatment of HER2-negative breast cancer
Study Protocol:	GBG 90 (Version 3 – 26-Mar-18)
Phase:	II
Report Version:	V2.0
First Patient Enrolled:	September 21, 2016
Last Patient Completed:	January 23, 2019
Coordinating Investigator	Prof. Dr. Peter A. Fasching Universitätsklinikum Erlangen Universitätsstraße 21-23, 91054 Erlangen
Sponsor	GBG Forschungs GmbH Martin-Behaim-Straße 12 63263 Neu-Isenburg
Date of this report:	September 10, 2020
Date of any previous reports:	n.a.

2. SYNOPSIS

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Title of Study:

A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients with HER2-negative early breast cancer with Homologous Recombinant Deficiency (HRD) (HRD patients with deleterious BRCA1/2 tumor or germline mutation and/or HRD score high) (GeparOLA)

Changes in the Conduct of the Study

The original study protocol (Version 1 from 17.02.16) was amended two times.

Amendment 1: The study protocol version 1.0 from 17.02.2016 was submitted for approval only by the respective Ethics Committees. This version was amended before submission of the study protocol for approval by the respective competent federal authority (BfArM) and included the following changes:

- The protocol version 1.0 was updated to version 2.0 (11.05.2016);
- The Gepar-PET-substudy was dropped;
- The title of the radiotherapy appendix 18.5 was renamed;
- Editing of the text was performed.

Amendment 2: The protocol amendment 2 (protocol version 3 from 26.03.2018) included the following changes:

- The Protocol version 2.0 was updated to version 3.0 (26.03.2018);
- Inclusion criterion #6 from the study protocol was modified as follows: performance of MRI assessment was allowed;
- In the German synopsis of the study protocol, exclusion criteria #12 was edited;
- In Section 9.8.1.2: Prohibited Medications of the study protocol, the text was corrected as follows: Sex hormones are not allowed. Prior treatment should be stopped before study entry. The use of GnRH- analogues for ovarian protection is permitted;
- Subboard members were updated.

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Publication (reference):

- Fasching PA, Blohmer JU, Burchardi N et al. A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel / carboplatin followed by epirubicin / cyclophosphamide as

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neoadjuvant chemotherapy in patients with HER2-negative early breast cancer and homologous recombination deficiency (HRD): GeparOLA. J Clin Oncol 2016; 34.15_suppl.TPS1096; trial in progress

- Fasching PA, Jackisch J, Rhiem K et al. GeparOLA: A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients (pts) with HER2-negative early breast cancer (BC) and homologous recombination deficiency (HRD). J Clin Oncol 2019; 37.15_suppl.506; oral presentation

Studied Period (years):

Date of the first patient enrolled: September 21, 2016

Date of the last patient completed: January 23, 2019

Phase of Development:

Phase II

Objectives:

Primary Objectives:

To assess the pathological complete response rate (pCR=ypT0/is ypN0) of neoadjuvant paclitaxel plus olaparib (PO) followed by epirubicin and cyclophosphamide (EC) (PO→EC) in patients with early breast cancer and HRD tumors defined as either tumor (t) or known germline (g) *BRCA*1/2 mutation or HRD score high.

Secondary Objectives:

Short-term secondary objectives:

- To assess the pCR rates (ypT0/is ypN0) of patients receiving paclitaxel and carboplatin (PCb) followed by EC (PCb→EC) and to compare them with the pCR rates of patients receiving PO→EC
- To assess the pCR rates (ypT0/is ypN0) in the stratified subgroups of hormone receptor (HR) status (HR-positive vs HR-negative) and age (<40 years vs ≥40 years)
- To determine other pCR rates (ypT0 ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT(any) ypN0) of patients receiving PO→EC and to compare them with the pCR rates of patients receiving PCb→EC
- To assess the pCR rate in HRD tumors with vs without t*BRCA* 1/2 mutation
- To determine the clinical/imaging response rates after taxane and before surgery based on physical examination and imaging tests (sonography, mammography, or MRI) with PO→EC and to compare it with PCb→EC
- To determine the breast conservation rate with PO→EC and to compare it with PCb→EC
- To assess the toxicity and compliance of PO→EC and to compare it with PCb→EC

Long-term secondary objectives (to be analyzed at a later time point):

- Invasive disease-free survival (iDFS)
- Distant disease-free survival (DDFS)
- Locoregional invasive recurrence-free survival (LRRFS) changed to locoregional invasive recurrence-free interval (LRRFI) in the SAP
- Local recurrence-free survival (LRFS) changed to local invasive recurrence-free interval (LRRFI) in the SAP
- Regional recurrence-free survival (RRFS) changed to regional recurrence-free interval (RRFI) in the SAP
- Overall survival (OS)

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The LRFI and RRFI objectives will not to be analyzed due to the small number of planned patients that will result in low number of events.

