



Clinical trial results:

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 BRCA1/2 tumor or germline mutation and/or HRD score high) (GeparOLA)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-003509-41 |
| Trial protocol | DE |
| Global end of trial date | 27 February 2019 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 02 May 2021 |
| First version publication date | 02 May 2021 |
| Summary attachment (see zip file) | GeparOLA summary results, synopsis (CSR_Synopsis_GeparOla_v2.0_10Sep2020_.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | GBG90 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02789332 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GBG Forschungs GmbH |
| Sponsor organisation address | Martin Behaim Str. 12, Neu-Isenburg, Germany, 63263 |
| Public contact | Medicine and Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.de |
| Scientific contact | Medicine and Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.de |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 February 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 January 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 February 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the pathological complete response rate (pCR=ypT0/is ypN0) of neoadjuvant paclitaxel plus olaparib followed by epirubicin and cyclophosphamide in patients with early breast cancer and HRD tumors defined as either tumor (t) or known germline (g) BRCA1/2 mutation or HRD score high.

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving. IDMC was to ensure the ethical conduct of the trial and to protect patients' safety interests in this study.

Background therapy:

For all patients 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
These agents are used according to marketed formulation via normal procedures at each site and applied according to recommendations of the manufacturers.

Evidence for comparator:

Standard of Care (SoC)

| | |
|---|---------------------|
| Actual start date of recruitment | 21 September 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Scientific research |
| Long term follow-up duration | 10 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 106 |
| Worldwide total number of subjects | 106 |
| EEA total number of subjects | 106 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 100 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Approximately 24 months (Q-III 2016 –Q-II 2018). 107 patients were randomized and 106 patients (69 in olaparib arm and 37 in carboplatinum 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.

Pre-assignment

Screening details:

Patients of at least 18 years of age with untreated primary HER2-negative cT2-cT4a-d or cT1c with either cN+ or pNSLN+ or cT1c and triple-negative breast cancer (TNBC) or cT1c and Ki-67>20% BC with HRD were included in the study. 274 patients at 32 sites were screened, of whom 107 were entered into the randomised study and 106 started treatment.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | olaparib plus paclitaxel |

Arm description:

A total of 69 patients were randomized to receive olaparib plus paclitaxel followed by epirubicin and cyclophosphamide (experimental arm) and started treatment; 67 patients received surgery (surgery data was not available for 2 patients due to withdrawal of informed consent).

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lynparza® (Olaparib) |
| Investigational medicinal product code | EU/1/14/959/001 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Olaparib 4 x 25mg tablets twice daily for 12 weeks

| | |
|------------------|-------------------------------|
| Arm title | carboplatinum plus paclitaxel |
|------------------|-------------------------------|

Arm description:

A total of 38 patients were randomized to receive carboplatinum plus paclitaxel followed by epirubicin and cyclophosphamide (control arm), and 37 patients started treatment (1 patient did not start treatment due to withdrawal of informed consent).

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Carboplatinum |
| Investigational medicinal product code | 39079.00.00 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin: i.v. infusion over 15 – 60 minutes; AUC 2 given on day 1, 8, 15, q d 22 for 4 cycles. It was administered according to recommendations of the manufacturers.

| Number of subjects in period 1 | olaparib plus paclitaxel | carboplatinum plus paclitaxel |
|---------------------------------------|-----------------------------|----------------------------------|
| Started | 69 | 37 |
| Completed | 67 | 37 |
| Not completed | 2 | 0 |
| Consent withdrawn by subject | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | olaparib plus paclitaxel |
|-----------------------|--------------------------|

Reporting group description:

A total of 69 patients were randomized to receive olaparib plus paclitaxel followed by epirubicin and cyclophosphamide (experimental arm) and started treatment; 67 patients received surgery (surgery data was not available for 2 patients due to withdrawal of informed consent).

| | |
|-----------------------|-------------------------------|
| Reporting group title | carboplatinum plus paclitaxel |
|-----------------------|-------------------------------|

Reporting group description:

A total of 38 patients were randomized to receive carboplatinum plus paclitaxel followed by epirubicin and cyclophosphamide (control arm), and 37 patients started treatment (1 patient did not start treatment due to withdrawal of informed consent).

