GBG 69 GeparSepto Clinical Study Report Addendum for Time-To-Event and Amendment 3 Analysis

GeparSepto: A Randomized Phase III Trial Comparing Nanoparticle-Based Paclitaxel With Solvent-Based Paclitaxel As Part Of Neoadjuvant Chemotherapy For Patients With Early Breast Cancer

Indication studied:	*Neoadjuvant treatment of operable and locally advanced early breast cancer*
Developmental phase of study:	*Phase 3*
First subject first visit:	*30 Jul 2012*
Last subject last visit:	*03 Jul 2015*
Data base lock (survival analysis)	*18 Jun 2018*
Data base lock (Amendment 3)	06 July 2018
Date of report:	*28 September 2018 / 09 November 2018*

Sponsor's Responsible Medical Officer:	*Prof. Sibylle Loibl, MD* *Phone:+49(0)6102 7480426* *Fax: +49 (0) 6102 7480440*

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline and is being submitted in accordance with 21 Code of Federal Regulation (CFR) 312.120.

SYNOPSIS ADDENDUM

Title of Study:

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) – GBG 69

Investigators:

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Study Center(s): See Annex 1.

Publication update:

- Untch M, Jackisch C, Schneeweiss A et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016;17(3):345-56.
- Loibl S, Jackisch C, Schneeweiss A et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. Ann Oncol. 2017;28(3):497-504.
- Furlanetto J, Jackisch C, Untch M et al. Efficacy and safety of nab-paclitaxel 125 mg/m^2 and nab-paclitaxel 150 mg/m^2 compared to paclitaxel in early high-risk breast cancer. Results from the neoadjuvant randomized GeparSepto study (GBG 69). Breast Cancer Res Treat. 2017;163(3):495-506.
- Untch M, Jackisch C, Schneeweiss A et al. Nab-paclitaxel improves Disease free Survival in early breast cancer-GBG 69 – GeparSepto (submitted for publication).

Studied Period (years):

Date first patient enrolled: 30 Jul 2012

Data base lock for survival analysis: 18 Jun 2018

Data base lock for amendment 3: 06 Jul 2018

Phase of Development:

Phase 3

Objectives presented in the addendum for Time-to-Event Analysis:

- Determine loco-regional invasive recurrence free interval (LRRFI), distant-disease-free survival (DDFS), invasive disease-free survival (iDFS), disease-free survival (DFS – post-hoc), overall survival (OS) and event-free survival (EFS) in both arms

and according to stratified subpopulations.

Objectives presented in the addendum for Amendment 3:

- To assess quality of life (QoL) with a focus on persisting peripheral neuropathy using the FACT Taxane (Version 4) questionnaire, treatment of peripheral sensory neuropathy (PNP), and cardiac toxicity
- To assess smoking habits and alcohol consumption before and after treatment.

Number of patients (planned and analyzed):

The study planned to recruit 1200 patients with approximately 400 patients with HER2+ disease.

In total, 1229 patients were randomized, of them 402 patients with HER2+ disease. Overall, 631 patients consented to Amendment 3 (52.3%).

Details on **Study Methodology, Test Products, Dose and Mode of Administration, Batch Number, Duration of Treatment, Reference Therapy, Dose and Mode of Administration** have been previously reported (Clinical Study Report 11 October 2016).

Criteria for Evaluation:

Efficacy:

Secondary Endpoints for Time-to-Event Analysis

- **Loco-regional invasive recurrence free interval (LRRFI)**, defined as: time in months from randomization until any loco-regional (ipsilateral breast (invasive or DCIS), local/regional lymph nodes) recurrence of disease, any contralateral breast cancer whichever occurs first. Progression under therapy is not considered as an event for LRRFI. Distant metastases, secondary malignancy or death due to any cause are considered competing events.
- **Distant disease free survival (DDFS)**, defined as: time in months from randomization until any distant recurrence of disease, any secondary malignancy or death due to any cause whichever occurs first. Patients without event were censored at the date of the last contact.
- **Invasive disease-free survival (iDFS)**, defined as: time in months from randomization until any invasive loco-regional (ipsilateral breast, local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant recurrence of disease, any secondary malignancy or death due to any cause whichever occurs first. Progression under therapy is not considered as an event for iDFS. Patients without event were censored at the date of the last contact.
- **Disease-free survival (DFS)**, defined as time in months from randomization until any (invasive or non-invasive) loco-regional (ipsilateral breast, local/regional lymph nodes) recurrence of disease, any (invasive or non-invasive) contralateral breast cancer, any distant recurrence of disease, any secondary malignancy or death due to any cause whichever occurs first. Progression under therapy is not considered as an event for DFS. Patients without event were censored at the date of the last contact.
- **Overall survival (OS)**, defined as: time in months from randomization until death due to any cause. Patients alive were censored at the date of the last contact.

- **Event free survival (EFS)**, defined as: time in months from randomization until disease progression under neo-adjuvant therapy resulting in inoperability, any invasive loco-regional (ipsilateral breast, local/regional lymph nodes) recurrence of disease after neoadjuvant therapy, any invasive contralateral breast cancer, any distant recurrence of disease or death due to any cause, whichever occurs first. Patients without event were censored at the date of the last contact. Secondary malignancies are not considered as events.

