CLINICAL STUDY REPORT

- SYNOPSIS –

Neo- / adjuvant phase III trial to compare intense dose-dense chemotherapy to tailored dose-dense chemotherapy in patients with high risk early breast cancer (GAIN-2)

EudraCT No.: 2011-005214-11

Investigational Products:	Nab-Paclitaxel, Epirubicin, Cyclophosphamide, Docetaxel, Trastuzumab, Pertuzumab
Indication:	Neo-/adjuvant treatment of high-risk early breast cancer patients
Study Protocol:	GBG 68 (including Protocol Amendment 3, Version 8 – 28-Apr-2016)
Phase:	III
Report Version:	Final Version V2.0
First Patient Enrolled:	October 01, 2012
Last Patient Completed:	September 12, 2018
Coordinating Investigator:	Prof. Dr. Volker Möbus Klinikum Frankfurt-Höchst Gotenstraße 6-8 65929 Frankfurt am Main, Germany
Sponsor:	GBG Forschungs GmbH Martin-Behaim-Straße 12 63263 Neu-Isenburg, Germany
Date of this report:	July 23, 2020
Date of any previous reports:	Version 1.0 December 12, 2019

1. SYNOPSIS

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Title of Study:

Neo- / adjuvant phase III trial to compare intense dose-dense chemotherapy to tailored dose-dense chemotherapy in patients with high risk early breast cancer (GAIN-2)

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Publication (reference):

Noeding S, Forstbauer H, Wachsmann G et al. GAIN2: Adjuvant phase III trial comparing an intensified dose-dense adjuvant therapy with EnPC compared to a dose-dense, dose-adapted therapy with dtEC dtDocetaxel in patients with primary breast cancer and a high risk of recurrence. Ann Oncol 2014, 25 (suppl_4): iv90.

Moebus V, Lück H-J, Forstbauer H et al. GAIN-2: Adjuvant Phase III Trial to Compare Intense dose-dense (idd) Treatment with EnPC to Tailored dose-dense (dt) Therapy with dtEC-dtD for Patients with high-risk Early Breast Cancer: Results of the Second Safety Interim Analyses. Cancer Res 2016, 76(4 Suppl): P1-13-05.

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Moebus V, Noeding S, Ladda E et al. Neo-/adjuvant phase III trial to compare intense dose-dense (idd) treatment with EnPC to tailored dose-dense (dt) therapy with dtEC-dtD for patients with high-risk early breast cancer: results on pathological complete response (pCR) for patients treated within the neoadjuvant setting. J Clin Oncol 2018, 36.15_suppl.568.

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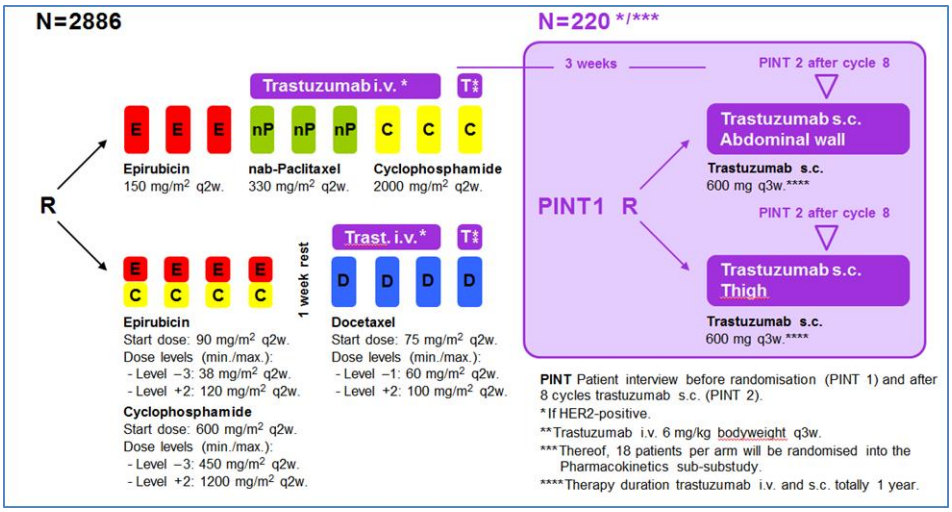
Studied Period (years):

Date of the first patient enrolled: 01 October 2012
Date of the last patient completed: September 12, 2018

Phase of Development:

Phase III

GAIN-2 Trial Design



Objectives:

Primary Objectives:

To compare the invasive disease-free survival after neo-/ adjuvant chemotherapy with intense, dose-dense epirubicin, nab-paclitaxel, and cyclophosphamide (EnPC) or dose-dense, dose-tailored epirubicin/ cyclophosphamide followed by dose-dense, dose-tailored docetaxel (dtEC-dtD) in patients with early node-positive or high-risk node-negative breast cancer.

