GeparOLA - GBG 90

A Randomized Phase II Trial to Assess the Efficacy of Paclitaxel and Olaparib in Comparison to Paclitaxel and Carboplatin Followed by Epirubicin and Cyclophosphamide as Neoadjuvant Chemotherapy in Patients with HER2 Negative Early Breast Cancer and Homologous Recombination Deficiency

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-This is a joint study by GBG and AGO-B-
The efficacy and toxicity of olaparib in early breast cancer (BC) patients with homologous recombination deficiency (HRD) is not well described.

- Carboplatin increased the pathological complete response (pCR) rate in triple negative breast cancer (TNBC) patients (GeparSixto, CALBG 40603, BrighTNess).  
  1, 2, 3
- pCR (ypT0/is ypN0) rates were even higher in patients with gBRCA 1/2 mutations (65%) and HRD score high (63%).  
  4, 5
- The TNT study showed a doubling in objective response rate (68% versus 33%) for patients with gBRCA 1/2 mutations receiving carboplatin vs docetaxel.  
  6
- The BrighTNess study could show an improved rate of pCR with the addition of veliparib and carboplatin relative to control (53% vs. 31%), but not compared to the addition of carboplatin (53% vs. 58%).  
  3

Overlap of HRD-Score and g/tBRCA Mutation

GeparSixto Study

TNBC samples analyzed (N=193)

Homologous Recombination
NON-DEFICIENT
N=56, 29.0%

Homologous Recombination
DEFICIENT
N=137, 71.0%

HRD Score high (N=129, 66.8%)

g/tBRCA mutant (N=56, 29.0%)

N=81

N=8

N=56

N=48

Response TNBC by HRD Status

GeparSixto Study

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PM 20.0%  29.6%  PMcB 33.9%  PMcB 63.5%

OR=1.7 (0.5-5.7)  p=0.399

OR=3.4 (1.7-6.9)  p=0.001

HR deficiency was defined as either a high HRD score or tBRCA mutation

Paclitaxel 80 mg/m²/ nonpegylated liposomal doxorubicin 20 mg/m² q1w/ bevacizumab 15mg/kg q3wk (PM)

Paclitaxel 80 mg/m² / nonpegylated liposomal doxorubicin 20 mg/m² q1w/ bevacizumab 15mg/kg q3wk plus carboplatin AUC2 q1wk (PMcB)

GeparOla Study Design

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Study Design

~2:1  
→PO N=65; PCb N=37

12 x Paclitaxel weekly 80mg/m² + Olaparib tablets 100mg twice daily (PO)

Epirubicin/Cyclophosphamide 90/600 mg/m² q2w or q3w

12x Paclitaxel weekly 80mg/m² + Carboplatin AUC 2 (PCb)

Epirubicin/Cyclophosphamide 90/600 mg/m² q2w or q3w

Surgery

Blood Collection

Screening

Chemotherapy

After PO/PCb

Chemotherapy

Surgery

Core Biopsies

N=102
Homologous Recombination Deficiency (HRD)*
HER2-

Stratification Factors:
- Age (<40 years vs ≥ 40 years)
- Hormone Receptor Status (HR+ vs HR-)

* Patients with either a known somatic or germline BRCA1/2 mutation or HRD score high

1 Timms et al. Breast Cancer Res 2014
Objectives and Endpoints

Primary Objective and Endpoint:

- To assess the pathological complete response (ypT0/is ypN0) rate of neoadjuvant treatment of olaparib and paclitaxel followed by epirubicin and cyclophosphamide (PO→EC) in patients with early BC and HR deficient tumors (defined as either tBRCA1/2 mutation and/or HRD score high and/or known gBRCA mutation).