Endpoints for Amendment 3:

- Number and percentage of patients with PNP grade 2-4 and 3-4 unresolved until end of treatment (EOT) but resolved afterwards
- Time to resolution of grade 2-4 and grade 3-4 PNP including additional data collected according to Amendment 3
- Number and percentage of patients with PNP new/worsened after EOT
- PNP grades at different time points after EOT
- FACT Taxane scores at different time points after EOT
- Number and percentage of patients choosing the worst 2 items on FACT Taxane subscales at different time points after EOT
- Cardiac toxicity: Left ventricular ejection fraction (LVEF) decrease and other findings in cardio echography, at different time points after EOT
- Smoking/alcohol consumption questionnaires

Statistical Methods for Time-to-Event Analysis:

All time-to-event analyses were performed in the mITT set, meaning all patients randomized and received at least one dose of study medication were included.

For iDFS, DFS, EFS, DDFS, and OS curves were estimated using the Kaplan-Meier method, based on the mITT population. Kaplan-Meier estimates of 3-, 4- and 5-year probability of survival were provided together with the 95% CI. For LRRFI the cumulative incidence function was estimated; estimates of 3-, 4- and 5-year probability of survival were provided together with the 95% CI. 2-sided log-rank test was used to compare iDFS, DFS, EFS, DDFS and OS between treatment arms. 2-sided Gray's test was used to compare LRRFI between treatment arms.

Univariate and multivariate Cox proportional hazards model was used for iDFS, DFS, EFS, DDFS, OS to report hazard ratios with 95% CI and to adjust for prespecified covariates.

The results are presented in tables and graphically as forest plots.

Univariate Fine-Gray model was used for LRRFI to report hazard ratio with 95% CI.

iDFS, DFS, EFS, DDFS, OS were analyzed in the following subgroups (as stratified): breast cancer subtype (HER2-positive/HR-negative vs. HER2-positive/HR-positive vs. HER2-negative/HR-negative vs HER2-negative/HR-positive), Ki 67 at baseline (≤20% vs. >20%), SPARC (negative vs positive), HER2 (positive vs negative), HR (ER and/or PgR positive vs ER and PgR negative), pCR.

There was no adjustment for multiple comparisons in the analyses in subgroups which are to be considered explorative. The interaction with treatment arm was assessed by including and

interaction term into Cox proportional model.

Statistical Methods for Amendment 3 Analysis:

Categorical variables were summarized as number and percent of patients in each category. Continuous quality of life scales were reported as mean (StD). Time to resolution of PNP was presented using Kaplan-Meier product-limit estimator. The significance level is set to a two-sided $\alpha = 0.05$. The p-values are to be considered as exploratory, without adjustments for multiplicity. The time after EOT is defined ±3 months.

Subject Accountability: The number of patients who consented to the Amendment 3 was reported per treatment arm, in Dose Day 1 subgroups and overall. The length of PNP follow-up (time in weeks between randomization in GeparSepto study and last Amendment 3 assessment for patients who consented to Amendment 3, or the last date with known PNP status for patients with PNP unresolved until EOT who did not consent to Amendment 3 but provided information on their PNP status or EOT for all other patients) was estimated for the safety set in each treatment arm, Dose Day 1 group and overall, using inverse Kaplan-Meier censored at resolution to ≤ grade 1 date.

PNP Analyses: The number and percentage of patients in whom PNP grade 2-4 or grade 3-4 was resolved to grade ≤1 before or after EOT were reported per treatment arm, Dose Day 1 group and overall for the safety set and for the Amendment 3 set. Time of resolution of grade 2-4 and grade 3-4 PNP to PNP grade ≤1 was analyzed using Kaplan-Meier curves (median and its 95% CI were reported) and compared between Dose Day 1 groups with log-rank test (overall for 3 groups and pairwise). Patients in which peripheral sensory neuropathy is persistent grade ≥2 were censored at the date of the last assessment. For patients from PNP resolution set who did not consent to all the assessments according to Amendment 3 but volunteered information on the current PNP grade, this information was included in the analysis.

Patients with grade 2-4 PNP unresolved pre-EOT who consented to the Amendment 3 were listed with their current PNP grade and treatment received for PNP.

Further analysis: Additionally, for the Amendment 3 subset the following were presented: the number and percentage of patients in whom PNP grade 2-4 newly occurred, list of newly occurred PNP; the list of patients in whom PNP aggravated; table with PNP G0/G1(resolved), G2, G3, G4 per arm at different time points after EOT.

FACT-Taxane analysis: 5 scales (Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and Taxane Subscale (“additional concerns”) as well as the FACT-Taxane Trial Outcome Index (FACT-Taxane TOI), the FACT-G total score and the FACT-Taxane total score were computed per completed questionnaire according to the scoring guideline and were presented per treatment arm and Dose Day 1 subgroup, according to the time after EOT, in tables as mean and StD. Number and percentage of patients choosing the worst two item categories were reported for each of 5 subscales per arm and Dose Day 1 subgroup, according to the time after EOT. The higher the score, the better is the QoL. Numbers of evaluable questionnaires were reported per time point.