Translational exploratory objectives (to be analyzed at a later time point):

- To correlate co-occurring mutations detected by next generation sequencing (NGS) in lymphocytes or in tumor cells with pCR
- To investigate potential biomarkers predicting safety and compliance, like SNPs, TILs, PARP, 53BP1, REV7 and other biomarkers considered for breast cancer

Methodology:

This was a multicenter, prospective, randomized, open-label phase II study evaluating the efficacy and safety of PO→EC as neoadjuvant treatment for operable and locally advanced breast cancer in patients with HRD. Randomization was stratified by HR status (HR-positive vs HR-negative) and age (< 40 years vs ≥ 40 years).

In both study arms, treatment was given until surgery, disease progression, unacceptable toxicity, or withdrawal of patient's consent.

Number of patients (planned and analyzed):

planned: 102, screened: 274, randomized: 107, analyzed (efficacy, mITT set): 106, analyzed (safety set): 106

Diagnosis and Main Criteria for Inclusion:

The study included patients of at least 18 years of age with unilateral or bilateral primary carcinoma of the breast, histologically confirmed by core biopsy and measurable disease (i.e. tumor lesion in the breast with maximum diameter ≥2 cm by palpation or ≥1 cm by sonography; measurable in two dimensions).

Patients had to have stage cT2-cT4a-d disease or cT1c and cN-positive or cT1c and pN_{SNB} (sentinel-node biopsy)-positive, or cT1c and both estrogen receptor (ER)-negative and progesterone receptor (PgR)-negative, or cT1c and Ki-67 >20%. Patients with centrally confirmed negativity of human epidermal growth factor receptor 2 (HER2) status (defined as either immunohistochemistry less than 3+ or *in-situ* hybridisation of ratio <2.0), ER and PgR status (positivity defined as ≥1% stained cells) and Ki-67 status detected on core biopsy were eligible.

Homologous Recombinant Deficiency (t*BRCA*1/2 mutation and/or HRD high) of the tumor had to be centrally confirmed prior to randomization. Patients with known g/t *BRCA*1/2 mutation could be enrolled prior to the central test results available. Only patients with no prior use of a PARP-inhibitor were eligible.

Investigational Products, Dose and Mode of Administration, Batch Number:

- Olaparib 4 x 25mg tablets twice daily for 12 weeks; batch numbers: 092016, 072017
- Carboplatin AUC 2 on day 1, 8, 15, q day 22 for 4 cycles

Non-investigational products, Dose and Mode of Administration

- Paclitaxel 80 mg/m² i.v. weekly for 12 weeks (day 1, 8, 15, q d 22 for 4 cycles).
- Epirubicin: 90 mg/m² i.v. on day 1 q day 15 or 22 in combination with cyclophosphamide 600 mg/m² i.v. on day 1 q day 15 or 22 for 4 cycles

Olaparib was provided as trial medication. Carboplatin, paclitaxel and EC were used according to marketed formulation via standard procedures at each site and applied according to recommendations of the manufacturers.

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Test Therapy:

Paclitaxel and olaparib followed by epirubicin/ cyclophosphamide

Duration of Treatment:

PO→EC treatment: paclitaxel and olaparib were given for 12 weeks, followed by 8 or 12 weeks of EC.

PCb→EC treatment: paclitaxel and carboplatin were given for 12 weeks, followed 8 or 12 weeks of EC.

The entire treatment period was 2.5 years (24 months recruitment + 6 months treatment duration).

Reference Therapy, Dose and Mode of Administration, Batch Number:

Paclitaxel and carboplatin followed by epirubicin/ cyclophosphamide. See above for details on dose and mode of administration

Criteria for Evaluation:

Efficacy:

Primary endpoint: pCR of breast and lymph nodes (ypT0/is ypN0) defined as no microscopic evidence of residual invasive viable tumor cells in all resected specimens of the breast and axilla.

Secondary endpoints:

Short-term secondary endpoints:

- pCR defined as ypT0 ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT(any) ypN0 according to the TNM classification (Edition 7)
- Breast conservation rate defined as tumorectomy, segmentectomy or quadrantectomy as most radical surgery after each treatment
- Clinical /imaging response after taxane and before surgery

Long-term secondary endpoints and translational exploratory endpoints will be analyzed at a later time point and are not part of this report.

Safety:

Tolerability and safety were assessed on the basis of adverse events, serious adverse events, adverse events of special interest, and treatment discontinuations. Toxicity grades were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Statistical Methods: Analyses were based on the modified intent-to-treat (mITT) set, the Per-Protocol analysis set and the Evaluable Subset for Safety (safety set).

