Clinical trial results:
A randomized phase III trial comparing nanoparticle-based paclitaxel with solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer (GeparSepto)

Summary

EudraCT number	2011-004714-41
Trial protocol	DE
Global end of trial date	31 March 2018
Results information	
Result version number	v1 (current)
This version publication date	15 May 2022
First version publication date	15 May 2022
Summary attachment (see zip file)	GeparSepto CSR Synopsis (GBG 69 - GeparSepto CSR Synopsis Addendum.pdf) GeparSepto CSR Synopsis addendum (GeparSepto time to event & amendment 3 analysis_CSR synopsis addendum.pdf)

Trial information

Trial identification	
Sponsor protocol code	GBG69
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01583426
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	05 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 July 2015
Global end of trial reached?	Yes
Global end of trial date	31 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the pathological complete response (pCR=ypT0 ypN0) rates of neoadjuvant treatment of nab-paclitaxel with solvent-based paclitaxel as part of neoadjuvant treatment of operable or locally advanced primary breast cancer.

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 study was conducted in accordance with the Declaration of Helsinki and its revisions, the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and in accordance with applicable laws of the pertinent regulatory authorities 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: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2012
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: 1229
Worldwide total number of subjects	1229
EEA total number of subjects	1229

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)	1104
From 65 to 84 years	125
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 17 months (Q-III 2012 –Q-IV 2013) in 69 German sites. 1373 patients were screened, 1229 patients were
randomized and 1206 started treatment (606 with
nab-paclitaxel and 600 with solvent-based paclitaxel).

Pre-assignment

Screening details:

Women >=18 yrs with Karnofsky index >=80% and previously untreated uni- or bilateral primary invasive BC. Central assessment of core biopsies for HR and HER2 status, Ki67 and SPARC expression, and presence of TILs. Tumor >2cm (cT2 - cT4a–d) without additional risk factors or 1-2cm (cT1c) with one of the following: cN+/pN+ orHR- or HER2+ or Ki67>20%

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	nab-paclitaxel weekly

Arm description:

nab-paclitaxel weekly (on days 1, 8, and 15, for four 3-week cycles). After taxane treatment, all patients received epirubicin 90 mg/m² intravenously plus cyclophosphamide 600 mg/m² intravenously on day 1 for four 3-week cycles. Patients with HER2-positive tumours received trastuzumab 8 mg/kg (loading dose) intravenously followed by 6 mg/kg intravenously every 3 weeks (day 21 of the same 3 week cycle) and pertuzumab 840 mg intravenously followed by 420 mg intravenously every 3 weeks simultaneously with all chemotherapy cycles.

Arm type	Experimental
Investigational medicinal product name	nab-paclitaxel
Investigational medicinal product code	ABI-007
Other name	Abraxane
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

nab-paclitaxel (Abraxane; Celgene Corporation, Summit, NJ, USA) was given intravenously on days 1, 8, and 15, for four 3-week cycles initially at 150 mg/m². The dose was later reduced to 125 mg/m² based on a recommendation of the independent data monitoring committee after recruitment of 464 patients (protocol version March 28, 2013).

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab (in HER2-positive subjects) was dosed at 840 mg, i.v., on Day 1 of the first cycle, followed by 420 mg, i.v., on Day 1 of each following cycle. Transfusion time of pertuzumab was

60 (±10) min and was started after the infusion of trastuzumab.

Arm title	solvent-based paclitaxel

Arm description:

solvent-based paclitaxel 80 mg/m² intravenously on days 1, 8, and 15, for four 3-week cycles. After taxane treatment, all patients received epirubicin 90 mg/m² intravenously plus cyclophosphamide 600 mg/m² intravenously on day 1 for four 3-week cycles. Patients with HER2-positive tumours received trastuzumab 8 mg/kg (loading dose) intravenously followed by 6 mg/kg intravenously every 3 weeks (day 21 of the same 3 week cycle) and pertuzumab 840 mg intravenously followed by 420 mg intravenously every 3 weeks simultaneously with all chemotherapy cycles.

Arm type	Active comparator
Investigational medicinal product name	solvent-based paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

solvent-based paclitaxel 80 mg/m2, i.v., in a dose-dense regimen of once weekly (QW) doses for 12 weeks

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab (in HER2-positive subjects) was dosed at 840 mg, i.v., on Day 1 of the first cycle, followed by 420 mg, i.v., on Day 1 of each following cycle. Transfusion time of pertuzumab was 60 (±10) min and was started after the infusion of trastuzumab.