| Reporting group values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | Total |
|-----------------------------------|--------------------------|-------------------------------|-------|
| Number of subjects | 69 | 37 | 106 |
| Age categorical | | | |
| age at randomization, categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 65 | 35 | 100 |
| From 65-84 years | 4 | 2 | 6 |
| Age continuous | | | |
| age at randomization, continuous | | | |
| Units: years | | | |
| median | 48 | 45 | |
| full range (min-max) | 25 to 71 | 26 to 67 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 68 | 37 | 105 |
| Male | 1 | 0 | 1 |
| cT | | | |
| Tumor size | | | |
| Units: Subjects | | | |
| cT1 | 25 | 13 | 38 |
| cT2 | 41 | 23 | 64 |
| cT3 | 2 | 1 | 3 |
| cT4 | 0 | 0 | 0 |
| missing | 1 | 0 | 1 |
| cN | | | |
| Nodal status | | | |
| Units: Subjects | | | |
| cN0 | 52 | 19 | 71 |
| cN1 | 13 | 14 | 27 |
| cN2 | 3 | 2 | 5 |
| cN3 | 1 | 0 | 1 |
| missing | 0 | 2 | 2 |
| Grading (G) | | | |

| | | | |
|---|----|----|----|
| Tumor grading | | | |
| Units: Subjects | | | |
| G1 | 0 | 0 | 0 |
| G2 | 11 | 3 | 14 |
| G3 | 58 | 34 | 92 |
| ER/PgR | | | |
| Hormone (ER=estrogen receptor/PgR=progesteron receptor) receptor status | | | |
| Units: Subjects | | | |
| ER/PgR both negative | 50 | 27 | 77 |
| ER and/or PgR positive | 19 | 10 | 29 |
| Ki-67 | | | |
| Ki-67 status with cut-off 20% | | | |
| Units: Subjects | | | |
| Ki-67≤20% | 6 | 5 | 11 |
| Ki-67>20% | 63 | 32 | 95 |

End points

End points reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | olaparib plus paclitaxel |
|-----------------------|--------------------------|

Reporting group description:

A total of 69 patients were randomized to receive olaparib plus paclitaxel followed by epirubicin and cyclophosphamide (experimental arm) and started treatment; 67 patients received surgery (surgery data was not available for 2 patients due to withdrawal of informed consent).

| | |
|-----------------------|-------------------------------|
| Reporting group title | carboplatinum plus paclitaxel |
|-----------------------|-------------------------------|

Reporting group description:

A total of 38 patients were randomized to receive carboplatinum plus paclitaxel followed by epirubicin and cyclophosphamide (control arm), and 37 patients started treatment (1 patient did not start treatment due to withdrawal of informed consent).

Primary: pathological complete response (pCR=ypT0/is ypN0) in olaparib arm

| | |
|-----------------|---|
| End point title | pathological complete response (pCR=ypT0/is ypN0) in olaparib arm |
|-----------------|---|

End point description:

The primary endpoint was summarized as pCR (ypT0/is ypN0) rate for the olaparib group. One group chi-square test was performed to exclude a pCR rate of 55% or lower in the olaparib arm. Two-sided 90% CIs were calculated according to Pearson and Clopper (Pearson and Clopper 1934). The significance level was set to two-sided $\alpha=0.1$. The analysis was performed in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy. Note, the primary endpoint was to assess pCR=ypT0/is ypN0 rate only in olaparib plus paclitaxel arm but the pCR rate in carboplatinum plus paclitaxel arm is also shown as required by the system

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

from start of treatment to surgery, 12 weeks

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|----------------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| pCR | 55.1 (44.5 to 65.3) | 48.6 (34.3 to 63.2) | | |

Statistical analyses

| | |
|----------------------------|---------------------------|
| Statistical analysis title | one-group chi-square test |
|----------------------------|---------------------------|

Statistical analysis description:

This is a non-comparative phase II study design investigating an addition of olaparib to paclitaxel as part of neoadjuvant chemotherapy in early HER2-negative BC patients with HRD. One group chi-square test was performed to exclude a pCR rate of 55% or lower in the olaparib plus paclitaxel arm. Note, for the primary endpoint there was not a comparison group.

| | |
|---|--|
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.99 ^[2] |
| Method | Chi-squared |
| Parameter estimate | pCR rate |
| Point estimate | 55.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 44.5 |
| upper limit | 65.3 |

Notes:

[1] - One-group chi-square test to exclude a pCR rate of $\leq 55\%$ in the olaparib arm

[2] - one-group chi-square test to exclude a pCR rate of $\leq 55\%$ in the olaparib arm

Secondary: Difference - pCR rates between treatment arms

| | |
|---|---|
| End point title | Difference - pCR rates between treatment arms |
| End point description: pCR rate (ypT0/is ypN0) in carboplatinum plus paclitaxel arm and the absolute difference of pCR rates (ypT0/is ypN0) between the two treatment arms. The analysis was performed in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy. | |
| End point type | Secondary |
| End point timeframe: from start of treatment to surgery, 12 weeks | |

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|----------------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| pCR | 55.1 (44.5 to 65.3) | 48.6 (34.3 to 63.2) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Difference - pCR rates between the treatment arms |
| Statistical analysis description: 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. | |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |

| | |
|---|------------------------|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | = 0.669 ^[4] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 6.4 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -10.3 |
| upper limit | 23.1 |

Notes:

[3] - The significance in differences of pCR rates was tested using a continuity corrected chi-square test with a two-sided significance level of $\alpha=0.1$.