Sample Size: the sample size calculation was based on the following assumptions:

- pCR rate of 55% or lower was to be excluded with α=0.1 and power 1-β=80% to support a subsequent phase III study. Assuming a pCR rate of 70%, this required 65 evaluable patients treated with PO→EC for two-sided one group chi-square test. The study would be positive, if the observed pCR was ≥ 65% since the observed pCR rate had to be ≥ 65% for the lower 90% confidence interval (CI) not to include 55%.
- pCR rate in the PCb→EC was expected to be between 50 and 60% based on previous data (von Minckwitz et al. 2014; Sikov et al. 2015) and therefore an inclusion of 37 patients in this randomization arm would provide a point estimate with a 90% CI of 27% width (point estimate – 13.5%, point estimate + 13.5%)

It was planned to recruit 102 (65+37) eligible subjects into this study.

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Primary efficacy endpoint analysis: The primary endpoint was summarized as pCR (ypT0/is ypN0) rate for the PO→EC group. One group chi-square test was performed to exclude a pCR rate of 55% or lower in the PO→EC arm. Two-sided 90% CIs were calculated according to Pearson and Clopper (Pearson and Clopper 1934). The significance level was set to two-sided α=0.1. There was no adjustment for multiple comparisons in the analyses for the stratified subpopulations. A logistic regression analysis correcting for the stratification factors (HR status and age) and other baseline factors was conducted for an exploratory comparison of the two treatment arms regarding the primary endpoint.

Secondary efficacy endpoint analysis: The key secondary exploratory short-term endpoint was summarized as a pCR (ypT0/is ypN0) rate for carboplatin group. The difference in the pCR (ypT0/is ypN0) rates between the treatment arms was evaluated as odds ratio (OR) and the significance was tested with a two-sided continuity corrected chi-square test. The other short-term efficacy endpoints (ypT0 ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT(any) ypN0, responses assessed by histological examination as well as breast conservation rates) were summarized as rates in each treatment group, two-sided 90% CIs were calculated according to Pearson and Clopper, and the continuity corrected chi-square test was performed to evaluate the difference of rates in treatment arms; these tests were considered explorative. For clinical/ imaging response (complete response, partial response, stable disease, or progression) the proportion of patients with success was determined and appropriate confidence intervals were calculated. Patients in whom success could not be determined (e.g. patients in whom histology was not evaluable) were to be included in the denominator, i.e. these patients would affect the success rate in the same way as treatment failures.

Tolerability and Safety: Frequencies of patients, whose treatment had to be reduced, delayed or prematurely discontinued, were to be given for both treatment arms. The reasons for discontinuation included aspects of efficacy (e.g. termination due to tumor progression), safety (e.g. termination due to adverse events) and compliance (e.g. termination due to patient's withdrawal of consent). Incidence of adverse events (AE), serious adverse events (SAE), adverse events of special interest (AESI) were to be descriptively displayed for both treatment arms.

SUMMARY

Efficacy Results (mITT set):

In the GeparOLA study a total of 106 patients (69 in PO→EC arm and 37 in the PCb→EC arm) started therapy, of whom 104 (98.1%; 2 patients in the olaparib arm did not have available data on surgery due to withdrawal of informed consent) underwent surgery.

Primary efficacy results: The analysis of the primary efficacy endpoint showed that 38 out of 69 patients (55.1%, [90%CI 44.5%, 65.3%]) who were treated with olaparib achieved a pCR. A two-sided one-group chi-square test could not exclude a pCR rate of 55% or lower in the olaparib arm (p=0.990) (Table 1).

Short-term secondary efficacy results: exploratory analysis of the key secondary short-term efficacy endpoint demonstrated that 18 out of 37 patients (48.6%, [90%CI 34.3%, 63.2%]) treated with carboplatin achieved a pCR. There was no significant difference in the pCR rates between the two treatment groups (p=0.669), the absolute difference of pCR rates was 6.4% (90%CI -10.3%, 23.1%) with an OR of 1.29 [95%CI 0.58, 2.88]; Wald p=0.528 (Table 1). The pCR (ypT0/is ypN0) rates were numerically higher but not statistically significant in patients treated with olaparib compared to carboplatin with regards to HR-positive status (52.6% [32.0%-72.6%] vs 20.0% [3.7%, 50.7%]; p=0.194) and age < 40 years (76.2% [90%CI 56.3%-90.1%] vs 45.5% [20.0%-72.9%]; p=0.178) (Table 2).

An exploratory multivariate logistic regression analysis confirmed that treatment with olaparib did not predict

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for achievement of a pCR after adjustment for baseline and stratification factors (PO⟶EC vs PCb⟶EC, OR 1.05 [95%CI 0.44-2.48]; p=0.912). Among the stratification factors, only young age was a significant independent predictor for achievement of pCR (≥40 years vs <40 years, OR 0.37 [95% 0.15-0.94]; p=0.036).