Cardiac toxicity: LVEF decreased by ≥10% from baseline and under institution LLN in any beyond-trial assessment was reported per patient, per treatment arm and overall; it was not categorized in ≥40%, 30%-<40%, <30% as planned due to very few data reported at all and many missing of the actual LVEF level (only decrease yes/no reported), according to the time

after EOT: before start of Amendment (in some patients the LVEF assessment performed between EOT and start of Amendment 3 were reported, this data is included in this report), 18 ±3 months, 24±3 months etc. Other findings in cardiac ultrasound were listed according to the time after EOT.

Smoking habits and alcohol consumption: Smoking regularly for more than 6 month in the patient's life, smoking before chemotherapy start, change of smoking habits after chemotherapy start for patients who smoked before chemotherapy start are presented in cross-tables per patient; per Amendment 3 visit smoking yes vs no is presented.

Alcohol consumption before chemotherapy start (frequency of having a drink containing alcohol, number of drinks on a typical day and frequency of having 6 or more drinks) and change of alcohol consumption habits after chemotherapy start are presented in cross-tables per patient; per Amendmet 3 visit frequency of having a drink containing alcohol, number of drinks on a typical day and frequency of having 6 or more drinks are presented.

SUMMARY

Between June 2012 and January 2014, a total of 1373 patients were screened at 69 sites for eligibility of whom 1229 were randomized and 1206 started treatment (606 with nab-paclitaxel and 600 with sb-paclitaxel, representing the mITT set).

Data on the primary efficacy endpoint and on safety were previously reported (Clinical Study Report 11 October 2016).

Efficacy Results (mITT set): Addendum For Time-To-Event Analysis

The required number of 248 events (243 for iDFS and 248 for DFS) in the time-to-event endpoint analysis, including 20 deaths, was observed after a median follow-up of 49.7 months (range 0.5-64 months). Overall 142 distant relapses, 58 invasive locoregional relapses, 17 secondary malignancies 4 contralateral breast cancers and 2 non operable progressions during neoadjuvant therapy were reported as first event.

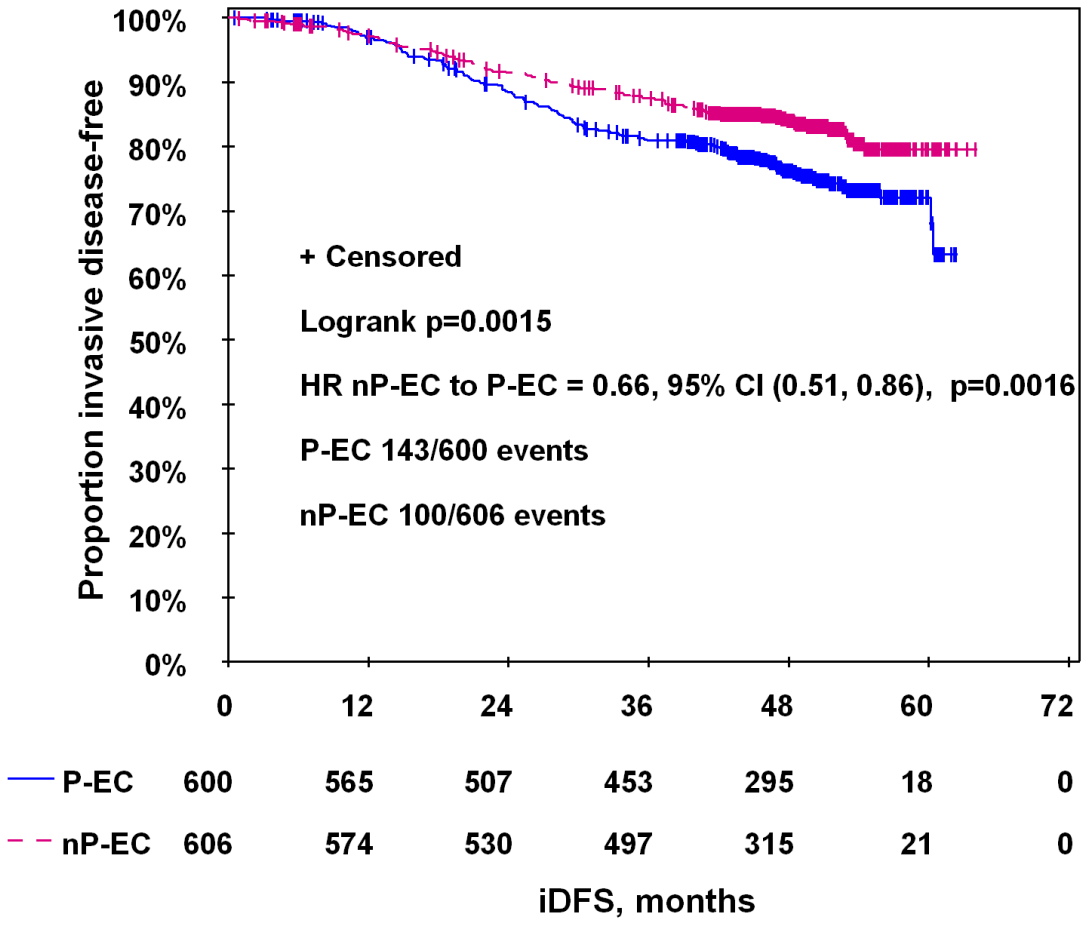
In total, 243 iDFS events were reported, with 100 patients in the nab-paclitaxel group (16.5%) and 143 (23.8%) in the sb-paclitaxel group.