[4] - the significance was tested with a two-sided continuity corrected chi-square test.

Secondary: pCR comparison between treatment arms - odds ratio

| | |
|--|--|
| End point title | pCR comparison between treatment arms - odds ratio |
| End point description: | |
| pCR (ypT0/is ypN0) comparison between treatment arms; pCR rates between treatment arms were assessed by two-sided continuity corrected chi-square tests with 90% confidence intervals, and the difference in the pCR rates between the two treatment arms was evaluated as odds ratio and its 95% CI. The analysis was performed in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy. | |
| End point type | Secondary |
| End point timeframe: | |
| 12 weeks | |

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|----------------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| pCR | 55.1 (44.5 to 65.3) | 48.6 (34.3 to 63.2) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | pCR, comparison between treatment arms -odds ratio |
| Statistical analysis description: | |
| Comparison of pCR (ypT0/is ypN0) rates between olaparib plus paclitaxel and carboplatinum plus paclitaxel arms based on the mITT set was evaluated as odds ratio with 95% CI. | |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |

| | |
|---|----------------------|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.528 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 2.88 |

Notes:

[5] - Logistic regression

Secondary: pCR=ypT0 ypN0 rates between treatment arms

| | |
|---|--|
| End point title | pCR=ypT0 ypN0 rates between treatment arms |
| End point description: | |
| pCR of breast and lymph nodes defined as ypT0 ypN0 between treatment arms. The analysis was performed in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy. | |
| End point type | Secondary |
| End point timeframe: | |
| 12 weeks | |

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|----------------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| pCR | 49.3 (38.8 to 59.8) | 45.9 (31.8 to 60.6) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | pCR=ypT0 ypN0 rates between the treatment arms |
| Statistical analysis description: | |
| Two-sided continuity corrected chi-square tests were used to compare pCR=ypT0 ypN0 rates between treatment arms | |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |

| | |
|---|------------------------|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0.902 ^[7] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 3.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -13.4 |
| upper limit | 20.1 |

Notes:

[6] - continuity corrected chi-square test

[7] - p-value of continuity corrected chi-square test

Secondary: Breast conservation rates between treatment arms

| | |
|------------------------|---|
| End point title | Breast conservation rates between treatment arms |
| End point description: | To assess breast conservation rate defined as tumorectomy, segmentectomy or quadrantectomy as most radical surgery after each treatment. The analysis was performed in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy. |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|----------------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| BCS | 52.2 (41.5 to 62.8) | 67.6 (52.8 to 80.1) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Breast conservation rates (BCS) in treatment arms |
| Statistical analysis description: | Breast conservation rates were analyzed in the mITT set. |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| P-value | = 0.191 |
| Method | Chi-squared corrected |

Notes:

[8] - Two-sided continuity corrected chi-square test was used to compare BCS vs mastectomy in both treatment arms

Secondary: clinical/ imaging response rates between treatment arms after taxane treatment

| | |
|-----------------|--|
| End point title | clinical/ imaging response rates between treatment arms after taxane treatment |
|-----------------|--|

End point description:

To determine the clinical/imaging response rates after taxane treatment based on physical examination and imaging tests (sonography, mammography, or MRI) in both treatment arms. Clinical /imaging response of the breast was defined as:

-Complete response (CR): complete disappearance of all tumor signs in the breast as assessed by all imaging tests

-Partial response (PR): reduction in the product of the two largest perpendicular diameters of the primary tumor size by 50% or more assessed by imaging test or palpation

-Stable disease (SD): no significant change in tumor size during treatment. This category includes no change, an estimated reduction of the tumor area by less than 50%, or an estimated increase in the size of the tumor area lesion of less than 25% measured by imaging test or palpation

-Progressive disease (PD): development of new, previously undetected lesions, or an estimated increase in the size of pre-existing lesions by 25% or more after at least 6 weeks therapy.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|-----------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: patients | | | | |
| CR | 14 | 13 | | |
| PR | 40 | 17 | | |
| ORR | 54 | 30 | | |
| SD | 9 | 4 | | |
| PD | 3 | 0 | | |
| missing | 3 | 3 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Clinical/imaging response rates-ORR after taxane |
|----------------------------|--|

Statistical analysis description:

ORR (overall response rate) after taxane treatment was defined as complete or partial response of the breast and analyzed in the mITT set, and the two-sided 90% CI was calculated according to Pearson and Clopper (Pearson & Clopper, 1934).

| | |
|-------------------|--|
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
|-------------------|--|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| P-value | = 0.588 |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | -6.4 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -18.4 |
| upper limit | 5.6 |

Notes:

[9] - Two-sided continuity corrected chi-square test was used to compare ORR rates between treatment arms after taxane treatment

Secondary: clinical/imaging response rates between treatment arms before surgery

| | |
|-----------------|---|
| End point title | clinical/imaging response rates between treatment arms before surgery |
|-----------------|---|

End point description:

To determine the clinical/imaging response rates before surgery based on physical examination and imaging tests (sonography, mammography, or MRI) in both treatment arms. Clinical /imaging response of the breast was defined as:

-Complete response (CR): complete disappearance of all tumor signs in the breast as assessed by all imaging tests

-Partial response (PR): reduction in the product of the two largest perpendicular diameters of the primary tumor size by 50% or more assessed by imaging test or palpation

-Stable disease (SD): no significant change in tumor size during treatment. This category includes no change, an estimated reduction of the tumor area by less than 50%, or an estimated increase in the size of the tumor area lesion of less than 25% measured by imaging test or palpation

-Progressive disease (PD): development of new, previously undetected lesions, or an estimated increase in the size of pre-existing lesions by 25% or more after at least 6 weeks therapy.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

before surgery (end of treatment)

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|-----------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: patients | | | | |
| CR | 28 | 15 | | |
| PR | 32 | 13 | | |
| ORR | 60 | 28 | | |
| SD | 4 | 4 | | |
| PD | 2 | 1 | | |
| missing | 3 | 4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Clinical/imaging response rates-ORR before surgery |
| Statistical analysis description: ORR (overall response rate) before surgery was defined as complete or partial response of the breast and analyzed in the mITT set, and the two-sided 90% CI was calculated according to Pearson and Clopper (Pearson & Clopper, 1934). | |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| P-value | = 0.572 |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 6.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -5.7 |
| upper limit | 17.9 |

Notes:

[10] - Two-sided continuity corrected chi-square test was used to compare ORR rates between treatment arms before surgery

Secondary: pCR=ypT0 ypN(any) between treatment arms

| | |
|--|--|
| End point title | pCR=ypT0 ypN(any) between treatment arms |
| End point description: pCR=ypT0 ypN(any) rates were defined based on the TNM classification and analyzed between treatment arms in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy. | |
| End point type | Secondary |
| End point timeframe: 12 weeks | |

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|----------------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| pCR | 55.1 (44.5 to 65.3) | 51.4 (36.8 to 65.7) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | pCR=ypT0 ypNany rates between treatment arms |
| Statistical analysis description: Two-sided continuity corrected chi-square tests were used to compare pCR (ypT0 ypNany) rates between treatment arms. | |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| P-value | = 0.871 ^[12] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 3.7 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -13 |
| upper limit | 20.4 |

Notes:

[11] - continuity corrected chi-square test

[12] - p-value of continuity corrected chi-square test

Secondary: pCR=ypT0/is ypN(any) between treatment arms

| | |
|------------------------|--|
| End point title | pCR=ypT0/is ypN(any) between treatment arms |
| End point description: | pCR defined as ypT0/is ypN(any) based on the TNM classification was evaluated between treatment arms in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy. |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|----------------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| pCR | 60.9 (50.3 to 70.7) | 54.1 (39.4 to 68.2) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | pCR=ypT0/is ypNany rates between treatment arms |
| Statistical analysis description: | Two-sided continuity corrected chi-square test was used to compare pCR (ypT0/is ypNany) rates between treatment arms. |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[13] |
| P-value | = 0.637 ^[14] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 6.8 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -9.8 |
| upper limit | 23.4 |

Notes:

[13] - continuity corrected chi-square test

[14] - p-value of continuity corrected chi-square test

Secondary: pCR=ypT(any) ypN0 rates between treatment arms

| | |
|------------------------|--|
| End point title | pCR=ypT(any) ypN0 rates between treatment arms |
| End point description: | pCR defined as ypT(any) ypN0 based on the TNM classification was analyzed between treatment arms in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy. |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|----------------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| pCR | 76.8 (66.9 to 84.9) | 73.0 (58.5 to 84.5) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | pCR=ypT(any) ypN0 rates between treatment arms |
| Statistical analysis description: | Two-sided continuity corrected chi-square test was used to compare pCR=ypT(any) ypN0 rates between treatment arms. |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[15] |
| P-value | = 0.841 ^[16] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 3.8 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -10.8 |
| upper limit | 18.5 |