Secondary Objectives:

- To compare overall survival between arms.
- To compare distant disease-free survival between arms.
- To compare locoregional relapse-free survival between arms.
- To compare local relapse-free survival between arms.
- To compare regional relapse-free survival between arms.
- To compare brain metastasis free survival (overall and in the subgroup of triple-negative and HER2 positive breast cancer separately) between arms.
- To evaluate the compliance in arms.
- To compare the safety between arms (including time to resolve neuropathy to grade 1).
- To measure the side effects of taxanes.
- To compare treatment effects by intrinsic subtypes; and by Ki-67 between arms.
- To compare treatment effects by pN0/1, pN2 or pN3 in the adjuvant cohort.
- To compare treatment effects by nodal status c/p N0/1, c/p N2; c/p N3 in the overall cohort.
- To compare the pathological complete response rates per arm in patients treated with neoadjuvant therapy.
- To assess the pathological complete response rates separately for the stratified subpopulations.
- To determine the rates of ypT0 ypN0; ypT(any) ypN0, ypT0 ypN0/+; ypT0/is ypN0/+.
- To determine the breast conservation rate after each treatment in patients treated with neoadjuvant therapy.
- To compare the breast conservation rate between adjuvant and neoadjuvant patients.
- To assess the survival endpoints by pathological complete response.
- To assess quality of life according to the FACT-Taxane questionnaire

Methodology:

This is a multicenter, prospective, randomized, open-label phase III trial comparing intense, dose-dense epirubicin, nab-paclitaxel, and cyclophosphamide (EnPC) and dose-dense, dose-tailored epirubicin/ cyclophosphamide followed by dose-dense, dose-tailored docetaxel (dtEC-dtD) as adjuvant or (since amendment 3) neoadjuvant chemotherapy for node-positive or high-risk node-negative early breast cancer. The NSABP-B18 trial and other studies have shown that neoadjuvant chemotherapy is as effective in preventing recurrences as adjuvant chemotherapy.

Patients were randomized in a 1:1 ratio to either intense dose-dense epirubicin followed by intense dose-dense nab-paclitaxel followed by intense dose-dense cyclophosphamide or to dose-dense, dose-tailored epirubicin / cyclophosphamide followed after 1 additional week of rest by dose-dense, dose-tailored docetaxel.

Patients with HER2 positive disease and treated in the neoadjuvant setting received trastuzumab and pertuzumab concomitantly and during all nab-paclitaxel and cyclophosphamide cycles in the EnPC arm and during all docetaxel cycles in the dtEC-dtD arm, respectively. They continued treatment with trastuzumab (as participants of the Trastuzumab s.c. substudy) after surgery for up to one year. Patients with HER2 positive disease treated in the adjuvant setting received trastuzumab simultaneously to all nab-paclitaxel and cyclophosphamide cycles in the EnPC arm and to all dtD cycles in the dtEC-dtD arm and then as monotherapy for up to one year.

Stratification factors for randomization were breast cancer subtypes (luminal A high risk vs. luminal B vs. HER2-positive, hormone-receptor-positive vs. HER2-positve, hormone-receptor-negative vs. triple negative) and nodal status (cN0/1 or pN0/1 vs. cN2 or pN2 vs. cN3 or pN3).

In both study arms, treatment was to be given until disease progression, unacceptable toxicity or withdrawal of consent of the patient or termination by the sponsor.

The Trastuzumab s.c. substudy (in effect since amendment 2) is a prospective, multi-center, controlled, non-blinded, randomized phase II substudy with pharmacokinetic evaluation.Patients who have received chemotherapy and i.v. trastuzumab according to the allocated treatment arm of the main protocol, were randomized in a 1:1 ratio to receive trastuzumab subcutaneously either into the thigh or into the abdominal wall.