The 4-year iDFS rate was 84% [95% CI 80.7%-86.8%] after nab-paclitaxel and 76.3% [95%CI 72.5%-79.6%] after sb-paclitaxel with a hazard ratio (HR) for iDFS event of 0.66 [95% CI 0.51-0.86], log rank p=0.0015 in favour of nab-paclitaxel.

Table: 3, 4, 5 year iDFS, overall

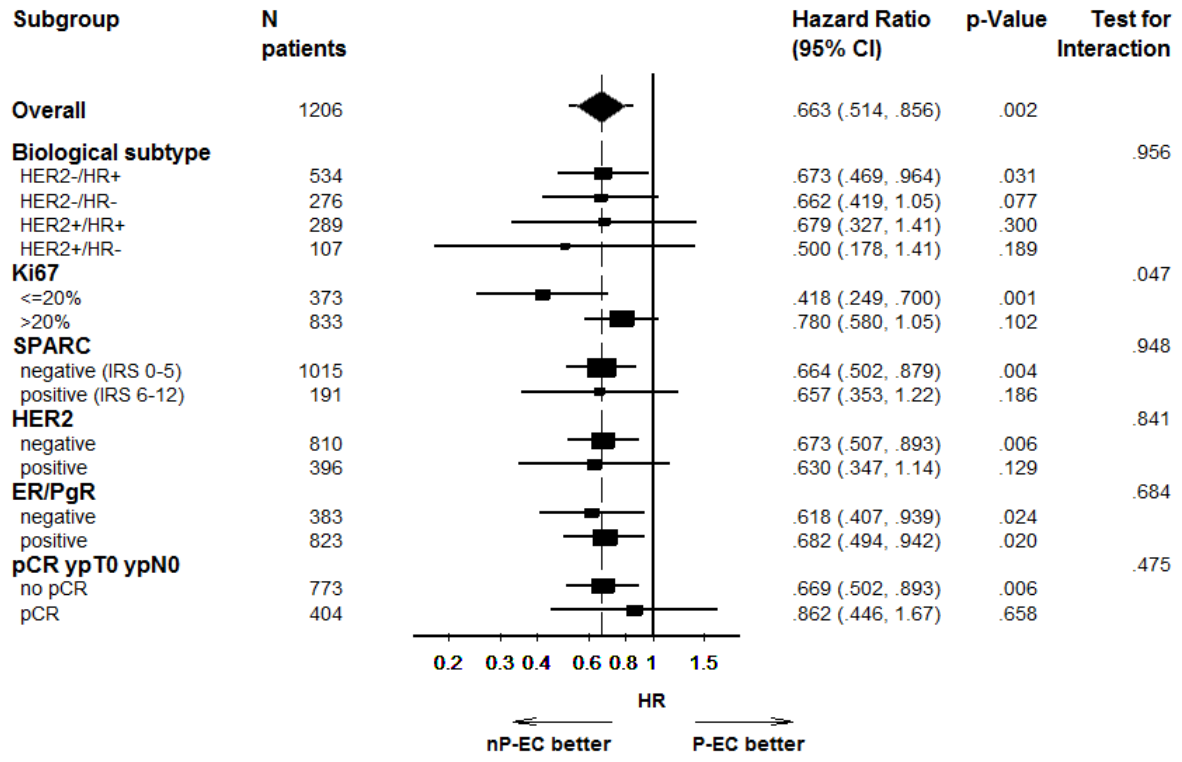
Time	*iDFS rate, P-EC*	*95% CI, P-EC*	*iDFS rate, nP-EC*	*95% CI, nP-EC*
36 months	80.9%	(77.5%, 83.9%)	87.5%	(84.5%, 89.9%)
48 months	76.3%	(72.5%, 79.6%)	84.0%	(80.7%, 86.8%)
60 months	72.1%	(67.3%, 76.3%)	79.6%	(75.0%, 83.4%)