Notes:

[15] - continuity corrected chi-square test

[16] - p-value of continuity corrected chi-square test

Secondary: To assess the pCR rates (ypT0/is ypN0) in subgroups

| | |
|-----------------|---|
| End point title | To assess the pCR rates (ypT0/is ypN0) in subgroups |
|-----------------|---|

End point description:

The pCR rates (ypT0/is ypN0) were analyzed in subgroups defined by:

- a) Stratification factors
 - hormone-receptor status (HR-positive vs HR-negative)
 - age (< 40 years vs ≥ 40 years)
 - b) Other baseline factors
 - tumor (t) BRCA1/2 status (mutated tBRCA1/2 vs non-mutated tBRCA1/2)
 - clinical nodal status (cN-negative [cN0] vs cN-positive [cN+]) assessed by sonography or if missing by palpation. This subgroup was not specified in the study protocol and was added post-hoc.
- The analysis was performed in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|----------------------------------|-----------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| HR-positive, pCR | 52.6 (32.0 to 72.6) | 20.0 (3.7 to 50.7) | | |
| HR-negative, pCR | 56.0 (43.4 to 68.0) | 59.3 (41.7 to 75.2) | | |
| Age < 40, pCR | 76.2 (56.3 to 90.1) | 45.5 (20.0 to 72.9) | | |
| Age ≥ 40, pCR | 45.8 (33.4 to 58.6) | 50.0 (32.7 to 67.3) | | |
| tBRCA1/2 mutated, pCR | 60.0 (44.7 to 74.0) | 60.0 (39.4 to 78.3) | | |
| tBRCA1/2 non mutated, pCR | 50.0 (33.9 to 66.1) | 37.5 (17.8 to 60.9) | | |
| cN0, pCR | 63.5 (51.1 to 74.6) | 50.0 (30.2 to 69.8) | | |

| | | | | |
|----------|---------------------|---------------------|--|--|
| cN+, pCR | 29.4 (12.4 to 52.2) | 50.0 (27.9 to 72.1) | | |
|----------|---------------------|---------------------|--|--|

Statistical analyses

| | |
|---|--|
| Statistical analysis title | pCR (ypT0/is ypN0) rates in subgroups, HR-positive |
| Statistical analysis description: | |
| In subgroup analyses according to the stratification parameters, all patients were included as stratified. Patients with missing values defining the subgroup were excluded from the corresponding analyses. There was no adjustment for multiple comparisons in the subgroup analyses. The subgroup analysis was to be considered explorative. | |
| pCR was analyzed separately for the subgroups according to HR status, age, tBRCA1/2 status and clinical nodal status (cN). | |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[17] |
| P-value | = 0.194 ^[18] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 32.6 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 4.6 |
| upper limit | 60.7 |

Notes:

[17] - pCR rates between treatment arms in the stratified HR-positive subgroup were estimated by two-sided continuity corrected chi-square test

[18] - p-value for HR-positive subgroup

| | |
|--|--|
| Statistical analysis title | pCR (ypT0/is ypN0) rates in subgroups, HR-negative |
| Statistical analysis description: | |
| In subgroup analyses according to the stratification parameters, all patients were included as stratified. Patients with missing values defining the subgroup were excluded from the corresponding analyses. There was no adjustment for multiple comparisons in the analyses in subgroups which are to be considered explorative. | |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[19] |
| P-value | = 0.973 ^[20] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | -3.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -22.6 |
| upper limit | 16.1 |

Notes:

[19] - pCR rates between treatment arms in the stratified HR-negative subgroup were estimated by two-sided continuity corrected chi-square test

[20] - p-value for HR-negative subgroup

| | |
|-----------------------------------|---|
| Statistical analysis title | pCR (ypT0/is ypN0) rates in subgroups, age<40 |
|-----------------------------------|---|

Statistical analysis description:

In subgroup analyses according to the stratification parameters, all patients were included as stratified. Patients with missing values defining the subgroup were excluded from the corresponding analyses. There was no adjustment for multiple comparisons in the subgroup analyses. The subgroup analysis was to be considered explorative. pCR was analyzed separately for the subgroups according to HR status, age, tBRCA1/2 status and clinical nodal status (cN)

| | |
|---|--|
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[21] |
| P-value | = 0.178 ^[22] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 30.7 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 1.7 |
| upper limit | 59.8 |

Notes:

[21] - pCR rates between treatment arms in the stratified age <40 years subgroup were estimated by two-sided continuity corrected chi-square test