Table 1: pCR (ypT0/is ypN0) rates in both treatment arms

pCR (ypT0/is ypN0)	PO⟶EC N(%) N=69	PCb⟶EC N(%) N=37	Overall N(%) N=106	p-value*	p-value**
no	31 (44.9)	19 (51.4)	50 (47.2)	0.990	0.669
yes	38 (55.1)	18 (48.6)	56 (52.8)		
90% CI	(44.5%, 65.3%)	(34.3%, 63.2%)			
Difference (90% CI)			6.4% (-10.3%, 23.1%)		

*one-group chi-square test to exclude a pCR rate of ≤55% in the PO⟶EC arm (primary endpoint); **continuity corrected chi-square test (secondary exploratory endpoint);

Note: 2 patients in the olaparib arm with no available data on surgery due to withdrawal of informed consent were counted as no pCR;

PO⟶EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb⟶EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; pCR, pathological complete response; CI, confidence interval; mITT, modified intent-to-treat.

Table 2: pCR (ypT0/is ypN0) rates in both treatment arms among subgroups

Subgroup	PO⟶EC N(%)	PCb⟶EC N(%)	Overall N(%)	p-value*
HR-positive	**N=19**	**N=10**	**N=29**	
no	9 (47.4)	8 (80.0)	17 (58.6)	0.194
yes	10 (52.6)	2 (20.0)	12 (41.4)	
90% CI	(32.0%, 72.6%)	(3.7%, 50.7%)		
Difference (90% CI)			32.6% (4.6%, 60.7%)	
HR-negative	**N=50**	**N=27**	**N=77**	
no	22 (44.0)	11 (40.7)	33 (42.9)	0.973
yes	28 (56.0)	16 (59.3)	44 (57.1)	
90% CI	(43.4%, 68.0%)	(41.7%, 75.2%)		
Difference (90% CI)			-3.3% (-22.6%, 16.1%)	
Age < 40 years	**N=21**	**N=11**	**N=32**	
no	5 (23.8)	6 (54.5)	11 (34.4)	0.178
yes	16 (76.2)	5 (45.5)	21 (65.6)	
90% CI	(56.3%, 90.1%)	(20.0%, 72.9%)		

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Difference (90% CI)			30.7% (1.7%, 59.8%)	
Age ≥ 40 years	**N=48**	**N=26**	**N=74**	
no	26 (54.2)	13 (50.0)	39 (52.7)	0.921
yes	22 (45.8)	13 (50.0)	35 (47.3)	
90% CI	(33.4%, 58.6%)	(32.7%, 67.3%)		
Difference (90% CI)			-4.2% (-24.2%, 15.8%)	
t*BRCA*1/2 mutated	**N=35**	**N=20**	**N=55**	
no	14 (40.0)	8 (40.0)	22 (40.0)	1.000
yes	21 (60.0)	12 (60.0)	33 (60.0)	
90% CI	(44.7%, 74.0%)	(39.4%, 78.3%)		
Difference (90% CI)			0.0% (-22.6%, 22.6%)	
t*BRCA*1/2 non-mutated	**N=30**	**N=16**	**N=46**	
no	15 (50.0)	10 (62.5)	25 (54.3)	0.617
yes	15 (50.0)	6 (37.5)	21 (45.7)	
90% CI	(33.9%, 66.1%)	(17.8%, 60.9%)		
Difference (90% CI)			12.5% (-12.4%, 37.4%)	
cN-positive	**N=17**	**N=16**	**N=33**	
no	12 (70.6)	8 (50.0)	20 (60.6)	0.394
yes	5 (29.4)	8 (50.0)	13 (39.4)	
90% CI	(12.4%, 52.2%)	(27.9%, 72.1%)		
Difference (90% CI)			-20.6% (-48.0%, 6.9%)	
cN-negative	**N=52**	**N=20**	**N=72**	
no	19 (36.5)	10 (50.0)	29 (40.3)	0.438
yes	33 (63.5)	10 (50.0)	43 (59.7)	
90% CI	(51.1%, 74.6%)	(30.2%, 69.8%)		
Difference (90% CI)			13.5% (-8.0%, 34.9%)	

*continuity corrected chi-square test (secondary exploratory endpoint);

PO→EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb→EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; HR, hormone receptor status; cN, clinical nodal status; t*BRCA1/2*, tumor *BRCA*1/2 mutation; CI, confidence interval; mITT, modified intent-to-treat; pCR, pathological complete response.

- There were no statistically significant differences between treatment groups in the pCR rates according to other definitions as secondary endpoints (Table 3).