Figure: iDFS, overall



The effect of nab-paclitaxel was homogenous in all predefined subgroups. A total of 455 patients were randomized before the amendment (28.03.2013) reducing the nab-paclitaxel dose from 150mg/m² to 125mg/m². In 49/229 nab-paclitaxel 150mg/m² treated patients iDFS events were reported compared to 70/226 events in sb-paclitaxel treated patients (HR=0.65 [95% CI 0.45-0.94], log rank p=0.0203). In 51/377 patients who started with nab-paclitaxel 125mg/m² after the amendment iDFS events were reported compared to 73/373 in the sb-paclitaxel treated patients (HR=0.67 [95%CI 0.47-0.96], log rank p=0.0299). Of the 276 patients with TNBC 32/139 (23.0%) reported an iDFS event in the nab-paclitaxel group and 43/137 (31.4%) in the sb-paclitaxel group (HR=0.66 [95%CI 0.42-1.05], log rank p=0.0750). Of the 534 patients with HER2-negative/HR-positive tumors 50/268 reported an iDFS event with nab-paclitaxel and 73/266 with sb-paclitaxel (HR=0.67 [95%CI 0.47-0.96], log rank p=0.0298). Despite being in the same direction, no significant difference was seen between the two arms for patients with HER2-positive/HR-positive (HR=0.68 [95%CI 0.33-1.41], log rank p=0.2966) or HER2-positive/HR-negative (HR=0.50 [95%CI 0.18-1.41], log rank p=0.1798).

Figure: iDFS, in subgroups, Cox regression, forest plot



Patients achieving a pCR had fewer iDFS events than patients without pCR (8.9%, 36/404 vs 25.6%, 198/773). Within the pCR group 16/232 relapsed after nab-paclitaxel and 20/172 relapsed after sb-paclitaxel (log rank p=0.658). In the non-pCR group 74/357 relapsed after nab-paclitaxel and 124/416 after sb-paclitaxel (log rank p=0.015). In the non-pCR group significantly more patients had very small tumor residuals of 5mm or less (128/350, 36.6%) after nab-paclitaxel compared to 120/410 after sb-paclitaxel (29.3%), p=0.0361.

Overall, 248 DFS events were reported, 103 for patients receiving nab-paclitaxel and 145 for patients receiving paclitaxel. The 4-year DFS rate was 83.7% [95% CI 80.3%-86.5%] after nab-paclitaxel and 75.9% [95%CI (72.1%- 79.3%)] after sb-paclitaxel (HR=0.67 [95% CI 0.52-0.87], log rank p=0.0015) in favour of nab-paclitaxel). Overall results and in subgroups are comparable to the iDFS results.

A total of 233 EFS events were observed including 2 non operable progressions. Results are comparable with regard to the iDFS results. The HR for EFS in favour of nab-paclitaxel for patients with TNBC and HER2-negative/HR-positive breast cancer was 0.62 [95% CI 0.39-0.99], log rank p=0.0443 and 0.65 [95%CI 0.45-0.94], log rank p=0.0214, respectively. Results for the HER2-positive subgroups, although not statistically significant, tended into the same direction.

DDFS was not significantly different neither overall nor in the predefined subgroups. A total of 203 events were observed. The 4-year DDFS rate was 85.6% [95% CI 82.5%-88.3%] after nab-paclitaxel and 81.0% [95%CI 77.5%- 84.1%] after sb-paclitaxel with a HR for DDFS event of 0.78, 95% CI [0.59-1.03], log rank p=0.0839 in favour of nab-paclitaxel. HR for DDFS in favour of

nab-paclitaxel for patients with TNBC and HER2-negative/HR-positive breast cancer was 0.81 [95% CI 0.48-1.36], log rank p=0.4197 and 0.75 [95%CI 0.51-1.10], log rank p=0.1389, respectively. Results for the HER2-positive subgroups tended into the same direction (HR 0.86 [95%CI 0.46-1.63], log rank p=0.6457).

The 4-year cumulative incidence of locoregional or contralateral relapse was 5.8% [95% CI 4.1-7.9] in nab-paclitaxel arm and 8.3% [95% CI 6.2-10.8] in paclitaxel arm (HR=0.65 [95%CI 0.42-1.002] Gray´s test p=0.049).

Overall 137/1206 patients (11.4%) died, 63 in the nab-paclitaxel group and 74 in the sb-paclitaxel group (HR=0.82 [95%CI 0.59-1.16], log rank p=0.2603). OS was not significantly different neither overall nor in the subgroups. The 4-year OS rate was 89.7% [95% CI 86.9%-92.0%] after nab-paclitaxel and 87.2% [95%CI 84.0%- 89.7%] after sb-paclitaxel with a HR for OS event of 0.82, 95% CI [0.59-1.16], log rank p=0.2603 in favour of nab-paclitaxel.

Amendment 3 Analysis Results:

With Amendment 3 of the study protocol a special focus was set on patient's QoL as well as on persisting toxicities after the end of treatment, especially PSN and cardiac toxicity. About a half of the patients enrolled in the GeparSepto trial gave their consent to collect data within Amendment 3.

The analysis on PSN was updated in light of the new information provided by the study sites within Amendment 3.