[22] - p-value for age <40 years subgroup

| | |
|-----------------------------------|--|
| Statistical analysis title | pCR (ypT0/is ypN0) rates in subgroups, age>=40 |
|-----------------------------------|--|

Statistical analysis description:

In subgroup analyses according to the stratification parameters, all patients were included as stratified. Patients with missing values defining the subgroup were excluded from the corresponding analyses. There was no adjustment for multiple comparisons in the subgroup analyses. The subgroup analysis was to be considered explorative. pCR was analyzed separately for the subgroups according to HR status, age, tBRCA1/2 status and clinical nodal status (cN).

| | |
|---|--|
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[23] |
| P-value | = 0.921 ^[24] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | -4.2 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -24.2 |
| upper limit | 15.8 |

Notes:

[23] - pCR rates between treatment arms in the age >= 40 years stratified subgroup were estimated by two-sided continuity corrected chi-square test

[24] - p-value for age >= 40 years subgroup

| | |
|--|--|
| | pCR(ypT0/is ypN0) rates in subgroups, tBRCAmut |
|--|--|

| Statistical analysis title | |
|---|--|
| Statistical analysis description: | |
| In subgroup analyses according to the stratification parameters, all patients were included as stratified. Patients with missing values defining the subgroup were excluded from the corresponding analyses. There was no adjustment for multiple comparisons in the subgroup analyses. The subgroup analysis was to be considered explorative. pCR was analyzed separately for the subgroups according to HR status, age, tumor BRCA1/2 status and clinical nodal status (cN). | |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[25] |
| P-value | = 1 ^[26] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -22.6 |
| upper limit | 22.6 |

Notes:

[25] - pCR rates between treatment arms in the predefined tBRCA1/2 mutated subgroup were estimated by two-sided continuity corrected chi-square test

[26] - p-value for tBRCA1/2 mutated subgroup

| Statistical analysis title | |
|---|--|
| pCR(ypT0/is ypN0) rates in subgroups, tBRCAnon-mut | |
| Statistical analysis description: | |
| In subgroup analyses according to the stratification parameters, all patients were included as stratified. Patients with missing values defining the subgroup were excluded from the corresponding analyses. There was no adjustment for multiple comparisons in the subgroup analyses. The subgroup analysis was to be considered explorative. pCR was analyzed separately for the subgroups according to HR status, age, tumor BRCA1/2 status and clinical nodal status (cN). | |
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[27] |
| P-value | = 0.617 ^[28] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 12.5 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -12.4 |
| upper limit | 37.4 |

Notes:

[27] - pCR rates between treatment arms in the predefined tBRCA1/2 non-mutated subgroup were estimated by two-sided continuity corrected chi-square test

[28] - p-value for tBRCA1/2 non-mutated subgroup

| Statistical analysis title | |
|---|--|
| pCR (ypT0/is ypN0) rates in subgroups, cN0 | |
| Statistical analysis description: | |
| In subgroup analyses according to the stratification parameters, all patients were included as stratified. Patients with missing values defining the subgroup were excluded from the corresponding analyses. There was no adjustment for multiple comparisons in the subgroup analyses. The subgroup analysis was | |

to be considered explorative. pCR was analyzed separately for the subgroups according to HR status, age, tumor BRCA1/2 status and clinical nodal status (cN).

| | |
|---|--|
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[29] |
| P-value | = 0.438 ^[30] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | 13.5 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -8 |
| upper limit | 34.9 |

Notes:

[29] - pCR rates between treatment arms in the cN0 subgroup were estimated by two-sided continuity corrected chi-square test post-hoc

[30] - p-value for cN0 subgroup

| | |
|-----------------------------------|--|
| Statistical analysis title | pCR (ypT0/is ypN0) rates in subgroups, cN+ |
|-----------------------------------|--|

Statistical analysis description:

In subgroup analyses according to the stratification parameters, all patients were included as stratified. Patients with missing values defining the subgroup were excluded from the corresponding analyses. There was no adjustment for multiple comparisons in the subgroup analyses. The subgroup analysis was to be considered explorative. pCR was analyzed separately for the subgroups according to HR status, age, tumor BRCA1/2 status and clinical nodal status (cN).

| | |
|---|--|
| Comparison groups | olaparib plus paclitaxel v carboplatinum plus paclitaxel |
| Number of subjects included in analysis | 106 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[31] |
| P-value | = 0.394 ^[32] |
| Method | Chi-squared corrected |
| Parameter estimate | absolute difference |
| Point estimate | -20.6 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -48 |
| upper limit | 6.9 |

Notes:

[31] - pCR rates between treatment arms in the cN+ subgroup were estimated by two-sided continuity corrected chi-square test post-hoc