Number of subjects in period 1[1]	nab-paclitaxel weekly	solvent-based paclitaxel
Started	606	600
Completed	444	477
Not completed	162	123
Discontinued Taxane, Started and Completed EC	83	42
Completed Taxane, Not Started EC	7	6
Completed Taxane, Started but Discontinued EC	32	37
Discontinued Taxane, Started but Discontinued EC	12	7
Discontinued Taxane, Not Started EC	28	31

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1229 patients were worldwide enrolled, however, only paients who started treatment were evaluated in the baseline period (modified intent-to-treat population)

Baseline characteristics

Reporting groups	
Reporting group title	nab-paclitaxel weekly
Reporting group description:	
nab-paclitaxel weekly (on days 1, 8, and 15, for four 3-week cycles). After taxane treatment, all patients received epirubicin 90 mg/m² intravenously plus cyclophosphamide 600 mg/m² intravenously on day 1 for four 3-week cycles. Patients with HER2-positive tumours received trastuzumab 8 mg/kg (loading dose) intravenously followed by 6 mg/kg intravenously every 3 weeks (day 21 of the same 3 week cycle) and pertuzumab 840 mg intravenously followed by 420 mg intravenously every 3 weeks simultaneously with all chemotherapy cycles.	
Reporting group title	solvent-based paclitaxel
Reporting group description:	
solvent-based paclitaxel 80 mg/m² intravenously on days 1, 8, and 15, for four 3-week cycles. After taxane treatment, all patients received epirubicin 90 mg/m² intravenously plus cyclophosphamide 600 mg/m² intravenously on day 1 for four 3-week cycles. Patients with HER2-positive tumours received trastuzumab 8 mg/kg (loading dose) intravenously followed by 6 mg/kg intravenously every 3 weeks (day 21 of the same 3 week cycle) and pertuzumab 840 mg intravenously followed by 420 mg intravenously every 3 weeks simultaneously with all chemotherapy cycles.	

Reporting group values	nab-paclitaxel weekly	solvent-based paclitaxel	Total
Number of subjects	606	600	1206
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	49	48	
inter-quartile range (Q1-Q3)	43 to 57	41 to 56	-
Gender categorical Units: Subjects			
Female	606	600	1206
Male	0	0	0

End points

End points reporting groups

Reporting group title	nab-paclitaxel weekly

Reporting group description:

nab-paclitaxel weekly (on days 1, 8, and 15, for four 3-week cycles). After taxane treatment, all patients received epirubicin 90 mg/m² intravenously plus cyclophosphamide 600 mg/m² intravenously on day 1 for four 3-week cycles. Patients with HER2-positive tumours received trastuzumab 8 mg/kg (loading dose) intravenously followed by 6 mg/kg intravenously every 3 weeks (day 21 of the same 3 week cycle) and pertuzumab 840 mg intravenously followed by 420 mg intravenously every 3 weeks simultaneously with all chemotherapy cycles.

Reporting group title	solvent-based paclitaxel

Reporting group description:

solvent-based paclitaxel 80 mg/m² intravenously on days 1, 8, and 15, for four 3-week cycles. After taxane treatment, all patients received epirubicin 90 mg/m² intravenously plus cyclophosphamide 600 mg/m² intravenously on day 1 for four 3-week cycles. Patients with HER2-positive tumours received trastuzumab 8 mg/kg (loading dose) intravenously followed by 6 mg/kg intravenously every 3 weeks (day 21 of the same 3 week cycle) and pertuzumab 840 mg intravenously followed by 420 mg intravenously every 3 weeks simultaneously with all chemotherapy cycles.

Primary: pCR (ypT0 ypN0)

End point title	pCR (ypT0 ypN0)

End point description:

End point type	Primary

End point timeframe:

from start of treatment to surgery, 24 weeks

End point values	nab-paclitaxel weekly	solvent-based paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	606	600		
Units: percent				
number (confidence interval 95%)	38.4 (34.6 to 42.3)	29.0 (25.4 to 32.6)		

Statistical analyses

Statistical analysis title	continuity corrected χ2-test nP vs P

Statistical analysis description:

The primary endpoint was summarized as pCR rate for each treatment group. Two-sided 95% confidence intervals
were calculated according to Pearson and Clopper (1934). The difference in the rates of pCR between groups was
evaluated as an odds ratio and its 95% confidence interval.