Table: Summary of Resolution to ≤ Grade 1 for Patients with Grade 2-4 Peripheral Neuropathy - by Day 1 Dose – Safety Population

group	*sb-Paclitaxel 80 mg/m2 (N=601)*	*nab-Paclitaxel 150 mg/m2 (N=220)*	*nab-Paclitaxel 125 mg/m2 (N=385)*	*nab-Paclitaxel subtotal (N=605)*	*Overall (N=1206)*
PNP grade 2-4 occurred prior to EOT	113 (18.8)	91 (41.4)	151 (39.2)	242 (40.0)	355 (29.4)
Grade 2-4 resolved to grade max. 1	102 (17.0)	75 (34.1)	131 (34.0)	206 (34.0)	308 (25.5)
- Resolved before EOT	80 (13.3)	57 (25.9)	106 (27.5)	163 (26.9)	243 (20.1)
- Resolved after EOT	22 (3.7)	18 (8.2)	25 (6.5)	43 (7.1)	65 (5.4)
Unresolved grade 2-4	11 (1.8)	16 (7.3)	20 (5.2)	36 (6.0)	47 (3.9)
- Unresolved before EOT, no new data	4 (0.7)	5 (2.3)	9 (2.3)	14 (2.3)	18 (1.5)
- Still unresolved in post-EOT data	7 (1.2)	11 (5.0)	11 (2.9)	22 (3.6)	29 (2.4)

Per data collected for Protocol Amendment 3 and data collected for patients who did not consent to

Amendment 3 but provided information on current PNP status.

Table: Summary of Resolution to ≤ Grade 1 for Patients with Grade 3-4 Peripheral Neuropathy - by Day 1 Dose – Safety Population

group	*sb-Paclitaxel 80 mg/m2 (N=601)*	*nab-Paclitaxel 150 mg/m2 (N=220)*	*nab-Paclitaxel 125 mg/m2 (N=385)*	*nab-Paclitaxel subtotal (N=605)*	*Overall (N=1206)*
PNP grade 3-4 occurred prior to EOT	16 (2.7)	32 (14.5)	32 (8.3)	64 (10.6)	80 (6.6)
Grade 3-4 resolved to grade max.1	16 (2.7)	22 (10.0)	22 (5.7)	44 (7.3)	60 (5.0)
- Resolved before EOT	10 (1.7)	12 (5.5)	13 (3.4)	25 (4.1)	35 (2.9)
- Resolved after EOT	6 (1.0)	10 (4.5)	9 (2.3)	19 (3.1)	25 (2.1)
Unresolved grade 3-4	0 (0.0)	10 (4.5)	10 (2.6)	20 (3.3)	20 (1.7)
- Unresolved before EOT, no new data	0 (0.0)	2 (0.9)	4 (1.0)	6 (1.0)	6 (0.5)
- Still unresolved in post-EOT data	0 (0.0)	8 (3.6)	6 (1.6)	14 (2.3)	14 (1.2)

Per data collected for Protocol Amendment 3 and data collected for patients who did not explicitly consent to Amendment 3 but provided information on current PNP status.

Median follow-up time for patients with PSN G2-4 was 220 months in sb-paclitaxel arm, 244 in nab-paclitaxel 150mg/m² arm and 214 in nab-paclitaxel 125mg/m^2 arm. The updated analysis for Amendment 3 showed similar results compared to the previous reported analysis. In particular, median time to resolve PSN G2-4 to ≤G1 was significantly lower for sb-paclitaxel compared to nab-paclitaxel 150mg/m^2 (7.0 weeks vs 12.7 weeks; p=0.019), as well as for nab-paclitaxel 125mg/m^2 compared to 150mg/m^2 (6.4 vs 12.7; p=0.014). No significantly difference was found for sb-paclitaxel compared to nab-paclitaxel 125mg/m^2 (p=0.740). Median time to resolve PSN G3-4 to G≤1 was 10.4 weeks for sb-paclitaxel, 32 weeks for nab-paclitaxel 125mg/m^2 and 157.3 weeks for nab-paclitaxel 150mg/m^2 (sb-paclitaxel vs nab-paclitaxel 150mg/m^2, p=0.001; sb-paclitaxel vs nab-paclitaxel 125mg/m^2, p=0.161; paclitaxel 150mg/m^2 vs paclitaxel 125mg/m^2 p=0.200).

Figure: Time to resolve grade 2-4 PNP to ≤ grade 1, sb-paclitaxel vs nab-paclitaxel 150 mg/m2 vs nab-paclitaxel 125 mg/m2