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Table 3: pCR rates analyzed as secondary endpoints [ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT(any) ypN0] (mITT Set)

Secondary endpoint definitions of pCR	PO→EC N(%) N=69	PCb→EC N(%) N=37	Overall N(%) N=106	p-value*
ypT0 ypN0				
no	35 (50.7)	20 (54.1)	55 (51.9)	0.902
yes	34 (49.3)	17 (45.9)	51 (48.1)	
90% CI	(38.8%, 59.8%)	(31.8%, 60.6%)		
Difference, 90%CI			3.3% (-13.4%, 20.1%)	
ypT0 ypNany				
no	31 (44.9)	18 (48.6)	49 (46.2)	0.871
yes	38 (55.1)	19 (51.4)	57 (53.8)	
90% CI	(44.5%, 65.3%)	(36.8%, 65.7%)		
Difference, 90%CI			3.7% (-13.0%, 20.4%)	
ypT0/is ypNany				
no	27 (39.1)	17 (45.9)	44 (41.5)	0.637
yes	42 (60.9)	20 (54.1)	62 (58.5)	
90% CI	(50.3%, 70.7%)	(39.4%, 68.2%)		
Difference, 90%CI			6.8% (-9.8%, 23.4%)	
ypTany ypN0				
no	16 (23.2)	10 (27.0)	26 (24.5)	0.841
yes	53 (76.8)	27 (73.0)	80 (75.5)	
90% CI	(66.9%, 84.9%)	(58.5%, 84.5%)		
Difference, 90%CI			3.8% (-10.8%, 18.5%)	

*continuity corrected chi-square test;

Note: 2 patients in PO→EC arm who did not receive surgery were counted as no pCR;

PO→EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb→EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; CI, confidence interval; pCR, pathological complete response; mITT, modified intent-to-treat

- No significant difference was observed between the olaparib and carboplatin group in the proportion of patients receiving breast conserving surgery (Table 4).

Table 4: Breast Conservation Rate (mITT set)

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Breast surgery	PO→EC N(%) N=69	PCb→EC N(%) N=37	Overall N(%) N=106	p-value
Mastectomy	32 (47.8)	12 (32.4)	44 (42.3)	0.191
BCS	35 (52.2)	25 (67.6)	60 (57.7)	
90% CI for BCS	(41.5%, 62.8%)	(52.8%, 80.1%)		
Missing surgery information	2	0	2	

PO→EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb→EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; BCS, Breast conserving surgery; CI, confidence interval; mITT, modified intent-to-treat

- No significant difference was observed between the olaparib and carboplatin group in clinical/ imaging response rates after taxane treatment and before surgery (Table 5).

Table 5: Clinical/ imaging response rates of the breast tumor after taxane and before surgery (mITT population)

	After taxane treatment			Before surgery		
Response	PO→EC N(%) N=69	PCb→EC N(%) N=37	Overall N(%) N=106	PO→EC N(%) N=69	PCb→EC N(%) N=37	Overall N(%) N=106
CR	14 (21.2)	13 (38.2)	27 (27.0)	28 (42.4)	15 (45.5)	43 (43.4)
PR	40 (60.6)	17 (50.0)	57 (57.0)	32 (48.5)	13 (39.4)	45 (45.5)
ORR (CR or PR)	54 (81.8)	30 (88.2)	84 (84.0)	60 (90.9)	28 (84.8)	88 (88.9)
90% CI for ORR	(72.2%, 89.2%)	(75.1%, 95.9%)		(82.8%, 96.0%)	(70.7%, 93.8%)	
Difference, with 90% CI			-6.4% (-18.4%, 5.6%)			6.1% (-5.7%, 17.9%)
p-value*			0.588			0.572
SD	9 (13.6)	4 (11.8)	13 (13.0)	4 (6.1)	4 (12.1)	8 (8.1)
PD	3 (4.5)	0 (0.0)	3 (3.0)	2 (3.0)	1 (3.0)	3 (3.0)
Non-evaluable/missing	3	3	6	3	4	7

*p-value for comparison of ORR;

PO→EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb→EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; CI, Confidence interval; CR, Complete response; ORR, Overall response rate; PD, Progressive disease; PR, Partial response; SD, Stable disease; mITT, modified intent-to-treat.

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Name of active ingredients: Olaparib, Carboplatin	Page:	

Safety Results:

There was no statistically significant difference between treatment arms in terms of overall treatment discontinuation (olaparib arm: 14.5%, carboplatin arm: 24.3%; p=0.288). In the olaparib arm 73.9% of patients and in the carboplatin arm 64.9% completed all study therapies regularly. Overall, the rate of treatment discontinuations with paclitaxel plus olaparib or with paclitaxel plus carboplatin was 10.1% and 16.2%, respectively due mainly to toxic effects (4.3% in the olaparib group and 16.2% in the carboplatin group). EC treatment was discontinued in 4.3% of patients who received paclitaxel plus olaparib and in 8.1% of patients who received paclitaxel plus carboplatin (Table 6).