Comparison groups	nab-paclitaxel weekly v solvent-based paclitaxel
Number of subjects included in analysis	1206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00065 [1]
Method	Chi-squared

Notes:

[1] - unadjusted p=0·00065;
OR 1·53, 95% CI 1·20–1·95;

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were analyzed for the whole 24-week treatment duration, during taxane treatment, and during EC treatment.

Adverse event reporting additional description:

Safety analyses were conducted in the Safety set. One subject, who was randomized to receive nab paclitaxel, instead received sb paclitaxel and was analyzed according to the actual treatment received (nP = 605, P= 601)
Predefined treatment-related AEs of any grade (1-4) are given. Other treatment-related AEs of any grade are given if occuring >20%

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	nab-Paclitaxel weekly

Reporting group description:

One subject, who was randomized to receive nab paclitaxel, instead received sb paclitaxel. This subject was analyzed in the Safety Set and the Per Protocol Set according to the actual treatment received.

Reporting group title	solvent-based Paclitaxel

Reporting group description:

One subject, who was randomized to receive nab paclitaxel, instead received sb paclitaxel. This subject was analyzed in the Safety Set and the Per Protocol Set according to the actual treatment received

Serious adverse events	nab-Paclitaxel weekly	solvent-based Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	156 / 605 (25.79%)	127 / 601 (21.13%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	3	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign and malignant (including cysts and polyps)			
subjects affected / exposed	1 / 605 (0.17%)	2 / 601 (0.33%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	17 / 605 (2.81%)	15 / 601 (2.50%)	
occurrences causally related to treatment / all	17 / 17	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
General disorders and administration site conditions	Additional description: SAEs were analyzed for the whole 24-week treatment Duration and tabulated by SOC, but not by preferred Terms. Relatedness was not tabulated for SAEs, therefore here we conservatively record all SAEs as related to treatment		
subjects affected / exposed	42 / 605 (6.94%)	38 / 601 (6.32%)	
occurrences causally related to treatment / all	42 / 42	38 / 38	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	4 / 605 (0.66%)	3 / 601 (0.50%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	3 / 605 (0.50%)	8 / 601 (1.33%)	
occurrences causally related to treatment / all	3 / 3	8 / 8	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	6 / 605 (0.99%)	4 / 601 (0.67%)	
occurrences causally related to treatment / all	6 / 6	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	7 / 605 (1.16%)	9 / 601 (1.50%)	
occurrences causally related to treatment / all	7 / 7	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	3 / 605 (0.50%)	7 / 601 (1.16%)	
occurrences causally related to treatment / all	3 / 3	7 / 7	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Nervous system disorders			

subjects affected / exposed	27 / 605 (4.46%)	2 / 601 (0.33%)	
occurrences causally related to treatment / all	27 / 27	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and the lymphatic system disorders			
subjects affected / exposed	31 / 605 (5.12%)	22 / 601 (3.66%)	
occurrences causally related to treatment / all	31 / 31	22 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	40 / 605 (6.61%)	22 / 601 (3.66%)	
occurrences causally related to treatment / all	40 / 40	22 / 22	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatobiliary disorders			
Hepato-biliary disorders			
subjects affected / exposed	1 / 605 (0.17%)	1 / 601 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	2 / 605 (0.33%)	0 / 601 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	0 / 605 (0.00%)	1 / 601 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal, connective tissue and bone disorders			
subjects affected / exposed	1 / 605 (0.17%)	1 / 601 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Infections and infestations			
subjects affected / exposed	30 / 605 (4.96%)	34 / 601 (5.66%)	
occurrences causally related to treatment / all	30 / 30	34 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolism and nutrition			
subjects affected / exposed	2 / 605 (0.33%)	4 / 601 (0.67%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	nab-Paclitaxel weekly	solvent-based Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	605 / 605 (100.00%)	600 / 601 (99.83%)	
Investigations			
Alanine aminotransferase increased	Additional description: Increased ALAT		
subjects affected / exposed	337 / 605 (55.70%)	340 / 601 (56.57%)	
occurrences (all)	337	340	
Aspartate aminotransferase increased	Additional description: Increased ASAT		
subjects affected / exposed	233 / 605 (38.51%)	215 / 601 (35.77%)	
occurrences (all)	233	215	
Alkaline phosphatase increased			
subjects affected / exposed	143 / 605 (23.64%)	123 / 601 (20.47%)	
occurrences (all)	143	123	
Increased creatinine			
subjects affected / exposed	58 / 605 (9.59%)	51 / 601 (8.49%)	
occurrences (all)	58	51	
Increased bilirubin			
subjects affected / exposed	17 / 605 (2.81%)	28 / 601 (4.66%)	
occurrences (all)	17	28	
Vascular disorders			
Epistaxis			
subjects affected / exposed	217 / 605 (35.87%)	212 / 601 (35.27%)	
occurrences (all)	217	212	