Main Secondary Objectives and Endpoints:

- pCR rate (ypT0/is ypN0) of patients receiving paclitaxel and carboplatin followed by EC (PCb→EC)
- pCR rate (ypT0/is ypN0) in stratified subgroups
- pCR rates according to different pCR definitions: ypT0 ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT_{any} ypN0
- pCR rate in HRD Score high with vs without tBRCA mutation
- Clinical response rate
- Breast conservation rate
- Toxicity and compliance
- Immune- and biomarker
Sample Size and Statistical Considerations

- A pCR rate in the PO→EC arm of 55% or lower should be excluded with $\alpha=0.1$ to support a subsequent phase III study.

- Assuming a pCR rate of 70% in PO→EC arm, 65 patients are needed for two-sided one group $\chi^2$-test to exclude a pCR rate of 55% or lower.

- No formal comparison between the two arms was planned.

- Since pCR rate in the PCb→EC arm is expected to be 50% - 60%, inclusion of 37 patients will provide a point estimate with a 90% CI of 27% width.
  - CALGB 40603 study: pCR rate of 49%; 3 weekly carboplatin combination; unselected patients with TNBC
  - GeparSixto study: pCR rate of 65%; weekly carboplatin combination; BRCA carriers with TNBC

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

Main Inclusion Criteria

- **Primary HER2-negative carcinoma of the breast**
- **Patients must be in the following stages of disease:**
  - cT2 - cT4a-d or
  - cT1c and cN+ or
  - cT1c and pN_{SLN}+ or
  - cT1c and ER-neg and PgR-neg or
  - cT1c and Ki-67>20%
- **Central testing of ER, PgR, HER2 status, Ki-67**
- **Centrally confirmed tumor Homologous Recombinant Deficiency**
  - tBRCA mutated and/or HRD score high
  - Patients with known gBRCA and/or tBRCA status could be enrolled prior to the central test results available
- **No prior use of a PARP-inhibitor**
### Main Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PO→EC N=69</th>
<th>PCb→EC N=37</th>
<th>Overall N=106</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median (range)</strong></td>
<td>48.0 (25.0, 71.0)</td>
<td>45.0 (26.0, 67.0)</td>
<td>47.0 (25.0, 71.0)</td>
</tr>
<tr>
<td><strong>Pre-/perimenopausal</strong></td>
<td>41 (59.4)</td>
<td>25 (67.6)</td>
<td>66 (62.3)</td>
</tr>
<tr>
<td><strong>cT1</strong></td>
<td>25 (36.8)</td>
<td>13 (35.1)</td>
<td>38 (36.2)</td>
</tr>
<tr>
<td><strong>cT2</strong></td>
<td>41 (60.3)</td>
<td>23 (62.2)</td>
<td>64 (61.0)</td>
</tr>
<tr>
<td><strong>cT3</strong></td>
<td>2 (2.9)</td>
<td>1 (2.7)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td><strong>cN+</strong></td>
<td>17 (24.5)</td>
<td>16 (45.7)</td>
<td>33 (31.8)</td>
</tr>
<tr>
<td><strong>ER and/or PgR positive</strong></td>
<td>19 (27.5)</td>
<td>10 (27.0)</td>
<td>29 (27.4)</td>
</tr>
<tr>
<td><strong>HER2-negative</strong></td>
<td>69 (100.0)</td>
<td>37 (100.0)</td>
<td>106 (100.0)</td>
</tr>
<tr>
<td><strong>G3</strong></td>
<td>58 (84.1)</td>
<td>34 (91.9)</td>
<td>92 (86.8)</td>
</tr>
<tr>
<td><strong>Ki-67 &gt; 20%</strong></td>
<td>63 (91.3)</td>
<td>32 (86.5)</td>
<td>95 (89.6)</td>
</tr>
</tbody>
</table>

* valid percent; ** central testing
Central Testing HRD

**Screening (N=274)**
- HR deficiency assessment negative (N= 97)
- Investigator’s/Patient’s decision/Other (N= 70)

**Randomisation (N=107)**
- Withdrawal (N=1)

**HRD Status central positive mITT-Set (N=106)**

- HRD Score high (N=96)
- HRD Score low (N=3)
- HRD Score not measurable (N=7)