Table 6: Summary of treatment discontinuations (mITT set)

Status	Reasons for discontinuations	PO→EC N (%)	PCb→EC N (%)	Overall N (%)	p-value
Completed all study medications		51 (73.9)	24 (64.9)	75 (70.8)	0.374
Discontinued at least one study medication		10 (14.5)	9 (24.3)	19 (17.9)	0.288
Discontinued paclitaxel+carboplatin/olaparib		7 (10.1)	6 (16.2)	13 (12.3)	0.370
	Local progression	2 (2.9)	0 (0.0)	2 (1.9)	0.541
	Adverse event	3 (4.3)	6 (16.2)	9 (8.5)	0.063
	Patient's decision	2 (2.9)	0 (0.0)	2 (1.9)	0.541
Discontinued EC		3 (4.3)	3 (8.1)	6 (5.7)	0.419
	Local progression	1 (1.4)	0 (0.0)	1 (0.9)	1.000
	Adverse event	0 (0.0)	2 (5.4)	2 (1.9)	0.120
	Patient's decision	1 (1.4)	1 (2.7)	2 (1.9)	1.000
	Investigator's decision	1 (1.4)	0 (0.0)	1 (0.9)	1.000
Never received EC		11 (15.9)	8 (21.6)	19 (17.9)	0.596
	Local progression	2 (2.9)	0 (0.0)	2 (1.9)	0.541
	Adverse event	0 (0.0)	1 (2.7)	1 (0.9)	0.349
	Patient's decision	1 (1.4)	0 (0.0)	1 (0.9)	1.000
	Investigator's decision*	8 (11.6)	7 (18.9)	15 (14.2)	0.382

*Patients who completed paclitaxel plus olaparib/carboplatin treatment and had no tumor tissue in the core biopsy, might undergo surgery to confirm a pCR per protocol;

PO→EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb→EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; mITT, modified intent-to-treat

The addition of olaparib did not lead to more frequent dose reductions of the underlying paclitaxel and EC therapy compared to carboplatin. A significantly higher frequency of paclitaxel dose reduction due to

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hematological toxicity was observed in the carboplatin arm compared to olaparib arm (10.8% vs 1.4%, respectively; p=0.049) (Table 7).

Table 7: Dose reduction (mITT Set)

Treatment and Reason for dose reduction*	PO→EC N(%) N=69	PCb→EC N(%) N=37	Overall N(%) N=106	p-value
Paclitaxel, any reason	8 (11.6)	9 (24.3)	17 (16.0)	0.102
Hematological AEs related to study medication	1 (1.4)	4 (10.8)	5 (4.7)	0.049
Cardiac toxicity	0 (0.0)	1 (2.7)	1 (0.9)	0.349
Other non-hematoligical AEs related to study medication	6 (8.7)	7 (18.9)	13 (12.3)	0.212
AEs not related to study medication	0 (0.0)	1 (2.7)	1 (0.9)	0.349
Other reasons	1 (1.4)	0 (0.0)	1 (0.9)	1.000
Olaparib, any reason	4 (5.8)			n.a.
Hematological AEs related to study medication	2 (2.9)			n.a.
Other non-hematoligical AEs related to study medication	2 (2.9)			n.a.
Carboplatin, any reason		7 (18.9)		n.a.
Hematological AE related to study medication		3 (8.1)		n.a.
Cardiac toxicity		1 (2.7)		n.a.
Other non-hematoligical AE related to study medication		5 (13.5)		n.a.
AE not related to study medication		1 (2.7)		n.a.
EC, any reason	1 (1.4)	0 (0.0)	1 (0.9)	1.000
Other reasons	1 (1.4)	0 (0.0)	1 (0.9)	1.000

*reasons not reported in both groups are not listed;

Note: Percents for reasons do not necessarily sum up to ANY REASON per patient, because a) reasons were captured as multiple choice and/or b) data are aggregated by patient;

PO→EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb→EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; AE, adverse event; mITT, modified intent-to-treat; n.a., not applicable

In the carboplatin group a significantly higher frequency of dose delays due to treatment-related hematological toxicity was observed for paclitaxel and EC compared to olaparib group (for paclitaxel: 35.1% vs 2.9%, respectively; p<0.001 and for EC: 10.8% vs none, respectively; p=0.013) (Table 8).

Table 8: Dose delays (mITT Set)

Treatment and Reason for dose delay*	PO→EC N(%) N=69	PCb→EC N(%) N=37	Overall N(%) N=106	p-value
Paclitaxel, any reason	41 (59.4)	28 (75.7)	69 (65.1)	0.134
Organizational reasons (up to 3 days)	31 (44.9)	19 (51.4)	50 (47.2)	0.547

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Name of active ingredients: Olaparib, Carboplatin	Page:	