[32] - p-value for cN+ subgroup

Secondary: To assess the pCR rates (ypT0 ypN0) in subgroups

| | |
|-----------------|--|
| End point title | To assess the pCR rates (ypT0 ypN0) in subgroups |
|-----------------|--|

End point description:

The pCR rates (ypT0 ypN0) were analyzed in subgroups defined by:

- a) Stratification factors
 - hormone-receptor status (HR-positive vs HR-negative)
 - age (< 40 years vs ≥ 40 years)
- b) Other baseline factors
 - tumor (t) BRCA1/2 status (mutated tBRCA1/2 vs non-mutated tBRCA1/2)
 - clinical nodal status (cN-negative [cN0] vs cN-positive [cN+]) assessed by sonography or if missing by palpation. This subgroup was not specified in the study protocol and was added post-hoc.

The analysis was performed in the modified intention-to-treat (mITT) set that included all patients who were randomized and started therapy.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 weeks | |

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|-------------------------------------|-----------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: percent | | | | |
| number (confidence interval 90%) | | | | |
| HR-positive, pCR=ypT0 ypN0 | 47.4 (27.4 to 68.0) | 20.0 (3.7 to 50.7) | | |
| HR-negative, pCR=ypT0 ypN0 | 50.0 (37.6 to 62.4) | 55.6 (38.2 to 72.0) | | |
| age <40 years, pCR=ypT0 ypN0 | 71.4 (51.3 to 86.8) | 45.5 (20.0 to 72.9) | | |
| age ≥40 years, pCR=ypT0 ypN0 | 39.6 (27.7 to 52.5) | 46.2 (29.2 to 63.8) | | |
| tBRCA1/2 mutated, pCR=ypT0 ypN0 | 54.3 (39.2 to 68.8) | 60.0 (39.4 to 78.3) | | |
| tBRCA1/2 non-mutated, pCR=ypT0 ypN0 | 43.3 (27.9 to 59.8) | 31.3 (13.2 to 54.8) | | |
| cN0, pCR=ypT0 ypN0 | 55.8 (43.5 to 67.6) | 50.0 (30.2 to 69.8) | | |
| cN+, pCR=ypT0 ypN0 | 29.4 (12.4 to 52.2) | 43.8 (22.7 to 66.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance -treatment discontinuations

| | |
|-----------------|--|
| End point title | Compliance -treatment discontinuations |
|-----------------|--|

End point description:

The compliance endpoints referred to dose reductions, treatment delays, treatment interruptions (including skipped intake of medication (infusions or tablets)) and premature treatment discontinuations.

Frequencies of patients, whose treatment had to be reduced, delayed or prematurely discontinued, were 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).

Compliance analysis was performed in the mITT set. The incidence and reasons of permanent discontinuation were reported per patient, for each treatment arm and overall.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 weeks | |

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|--|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: patients | | | | |
| Completed all study medication | 51 | 24 | | |
| Discontinued at least one study medication | 10 | 9 | | |
| Discontinued paclitaxel+carboplatinum/olaparib | 7 | 6 | | |
| Discontinued EC | 3 | 3 | | |
| Never received EC | 11 | 8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance - Dose reduction

| | |
|-----------------|-----------------------------|
| End point title | Compliance - Dose reduction |
|-----------------|-----------------------------|

End point description:

The compliance endpoints referred to dose reductions, treatment delays, treatment interruptions (including skipped intake of medication (infusions or tablets)) and premature treatment discontinuations.

Frequencies of patients, whose treatment had to be reduced, delayed or prematurely discontinued, were given for both treatment arms.

Compliance analysis was performed in the mITT set. The incidence and reasons of dose reductions and interruptions were reported per patient, for each treatment arm and overall; the premature discontinuation of a single drug was counted as an interruption. For dose reductions of olaparib, it was reported whether the reduction has been prescribed or not.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|-----------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: patients | | | | |
| Paclitaxel, any reason | 8 | 9 | | |
| Olaparib, any reason | 4 | 0 | | |
| Carboplatinum, any reason | 0 | 7 | | |
| EC, any reason | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance - Dose delays

| | |
|-----------------|--------------------------|
| End point title | Compliance - Dose delays |
|-----------------|--------------------------|

End point description:

The compliance endpoints referred to dose reductions, treatment delays, treatment interruptions (including skipped intake of medication (infusions or tablets)) and premature treatment discontinuations.

Frequencies of patients, whose treatment had to be reduced, delayed or prematurely discontinued, were given for both treatment arms.

