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
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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 cyclophosphamideand (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 cyclophosphamideand (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 cyclophosphamideand (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 α=0.1. The analysis was performed in the modified intention-to-treat (mITT) set that icluded all patients who were randomized and started therapy.
Note, the primary endpoint was to assess pCR=ypT0/is ypN0 rate only in olabarib 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 ≤55% in the olaparib arm

[2] - one-group chi-square test to exclude a pCR rate of ≤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 icluded 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 α=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 icluded 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 carbiplatinum 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 icluded 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 icluded 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 icluded 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 icluded 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 icluded 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 icluded 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 icluded 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	53 / 69 (76.81%)	25 / 37 (67.57%)	
occurrences (all)	53	25	
Dysgeusia			
subjects affected / exposed	28 / 69 (40.58%)	10 / 37 (27.03%)	
occurrences (all)	28	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	63 / 69 (91.30%)	35 / 37 (94.59%)	
occurrences (all)	63	35	
Leukopenia			
subjects affected / exposed	58 / 69 (84.06%)	33 / 37 (89.19%)	
occurrences (all)	58	33	
Thrombocytopenia			
subjects affected / exposed	28 / 69 (40.58%)	26 / 37 (70.27%)	
occurrences (all)	28	26	
Neutropenia			
subjects affected / exposed	47 / 69 (68.12%)	32 / 37 (86.49%)	
occurrences (all)	47	32	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	55 / 69 (79.71%)	29 / 37 (78.38%)	
occurrences (all)	55	29	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	38 / 69 (55.07%)	24 / 37 (64.86%)	
occurrences (all)	38	24	
Vomiting			
subjects affected / exposed	13 / 69 (18.84%)	10 / 37 (27.03%)	
occurrences (all)	13	10	
Diarrhoea			
subjects affected / exposed	26 / 69 (37.68%)	16 / 37 (43.24%)	
occurrences (all)	26	16	
Stomatitis			
subjects affected / exposed	33 / 69 (47.83%)	16 / 37 (43.24%)	
occurrences (all)	33	16	

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