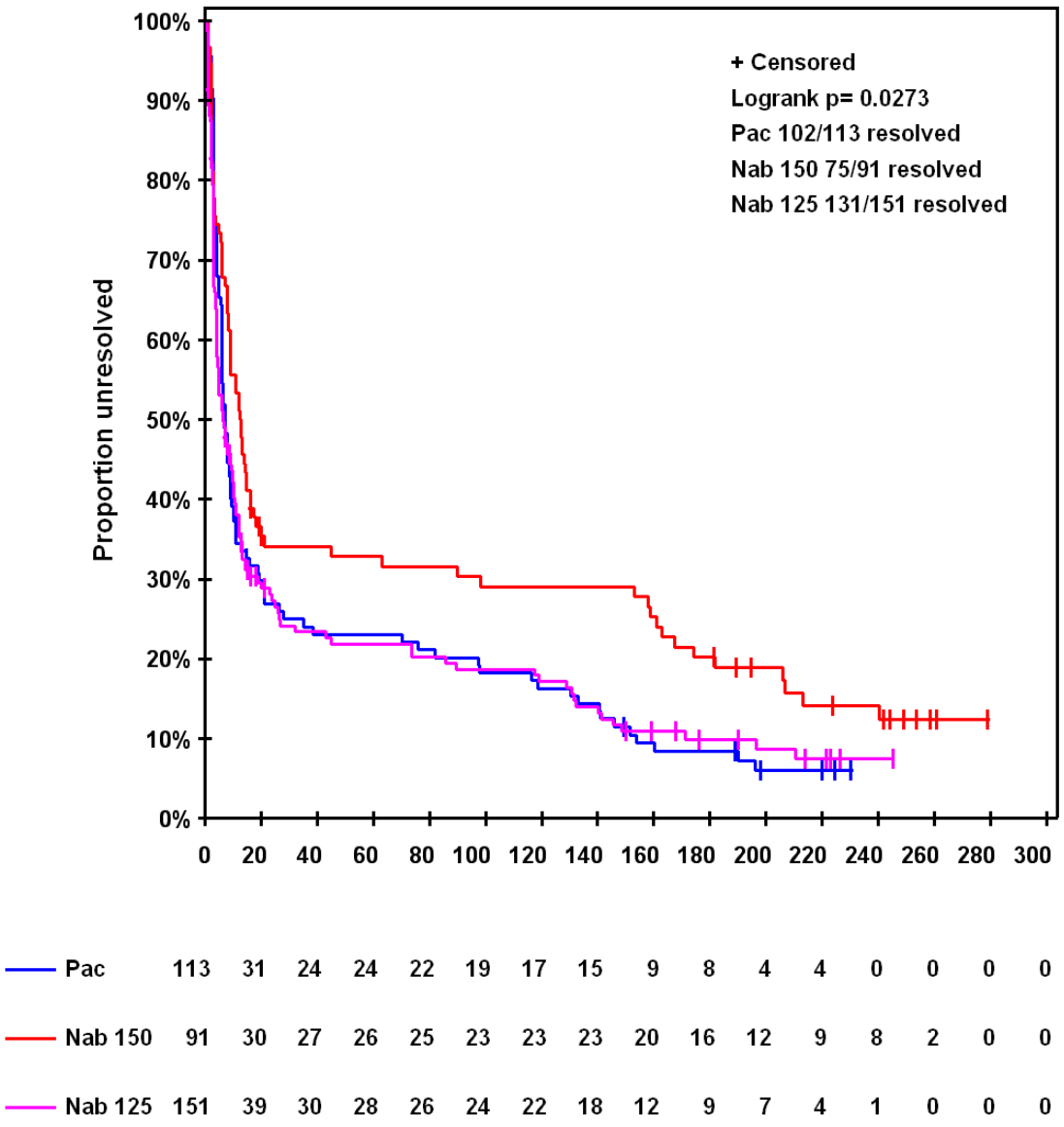
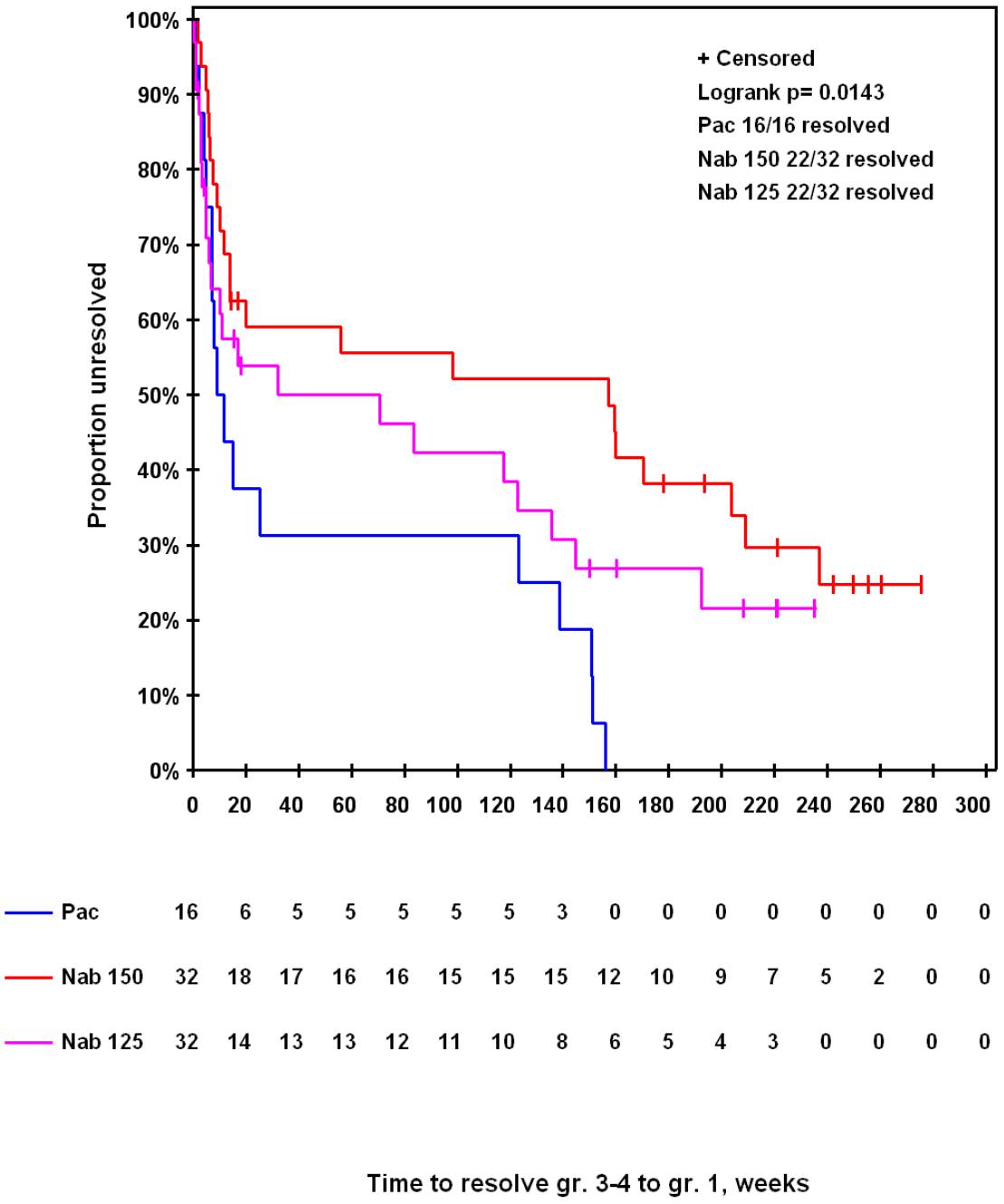