Compliance analysis was performed in the mITT set. The incidence and reasons of delays in paclitaxel, carboplatin and EC treatment was reported per patient for each treatment arm and overall. There were no delays of olaparib since patients had to take olaparib twice daily and were not to take an extra dose to make up for a missing one.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

| End point values | olaparib plus paclitaxel | carboplatinum plus paclitaxel | | |
|-----------------------------|--------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 37 | | |
| Units: patients | | | | |
| Paclitaxel, any reason | 41 | 28 | | |
| Carboplatinum, any reason | 0 | 28 | | |
| EC, any reason | 27 | 12 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the study treatment period were reported.

Adverse event reporting additional description:

Non-serious AEs are reported per patient; any grade (1-4) during the complete treatment duration for the overall safety population. AEs per patient occurring more frequently (> 20%) in both arms are shown.

Note, overall number of single AE occurrences per term was not assessed, only per patient.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | olaparib plus paclitaxel |
|-----------------------|--------------------------|

Reporting group description: -

| | |
|-----------------------|-------------------------------|
| Reporting group title | carboplatinum plus paclitaxel |
|-----------------------|-------------------------------|

Reporting group description: -

| Serious adverse events | olaparib plus paclitaxel | carboplatinum plus paclitaxel | |
|---|--------------------------|-------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 69 (13.04%) | 20 / 37 (54.05%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Compression fracture | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 4 / 37 (10.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|-----------------|--|
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | 2 / 37 (5.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 4 / 37 (10.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 69 (2.90%) | 8 / 37 (21.62%) | |
| occurrences causally related to treatment / all | 2 / 2 | 8 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 3 / 37 (8.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 5 / 37 (13.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess oral | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 2 / 69 (2.90%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 69 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | olaparib plus paclitaxel | carboplatinum plus paclitaxel | |
|---|-----------------------------|----------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 68 / 69 (98.55%) | 37 / 37 (100.00%) | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 20 / 69 (28.99%) | 18 / 37 (48.65%) | |
| occurrences (all) | 20 | 18 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 24 / 69 (34.78%) | 23 / 37 (62.16%) | |
| occurrences (all) | 24 | 23 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 38 / 69 (55.07%) | 29 / 37 (78.38%) | |
| occurrences (all) | 38 | 29 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 22 / 69 (31.88%) | 11 / 37 (29.73%) | |
| occurrences (all) | 22 | 11 | |
| Headache | | | |
| subjects affected / exposed | 30 / 69 (43.48%) | 11 / 37 (29.73%) | |
| occurrences (all) | 30 | 11 | |

| | | | |
|---|------------------------|------------------------|--|
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 53 / 69 (76.81%) 53 | 25 / 37 (67.57%) 25 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 28 / 69 (40.58%) 28 | 10 / 37 (27.03%) 10 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 63 / 69 (91.30%) 63 | 35 / 37 (94.59%) 35 | |
| Leukopenia subjects affected / exposed occurrences (all) | 58 / 69 (84.06%) 58 | 33 / 37 (89.19%) 33 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 28 / 69 (40.58%) 28 | 26 / 37 (70.27%) 26 | |
| Neutropenia subjects affected / exposed occurrences (all) | 47 / 69 (68.12%) 47 | 32 / 37 (86.49%) 32 | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 55 / 69 (79.71%) 55 | 29 / 37 (78.38%) 29 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 38 / 69 (55.07%) 38 | 24 / 37 (64.86%) 24 | |
| Vomiting subjects affected / exposed occurrences (all) | 13 / 69 (18.84%) 13 | 10 / 37 (27.03%) 10 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 26 / 69 (37.68%) 26 | 16 / 37 (43.24%) 16 | |
| Stomatitis subjects affected / exposed occurrences (all) | 33 / 69 (47.83%) 33 | 16 / 37 (43.24%) 16 | |

| | | | |
|---|------------------------|------------------------|--|
| Dyspepsia subjects affected / exposed occurrences (all) | 15 / 69 (21.74%) 15 | 7 / 37 (18.92%) 7 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 61 / 69 (88.41%) 61 | 27 / 37 (72.97%) 27 | |
| Skin reaction subjects affected / exposed occurrences (all) | 36 / 69 (52.17%) 36 | 18 / 37 (48.65%) 18 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 25 / 69 (36.23%) 25 | 12 / 37 (32.43%) 12 | |
| Epistaxis subjects affected / exposed occurrences (all) | 19 / 69 (27.54%) 19 | 12 / 37 (32.43%) 12 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 11 / 69 (15.94%) 11 | 12 / 37 (32.43%) 12 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 11 May 2016 | 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: <ul style="list-style-type: none">• 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. |
| 26 March 2018 | The protocol amendment 2 (protocol version 3 from 26.03.2018) included the following changes: <ul style="list-style-type: none">• 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; |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33098995>