The Protocol Board (Subboard Adjuvant) and the Independent Data Monitoring Committee reviewed and monitored the conduct of the study.

Number of Patients (planned and analyzed):

planned: 2886, screened: 3411, randomized: 2887, analyzed (safety): 2857, analyzed (short-term efficacy): 593, analyzed (long-term efficacy): 2857, per-protocol 2828, analyzed HER2+ substudy with s.c. trastuzumab: planned: 200, randomized: 226, analyzed: 219

Diagnosis and Main Criteria for Inclusion:

The study included female patients of at least 18 and at most 70 years of age with unilateral or bilateral primary carcinoma of the breast with a Karnofsky Performance status index ≥ 80% and an estimated life expectancy of at least 10 years irrespective of the breast cancer diagnosis.

In case of adjuvant therapy, patients had to have adequate surgical treatment with histological complete resection (R0) of the invasive breast tumor. Patients with centrally confirmed estrogen receptor and progesterone receptor (positivity defined as ≥ 1% stained cells), HER2 (positivity defined as immunohistochemistry 3+ in > 10% immunoreactive cells or fluorescent in-situ hybridisation or equivalent test ratio ≥ 2.0), and Ki-67 status detected on surgical removed tissue (for adjuvant patients) or from core biopsy (for neoadjuvant patients) were eligible.

High risk breast cancer was defined as HER2 positive or triple-negative tumors irrespective of nodal status or luminal B-like tumors (estrogen receptor and/or progesterone receptor positive, HER2 negative, Ki-67 > 20%) with involved lymph nodes or luminal A like patients with 4 or more involved lymph nodes.

Test Products, Dose and Mode of Administration, Batch Number:

Investigational products in this study were nab-Paclitaxel, epirubicin, cyclophosphamide, docetaxel, trastuzumab, and pertuzumab.

The maximum dose of nab-paclitaxel with which patients could safely be treated was determined in a run-in phase.

Nab-Paclitaxel

- Dose: 330mg/m² after determination during the run-in phase.
- Application: i.v. over 30-60 min.
- Schedule: on day 1 q day 14 for 3 cycles.
- Batch numbers provided: 12F0333, 12F0500, 13F0022, 13F0307, 13F0576, 14F0759, 15F1000, 16F2150, 17F0294

Trastuzumab s.c. (only for HER2 positive participants of the Trastuzumab s.c. substudy)

- Dose: 600mg fixed dose
- Application: injection, randomized to receive the injection into the abdominal wall or the thigh.
- Schedule: on day 1 q day 21; 14 cycles for patients in EnPC arm or 15 cycles for patients in dtEC-dtD arm.
- Batch numbers provided: B1001, B1033, B1042, B1015, B1029, B0012

Epirubicin

- Dose: 150mg/m² (EnPC) or tailored 38-120mg/m² (dtEC-dtD).
- Application: i.v. over 20 min via catheter to the subclavian vein or an implanted port system.
- Schedule: on day 1 q day 14 for 3 (EnPC) or 4 (dtEC-dtD) cycles.

Cyclophosphamide

- Dose: 2000mg/m² (EnPC) or tailored 450-1200mg/m² (dtEC-dtD).
- Application: i.v. over 120 (EnPC) or 60 (dtEC-dtD) min.
- Schedule: on day 1 q day 14 for 3 (EnPC) or 4 (dtEC-dtD) cycles.

Docetaxel

- Dose: tailored 60-100mg/m² (dtEC-dtD).
- Application: i.v. over 60 min.
- Schedule: on day 1 q day 14 for 4 cycles.

Tailoring (escalation or reduction) of dose during dtEC-dtD was to be performed according to protocol-defined toxicity criteria. Dose reductions or delays during EnPC were to be conducted for specific adverse events according to protocol-defined guidelines.

For patients with HER2 positive disease, trastuzumab was given at 8mg/kg body weight i.v. (loading dose) followed by 6mg/kg body weight i.v. (maintenance dose) every three weeks simultaneously to all nP and C cycles in the EnPC arm and to all dtD cycles in the dtEC-dtD arm for totally one year (i.v. or s.c as participants of the Trastuzumab s.c. substudy).