Hypotension			
subjects affected / exposed	49 / 605 (8.10%)	38 / 601 (6.32%)	
occurrences (all)	49	38	
Hot flush	Additional description: reported as free-text		
subjects affected / exposed	133 / 605 (21.98%)	140 / 601 (23.29%)	
occurrences (all)	133	140	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	513 / 605 (84.79%)	384 / 601 (63.89%)	
occurrences (all)	513	384	
Headache			
subjects affected / exposed	152 / 605 (25.12%)	134 / 601 (22.30%)	
occurrences (all)	152	134	
Taste or smell abnormalities	Additional description: reported as free-text		
subjects affected / exposed	134 / 605 (22.15%)	129 / 601 (21.46%)	
occurrences (all)	134	129	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	567 / 605 (93.72%)	550 / 601 (91.51%)	
occurrences (all)	567	550	
Anaemia			
subjects affected / exposed	560 / 605 (92.56%)	528 / 601 (87.85%)	
occurrences (all)	560	528	
Neutropenia			
subjects affected / exposed	530 / 605 (87.60%)	487 / 601 (81.03%)	
occurrences (all)	530	487	
Lymphopenia			
subjects affected / exposed	465 / 605 (76.86%)	445 / 601 (74.04%)	
occurrences (all)	465	445	
Thrombopenia			
subjects affected / exposed	144 / 605 (23.80%)	144 / 601 (23.96%)	
occurrences (all)	144	144	
Febrile neutropenia			
subjects affected / exposed	27 / 605 (4.46%)	22 / 601 (3.66%)	
occurrences (all)	27	22	
General disorders and administration site conditions			

Fatigue and asthenia			
subjects affected / exposed	485 / 605 (80.17%)	451 / 601 (75.04%)	
occurrences (all)	485	451	
Fever without neutropenia			
subjects affected / exposed	76 / 605 (12.56%)	73 / 601 (12.15%)	
occurrences (all)	76	73	
Immune system disorders			
Allergic reactions			
subjects affected / exposed	87 / 605 (14.38%)	121 / 601 (20.13%)	
occurrences (all)	87	121	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	414 / 605 (68.43%)	418 / 601 (69.55%)	
occurrences (all)	414	418	
Mucositis/stomatitis/esophagitis			
subjects affected / exposed	304 / 605 (50.25%)	284 / 601 (47.25%)	
occurrences (all)	304	284	
Diarrhoea			
subjects affected / exposed	297 / 605 (49.09%)	256 / 601 (42.60%)	
occurrences (all)	297	256	
Vomiting			
subjects affected / exposed	135 / 605 (22.31%)	130 / 601 (21.63%)	
occurrences (all)	135	130	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	101 / 605 (16.69%)	102 / 601 (16.97%)	
occurrences (all)	101	102	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	563 / 605 (93.06%)	556 / 601 (92.51%)	
occurrences (all)	563	556	
Rash maculo-papular			
subjects affected / exposed	193 / 605 (31.90%)	139 / 601 (23.13%)	
occurrences (all)	193	139	
Hand and foot syndrome			