Figure: Time to resolve grade 3-4 PNP to ≤ grade 1 in 3 treatment groups



Among patients with data available 18 months after EOT (n=80), 92.5% had PSN G0/1, 7.5% had PSN G2, no one had PSN G3 or 4. Among patients with data available 42 months after EOT (n=503), 88.3% had PSN G0/1, 9.1% had PSN G2, 2.6% PSN G3, no one had PSN G4. PSN treatment modalities were also collected within Amendment 3. In most of the cases no specific treatment for neuropathy was reported; if a medical approach was started, the most frequently used drug was pregabalin.

Among patients who consented to Amendment 3 and with LVEF assessment available, 7% (5/71) of patients under sb-paclitaxel compared to 6.7% (1/15) of patients treated with nab-paclitaxel 150mg/m^2 experienced a decrease in LVEF after completion of study treatment. No LVEF reduction was reported for patients receiving nab-paclitaxel 125mg/m^2. No LVEF reduction was reported after 48 months neither under sb-paclitaxel nor under nab-paclitaxel.

Quality of life was also a major point for the amended analysis. Eighteen months after EOT, no substantial differences were seen neither for patients treated with sb-paclitaxel or nab-paclitaxel nor for patients treated with different dose of nab-paclitaxel. Overall, the lowest mean scores were obtained for the functional part of the questionnaire. Results were consistent at the following time points. Eighteen months after EOT more patients receiving sb-paclitaxel compared to nab-paclitaxel 125mg/m^2 were more likely to choose the two worst categories for each subscale. At the following time points the different between the arms were still present but less marked.

Smoking and drinking habits were also analysed. Among patients with data available 43.2% had smoked regularly during their life. Interestingly, only 20% of the patients smoked before start of chemotherapy. Half of those changed their smoking habits after chemotherapy start, in particular almost all of them stopped smoking.

Before chemotherapy about one third of the patients had a drink containing alcohol 2-4 times a month with the majority consuming 1-2 drinks in one occasion and 6 or more drinks less than monthly. Interestingly, for a little less than one fourth of the patients alcohol consumption habits changed during chemotherapy. In particular the number of patients consuming only 1-2 drinks compared to more than 2 drinks in one occasion increased and more patients consumed less frequently 6 or more drinks in one occasion.

For a more detailed presentation of Amendment 3 endpoints, refer to “Statistical report, Amendment 3 analysis”.

CONCLUSIONS:

The GeparSepto study demonstrated that the higher pCR rate translated into an improved iDFS, DFS and EFS after nab-paclitaxel treatment compared to sb-paclitaxel. Patients with HER2-negative/HR- positive breast cancer derived the same relative improvement in iDFS as the whole cohort and as in other analyses. These results support the use of nab-paclitaxel instead of sb-paclitaxel in breast cancer patients which have the same inclusion criteria of the GeparSepto study. Finally, the Amendment 3 of the GeparSepto trial showed a lower time to resolution of PSN G2-4 to ≤G1 for nab-paclitaxel 125mg/m^2 compared to nab-paclitaxel 150mg/m^2, whereas for PSN G3-4, for sb-paclitaxel compared to nab-paclitaxel. No substantial difference emerged in QoL, cardiac toxicity, smoking and drinking habit between sb-paclitaxel, nab-paclitaxel 150 or 125mg/m^2.

Date of the Synopsis Addendum: 28 September 2018 / 09 November 2018