Pertuzumab (optional and only for patients receiving neoadjuvant therapy) was given at 840mg i.v. (loading dose) followed by 420mg i.v. (maintenance dose) every 3 weeks concomitantly with trastuzumab i.v. (see above) and during all nP and C cycles in the EnPC arm and all dtD cycles, respectively, in the dtEC-dtD arm

until surgery. Patients in the neoadjuvant setting were to continue with trastuzumab (i.v. or s.c as participants of the Trastuzumab s.c. substudy) after surgery for up to one year.

Duration of Treatment:

The entire treatment period was 18 weeks in EnPC arm and 17 weeks in dtEC-dtD in patients who did not receive anti HER2 treatment. Dose-dense EnPC was given as epirubicin followed by nabPaclitaxel followed by cylophosphamide, every 2 weeks for 3 cycles each; dtEC-dtD was given as dose-dense, dose-tailored epirubicin/cyclophosphamide every 2 weeks for 4 cycles followed by 1 week of rest and followed by dose-dense, dose-tailored docetaxel every 2 weeks for 4 cycles.

HER2 positive patients could be randomized in the Trastuzumab s.c. substudy to receive antiHER2-treatment for a total of one year.

Reference Therapy, Dose and Mode of Administration, Batch Number:

See above for details on therapy and dose

Criteria for Evaluation:

Efficacy

Primary endpoint

The primary efficacy endpoint of this study was invasive disease-free survival, defined as the time period between randomization and first event (local, loco-regional or distant recurrence, death from breast cancer, death from non-breast cancer cause, death from unknown cause, second primary invasive cancer [non-breast]).

Secondary endpoints:

Secondary efficacy endpoints were overall survival, locoregional relapse-free survival, regional relapse-free survival, local relapse-free survival, distant disease-free survival, and brain metastasis free survival, defined as the time period between randomization and first event.

Tolerability and Safety

Secondary endpoints included descriptive statistics for the two treatments on the number of patients whose treatment had to be reduced, delayed or permanently stopped. The reason for termination 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).

Additional Secondary Endpoint for Patients who were enrolled after the Amendment and treated preoperatively

Pathological complete response of breast and lymph nodes was defined as no microscopic evidence of residual viable tumor cells (invasive and non-invasive) in any resected specimen of the breast and axillary nodes (ypT0/ypN0).

Quality of Life (FACT-Taxane)

The FACT-Taxane questionnaires were used to assess quality of life. Endpoints included scoring according to five scales (Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and Additional Concerns) as well as the FACT-Taxane Trial Outcome Index (FACT-Taxane TOI) and the FACT-Taxane total score.

Trastuzumab s.c. Substudy

Co-primary endpoints of the GAIN-2 Trastuzumab substudy were patient preference for s.c. trastuzumab into the thigh or the abdominal wall compared to previous i.v. trastuzumab and pharmacokinetic profiles of s.c. trastuzumab into the thigh compared with those of s.c. trastuzumab into the abdominal wall.

Secondary endpoints of the s.c. trastuzumab substudy were detailed analyses of questions in patient

interview (PINT) 1 and patient interview 2 stratified by treatment arm.

Statistical Methods:

A modified 'intent-to-treat' analysis was conducted for all randomized patients who received at least one dose of study medication. In addition, a 'per-protocol' analysis was conducted for the primary efficacy endpoint.

A time driven final efficacy analysis was planned to be performed 45 months after end of accrual. At that time it was expected that 797 events have occurred.

Two safety interim analyses were to be performed after 200 and 900 patients had completed chemotherapy. At each interim look the protocol board was to judge on advice of the IDMC in how far the risk-benefit comparison between the arms allowed continuation with the study.