Hematological AEs related to study medication	2 (2.9)	13 (35.1)	15 (14.2)	<0.001
Other non-hematological AEs related to study medication	6 (8.7)	5 (13.5)	11 (10.4)	0.510
AEs not related to study medication	3 (4.3)	4 (10.8)	7 (6.6)	0.235
Other reasons	4 (5.8)	3 (8.1)	7 (6.6)	0.693
Carboplatin, any reason		28 (75.7)		n.a.
Organizational reasons (up to 3 days)		19 (51.4)		n.a.
Hematological AEs related to study medication		13 (35.1)		n.a.
Cardiac toxicity		1 (2.7)		
Other non-hematological AEs related to study medication		5 (13.5)		n.a.
AEs not related to study medication		3 (8.1)		n.a.
Other reasons		3 (8.1)		n.a.
EC, any reason	27 (39.1)	12 (32.4)	39 (36.8)	0.533
Organizational reasons (up to 3 days)	5 (7.2)	2 (5.4)	7 (6.6)	1.000
Hematological AEs related to study medication	0 (0.0)	4 (10.8)	4 (3.8)	0.013
Cardiac toxicity	0 (0.0)	1 (2.7)	1 (0.9)	0.349
Other non-hematological AEs related to study medication	2 (2.9)	1 (2.7)	3 (2.8)	1.000
AEs not related to study medication	2 (2.9)	1 (2.7)	3 (2.8)	1.000
Other reasons	18 (26.1)	4 (10.8)	22 (20.8)	0.081

*reasons not reported in both groups are not listed;

Note: Even if not intended in protocol, olaparib was delayed at least once in 2 patients. Percents for reasons do not necessarily sum up to ANY REASON per patient, because a) reasons were captured as multiple choice and/or b) data were aggregated by patient.

PO→EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb→EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; AE, adverse event; mITT, modified intent-to-treat; n.a., not applicable

In the overall safety population, all patients except one who discontinued treatment after first dose of paclitaxel (n=105) experienced at least one AE of any grade during the neoadjuvant treatment. Significant differences were seen in terms of high grade any AEs (52.2% in the olaparib arm vs 89.2% in the carboplatin arm; p<0.001) and high grade hematological AEs (46.4% vs 78.4%, respectively; p=0.002). Overall, 49 SAEs were reported (olaparib: 11 SAEs, carboplatin: 38 SAEs). A total of 29 (27.4%) patients reported at least one SAE with a significantly higher percentage observed in the carboplatin group compared to olaparib (carboplatin: 54.1% vs olaparib: 13.0%; p<0.001) (Table 9).

The most prominent differences between the two treatment groups with higher frequencies in the carboplatin arm were observed for the blood and lymphatic system disorders (carboplatin: 26 SAEs vs olaparib: 3 SAEs). There were no deaths reported during the conduct of the GeparOLA study.

Table 9: Summary of AEs and SAEs in both treatment arms (safety set)

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AEs	Grade	PO→EC N(%) N=69	PCb→EC N(%) N=37	Overall N(%) N=106	p-value
Any AE	any	68 (98.6)	37 (100)	105 (99.1)	1.000
	3-4	36 (52.2)	33 (89.2)	69 (65.1)	<0.001
Hematological AE	any	67 (97.1)	35 (94.6)	102 (96.2)	0.610
	3-4	32 (46.4)	29 (78.4)	61 (57.5)	0.002
Non-hematological AE	any	68 (98.6)	37 (100)	105 (99.1)	1.000
	3-4	16 (23.2)	15 (40.5)	31 (29.2)	0.075
Any AE, reported as free text	any	66 (95.7)	33 (89.2)	99 (93.4)	0.235
	3-4	13 (18.8)	8 (21.6)	21 (19.8)	0.800
Total SAEs		**11**	**38**	**49**	
Patients with at least one SAE		9 (13.0)	20 (54.1)	29 (27.4)	<0.001

PO→EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb→EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; AE, adverse event; SAE, serious adverse event.

Overall, the most frequent hematological AEs were any grade anemia (92.5%), leukopenia (85.8%) and neutropenia (74.5). A significantly higher rate of grade 3-4 leukopenia and neutropenia were observed in the carboplatin arm compared to olaparib arm (62.2% vs 33.3%; p=0.007 and 70.3% vs 43.5%; p=0.014, respectively) whereas high grade thrombocytopenia was reported only in the carboplatin group. Overall, the most common non-hematological AEs of any grade were alopecia (83.0%), fatigue (79.2%), peripheral sensory neuropathy (73.6%), increased alanine aminotransferase (ALAT, 63.2%) and nausea (58.5%). Patients in the carboplatin arm experienced a significantly higher rate of any grade increased aspartate aminotransferase (ASAT) and ALAT compared to those in the olaparib arm (62.2% vs 34.8% and 78.4% vs 55.1%, respectively) (Table 10).