<table>
<thead>
<tr>
<th>tBRCA</th>
<th>HRD Score high N (%)</th>
<th>HRD Score low N (%)</th>
<th>HRD Score not measurable* N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutated</td>
<td>49 (46.2)</td>
<td>3 (2.8)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Intact</td>
<td>46 (43.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Not measurable*</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>4 (3.8)**</td>
</tr>
</tbody>
</table>

- Eligible patients
- * Insufficient quality or quantity of DNA
- ** Eligibility criteria: gBRCA local positive
## Discontinuations

<table>
<thead>
<tr>
<th></th>
<th>PO→EC N=69 N (%)</th>
<th>PCb→EC N=37 N (%)</th>
<th>Overall N=106 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completed all treatments</strong></td>
<td>52 (75.4)</td>
<td>24 (64.9)</td>
<td>76 (71.7)</td>
</tr>
<tr>
<td><strong>Discontinued Paclitaxel + Carboplatin/Olaparib</strong></td>
<td>6 (8.7)</td>
<td>6 (16.2)</td>
<td>12 (11.3)</td>
</tr>
<tr>
<td>Local progression</td>
<td>2 (2.9)</td>
<td>0 (0.0)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>2 (2.9)</td>
<td>5 (13.5)</td>
<td>7 (6.6)</td>
</tr>
<tr>
<td>Patient's / Investigator's decision</td>
<td>2 (2.9)</td>
<td>1 (2.7)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td><strong>Never received EC</strong></td>
<td>11 (15.9)</td>
<td>8 (21.6)</td>
<td>19 (17.9)</td>
</tr>
<tr>
<td>Local progression</td>
<td>2 (2.9)</td>
<td>0 (0.0)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>0 (0.0)</td>
<td>1 (2.7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Patient's / Investigator's decision</td>
<td>9 (13.0)</td>
<td>6 (16.2)</td>
<td>15 (14.1)</td>
</tr>
<tr>
<td><strong>Discontinued EC</strong></td>
<td>3 (4.3)</td>
<td>3 (8.1)</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>Local progression</td>
<td>1 (1.4)</td>
<td>0 (0.0)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>0 (0.0)</td>
<td>2 (5.4)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Patient's / Investigator's decision</td>
<td>2 (2.8)</td>
<td>1 (2.7)</td>
<td>3 (2.8)</td>
</tr>
</tbody>
</table>
## Serious Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>PO→EC N=69</th>
<th>PCb→EC N=37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No of SAEs</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>Pts with at least 1 SAE</td>
<td>9 (13.0%)</td>
<td>19 (51.3%)</td>
</tr>
<tr>
<td>01. Infections and infestations</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>03. Blood and lymphatic system disorders</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>04. Immune system disorders</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>06. Metabolism and nutrition disorders</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>08. Nervous system disorders</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>14. Gastrointestinal disorders</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15. Hepatobiliary disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>22. General disorders</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>24. Injury, poisoning and procedural complications</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- No fatal SAEs or SUSARs occurred
Primary Endpoint – pCR ypT0/is ypN0

- **PO→EC**: 55.1% (90%CI: 44.5%-65.3%)
- **N=69**
- **PCb→EC**: 48.6% (90%CI: 34.3%-63.2%)
- **N=37**
Primary Endpoint – pCR ypT0/is ypN0

PO→EC
N=69
55.1%
(90%CI: 44.5%-65.3%)

PCb→EC
N=37
48.6%
(90%CI: 34.3%-63.2%)
Predefined Subgroup Analysis (ypT0/is ypN0)
Hormone Receptor Status

pCR rates and 90% CI in HR+ pts. (N=29)

- PO→EC: 52.6% (32.0%-72.6%)
- PCb→EC: 20.0% (3.7%-50.7%)

N=19

pCR rates and 90% CI in HR- pts. (N=77)