subjects affected / exposed	171 / 605 (28.26%)	106 / 601 (17.64%)	
occurrences (all)	171	106	
Nail changes	Additional description: reported as free-text		
subjects affected / exposed	286 / 605 (47.27%)	170 / 601 (28.29%)	
occurrences (all)	286	170	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	200 / 605 (33.06%)	190 / 601 (31.61%)	
occurrences (all)	200	190	
Myalgia			
subjects affected / exposed	173 / 605 (28.60%)	144 / 601 (23.96%)	
occurrences (all)	173	144	
Infections and infestations			
Infection			
subjects affected / exposed	194 / 605 (32.07%)	176 / 601 (29.28%)	
occurrences (all)	194	176	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	109 / 605 (18.02%)	100 / 601 (16.64%)	
occurrences (all)	109	100	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2012	Amendment 1 (20 Aug 2012): A window of opportunity sub-study (n = 60) was included, to compare the predictive value of several biomarkers for resistance to HER2 targeted therapy, in a cohort treated with either trastuzumab, pertuzumab, or a combination of both agents. In this substudy, HER2-positive subjects received 6 weeks of treatment with either trastuzumab, pertuzumab or combination of both. The clinical response after 6 weeks and biomarker profile was compared between groups and correlated to response after the addition of 4 cycles of taxane and at the end of the main study. Amendment 1 also changed the cut-off for definition of HER2-positive disease by in situ hybridization from ≥ 2.2 to ≥ 2.0 according to FDA as well American Society of Clinical Onocology (ASCO)/ College of American Pathologists (CAP) therapy recommendations.
28 March 2013	An interim safety analysis of data was performed for the first 60 subjects to complete systemic treatment with nab-paclitaxel 150 mg/m2 (n = 30) or sb-paclitaxel (n = 30) which revealed that the nab-paclitaxel dose of 150 mg/m2 was observed to have a higher incidence of non hematological toxicities (Jackisch, 2013). In particular, there was a higher incidence in the nab-paclitaxel group compared with the sb-paclitaxel group for the following: - Peripheral sensory neuropathy (73.3% vs 43.3% for all grades, and 10% vs 0% for Grade 3-4). - Incidence of treatment discontinuation (26.7% vs 3.3%, respectively) and - Incidence of dose reductions (33.3% vs 13.3%, respectively). These observations led to an agreement with the IDMC to amend the study and reduce the nab-paclitaxel dose to 125 mg/m2 QW. The amendment also required that subjects with Grade 2 PSN did not receive further nab-paclitaxel dosing until resolution to Grade ≤ 1. In case of resolution to Grade ≤ 1 therapy of the subsequent applications was continued with reduced dose in a 3 of 4 schedule, i.e. 3 applications, the next was cancelled, etc. If symptoms were not resolved to Grade ≤ 1 within 3 weeks, taxane treatment had to be stopped definitively. In case of Grade 3/4 PSN taxane treatment had to be stopped. An additional interim analysis was conducted to include another 60 subjects who were already enrolled and treated, in which a continued imbalance of PSN was observed which was higher for subjects in the nab-paclitaxel group compared with the sb-paclitaxel group. Prior to the implementation of the amended dose level, 38% (464/1229) of subjects had already been recruited into the Trial.

10 June 2015	Prior to Amendment 3, follow-up of subjects post-surgery was limited to the collection of health status based on yearly chart reviews or information from the GBG registry of previous study participants. Amendment 3 clarified that follow-up will continue until the analysis of invasive disease-free survival (IDFS) (and other time-to-event secondary endpoints) after 248 progression events have occurred. This is anticipated to occur at the end of 2017/early 2018, approximately 5 years after the first subject was enrolled. A secondary endpoint was added to assess quality of life, with a focus on PN (using the Functional Assessment of Cancer Therapy [FACT]-Taxane [version 4] questionnaire) and on cardiac toxicity. Secondary endpoints were also added to correlate pCR rate with circulating tumor DNA at the time of surgery, to identify early relapses based on circulating tumor deoxyribonucleic acid (DNA) during follow up, to collect information about BRCA status and other mutations, and to assess smoking habits and alcohol consumption in relation to efficacy and safety of treatment and genetic changes in the tumor. To support these objectives, the following information will be collected during follow up: - Clinical history (including smoking habits and alcohol consumption) and concomitant medication - Symptoms and toxicities (including cardiac toxicities) - FACT-Taxane (version 4) questionnaire to assess quality of life with a focus on PN - Treatment of (persisting) PN

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/26869049

http://www.ncbi.nlm.nih.gov/pubmed/31082269