Table 10: Summary of predefined AEs occurring more frequently (> 20%) in both arms

AE	Grade	PO→EC N (%) N=69	PCb→EC N (%) N=37	Overall N (%) N=106	p-value
Anaemia	any	63 (91.3)	35 (94.6)	98 (92.5)	0.710
	3-4	2 (2.9)	7 (18.9)	9 (8.5)	0.008
Leukopenia	any	58 (84.1)	33 (89.2)	91 (85.8)	0.568
	3-4	23 (33.3)	23 (62.2)	46 (43.4)	0.007
Thrombocytopenia	any	28 (40.6)	26 (70.3)	54 (50.9)	0.004
	3-4	0 (0.0)	10 (27.0)	10 (9.4)	<0.001
Neutropenia	any	47 (68.1)	32 (86.5)	79 (74.5)	0.060
	3-4	30 (43.5)	26 (70.3)	56 (52.8)	0.014
Blood AP increased	any	20 (29.0)	18 (48.6)	38 (35.8)	0.057
	3-4	1 (1.4)	1 (2.7)	2 (1.9)	1.000
ASAT increased	any	24 (34.8)	23 (62.2)	47 (44.3)	0.008
	3-4	1 (1.4)	1 (2.7)	2 (1.9)	1.000

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ALAT increased	any	38 (55.1)	29 (78.4)	67 (63.2)	0.021
	3-4	1 (1.4)	2 (5.4)	3 (2.8)	0.278
Fatigue	any	55 (79.7)	29 (78.4)	84 (79.2)	1.000
	3-4	1 (1.4)	0 (0.0)	1 (0.9)	1.000
Dizziness	any	22 (31.9)	11 (29.7)	33 (31.1)	1.000
	3-4	1 (1.4)	0 (0.0)	1 (0.9)	1.000
Headache	any	30 (43.5)	11 (29.7)	41 (38.7)	0.211
	3-4	1 (1.4)	0 (0.0)	1 (0.9)	1.000
Alopecia	any	61 (88.4)	27 (73.0)	88 (83.0)	0.058
Nausea	any	38 (55.1)	24 (64.9)	62 (58.5)	0.409
	3-4	0 (0.0)	2 (5.4)	2 (1.9)	0.120
Vomiting	any	13 (18.8)	10 (27.0)	23 (21.7)	0.335
	3-4	1 (1.4)	2 (5.4)	3 (2.8)	0.278
Diarrhoea	any	26 (37.7)	16 (43.2)	42 (39.6)	0.678
	3-4	1 (1.4)	1 (2.7)	2 (1.9)	1.000
Dysgeusia	any	28 (40.6)	10 (27.0)	38 (35.8)	0.205
Stomatitis	any	33 (47.8)	16 (43.2)	49 (46.2)	0.687
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Dyspepsia	any	15 (21.7)	7 (18.9)	22 (20.8)	0.806
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Skin reaction	any	36 (52.2)	18 (48.6)	54 (50.9)	0.839
	3-4	0 (0.0)	1 (2.7)	1 (0.9)	0.349
Peripheral sensory neuropathy	any	53 (76.8)	25 (67.6)	78 (73.6)	0.358
	3-4	1 (1.4)	0 (0.0)	1 (0.9)	1.000
Arthralgia	any	25 (36.2)	12 (32.4)	37 (34.9)	0.831
	3-4	0 (0.0)	1 (2.7)	1 (0.9)	0.349
Epistaxis	any	19 (27.5)	12 (32.4)	31 (29.2)	0.657
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Dyspnoea	any	11 (15.9)	12 (32.4)	23 (21.7)	0.082
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.

PO→EC, paclitaxel plus olaparib followed by epirubicin and cyclophosphamide; PCb→EC, paclitaxel plus carboplatin followed by epirubicin and cyclophosphamide; AE, adverse event; ALAT, Alanine aminotransferase; AP, Alkaline phosphatase; ASAT, Aspartate aminotransferase; n.a., not applicable

CONCLUSIONS:

The GeparOLA study investigating an addition of olaparib to paclitaxel as part of a neoadjuvant therapy in HER2-negative early breast cancer patients with HRD does not exclude a pCR rate of less than 55%. However, the pCR rate of 55.1% with paclitaxel plus olaparib followed by EC compared to 48.6% with paclitaxel plus carboplatin followed by EC is of interest especially given the better safety and tolerability profile. A trend of an olaparib benefit was observed in patients younger than 40 years and those with HR-positive HRD tumors.

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This effect has so far not yet been shown in breast cancer and is hypothesis generating. Furthermore, the addition of olaparib to paclitaxel in the GeparOLA trial was well tolerated and in line with observations derived from other trials investigating the use of PARP inhibitors. No new safety concerns have emerged from the trial and no death under therapy was reported. Therefore, the benefit from olaparib, particularly in terms of toxicity in patients with HER2-negative, HRD tumors prompts further investigation of using olaparib as part of a neoadjuvant therapy in patients with primary breast cancer and HRD.

Date of the Report:

10.09.2020