- PO→EC: 56.0% (43.4%-68.0%)
- PCb→EC: 59.3% (41.7%-75.2%)

N=50

N=27

CI: confidence interval

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Predefined Subgroup Analysis (ypT0/is ypN0)

Age

pCR rates and 90% CI in pts. < 40 years (N=32)

- PO→EC: 76.2% (53.3%-90.1%)
- PCb→EC: 45.5% (20.0%-72.9%)

pCR rates and 90% CI in pts. ≥ 40 years (N=74)

- PO→EC: 45.8% (33.4%; 58.6%)
- PCb→EC: 50.0% (32.7%-67.3%)

*CI: confidence interval*
Predefined Subgroup Analysis (ypT0/is ypN0)

BRCA Mutation

**pCR rates and 90% CI in pts. with g/tBRCA Mutation (N=60*)**

- PO→EC: N=39, 59.0% (44.6%-72.3%)
- PCb→EC: N=21, 57.1% (37.2%-75.5%)

**pCR rates and 90% CI in pts. with g/tBRCA wildtype† (N=45*)**

- PO→EC: N=29, 51.7% (35.2%-68.0%)
- PCb→EC: N=16, 37.5% (17.8%-60.9%)

*One patient without tBRCA result due to insufficient quantity of DNA→HRD Score high
† HRD Score high
GeparOLA investigates the addition of olaparib to paclitaxel as part of a neoadjuvant therapy in HER2 negative early breast cancer with HRD (t/gBRCA1/2 mutation and/or HRD Score high).

- Addition of olaparib to paclitaxel was well tolerated.

- GeparOLA could not exclude a pCR rate of ≤ 55% in the PO arm:
  - pCR rate was 55.1% (90% CI: 44.5%-65.3%)

- Subgroup analyses are hypothesis generating and need further confirmation:
  - patients with HR+ tumors (pCR rate PO 52.6% vs. PCb 20.0%)
  - patients <40 years (pCR rate PO 76.2% vs. PCb 45.5%)
  - HRD score high, BRCA1/2 wildtype patients (pCR rate PO 51.7% vs. PCb 37.5%)

- Olaparib as part of a neoadjuvant therapy should be further investigated in pts. with HRD.

- Further exploratory and translational research is ongoing.
Acknowledgement

- All patients and their families
- All participating sites

Central Pathology:
Carsten Denkert
Wolfgang Schmidt
Peggy Wolkenstein
Britta Beyer

HRD- Testing

Financial and Drug Support

Cryostorage Biomaterial

Patient Self-Registry

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Backup Material
Methodology: Myriad myChoice® HRD

- Test is utilizing Illumina HiSeq next generation sequencing (paraffin embedded tumor tissue)
- Myriad myChoice® HRD includes the following components:

1. HDR Score = Genomic Instability Status assay
   - NGS test → comprehensive signature for HRD by testing genome-wide single nucleotide variants in DNA
   - determined by measuring several elements including
     - loss of heterozygosity (LOH)
     - telomeric allelic imbalance (TAI)
     - large-scale state transitions (LST)

2. tBRCA1/2 sequence analysis

3. tBRCA1/2 large rearrangement analysis

<table>
<thead>
<tr>
<th>Myriad myChoice® HRD Result → HRD Status</th>
<th>Genomic Instability Status → HDR Score</th>
<th>tBRCA1/2 Mutation Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Negative/Low</td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive/High</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>Inconclusive or Incomplete</td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive/High</td>
<td>Inconclusive or Incomplete</td>
</tr>
</tbody>
</table>

Myriad myChoice® HRD Technical Specifications; Effective Date: June 2017
Predefined Analysis mITT ypT0/is ypNany
ypT0/is ypN any- Pathological Complete Response

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90% confidence interval

PO → EC
N=69
60.9%
(50.3%-70.7%)

PCb → EC
N=37
54.1%
(39.4%-68.2%)