The sample size calculation was based on the following assumptions:

- The invasive disease-free survival at 5 years of patients receiving dtEC-dtD was considered to be 75%.
- It was expected that there was an absolute improvement of 4% to 79% in 5-year invasive disease-free survival (hazard ratio 0.819) for patients receiving EnPC.
- The error rate for a false positive outcome (α) was set to 5%. The error rate for a false negative outcome (β) was set to 20%, i.e., the power of the trial was set to 80% for the difference of clinical interest.
- The common exponential drop-out rate was 5%.
- The accrual period during which patients entered the study was 66 months.
- The follow-up period from the end of accrual until the analysis of the data was 45 months.
- One efficacy interim analysis with an O'Brien-Fleming error-spending function was planned approximately 65 months after start of randomization when it was expected that 50% of the events have occurred.

The total number of patients that needed to be randomized into the trial was to be approximately 2886.

SUMMARY

Efficacy Results:

The primary study objective of the GAIN-2 study was to compare invasive disease-free survival (iDFS) after neo- / adjuvant chemotherapy with EnPC or dtEC-dtD in patients with early node-positive or high-risk node-negative breast cancer based on the mITT set. On March 2, 2020, 414 iDFS events had been documented and the interim analysis of the primary endpoint (planned with 50% of final events of 797) was completed in Q1 2020. Following IDMC advice, a futility analysis was performed. The futility boundary for the interim efficacy analysis was crossed, as the probability of having a clinically relevant difference in iDFS was equal to 2.77%, i.e. smaller than the predefined futility boundary of 15%). Therefore, the final analysis of all time-to-event-endpoints was performed.

In the GAIN-2 study a total of 2857 of the 2887 randomized patients started treatment and were included in the mITT set (EnPC: 1429 patients; dtEC-dtD: 1428 patients).

After a median follow-up of 45.8 months (range 0.0 - 88.3 months), 422 events for iDFS were reported. Overall, 256 distant relapses, 59 invasive locoregional relapses, 44 secondary malignancies, 36 deaths, 15 invasive contralateral breast cancers, 8 non-invasive ipsilateral breast relapses, and 4 non-invasive contralateral breast cancers occurred as first event. The 4-year iDFS rate was identical in both arms with 84.3% (95% CI 82.0% to 86.4%) and a hazard ratio of 1.01 (95% CI 0.83-1.23; p=0.9102) for EnPC vs dtEC-dtD. Subgroup analysis revealed that among all predefined subgroups, only luminal B/HER2- predicted for shorter iDFS in the EnPC arm with a hazard ratio of 1.44 (95% CI 1.02-2.02; p=0.036), but test for interaction for the biological subtype was not significant (p=0.088).

There was no difference between treatment arms in all other secondary long-term endpoints (overall survival, distant disease-free survival, locoregional relapse-free interval, local relapse-free interval). Since only four patients showed brain metastases, the event rate was too low for analysis of brain metastasis free survival.

Short-term efficacy endpoints of pCR and breast conservation rate have been analyzed for patients treated in the neoadjuvant setting. A total of 598 patients were randomized to be treated in the neoadjuvant setting. Of those, 593 (EnPC: 295 patients; dtEC-dtD: 298 patients) started treatment and were the basis for the modified intent-to-treat analysis of short-term efficacy endpoints of pCR.

pCR rates analyzed as secondary efficacy endpoints according to the following definitions were numerically higher but statistically not significant in the EnPC arm compared to the dtEC-dtD arm: 46.1% in EnPC vs 37.9% in dtEC-dtD (p=0.053) for ypT0 ypN0 and 70.2% in EnPC vs 67.4% in dtEC-dtD (p=0.531) for ypT(any) ypN0. pCR rates were significantly higher in the EnPC arm compared to the dtEC-dtD arm in the following definitions: 52.9% in EnPC vs 44.3% in dtEC-dtD (p=0.044) for ypT0 ypN0/+, 58.3% in EnPC vs 49.7% (p=0.043) in dtEC-dtD for ypT0/is ypN0/+.

The results on treatment group differences in subgroups with respect to the significant pCR definitions (ypT0 ypN0/+ and ypT0/is ypN0/+) revealed significant higher pCR rates for patients with cN0-1 and Ki67>20%. pCR rates in the breast were not statistically significantly different in any of the other subgroups analyzed.

According to univariate analyses, treatment predicted for achievement of pCR in the breast overall, in the subgroup of cN0-1, and Ki67> 20%, but tests for interaction were not significant. The results of the multivariate logistic regression analysis of the two different pCR in the breast definitions (ypT0 ypN0/+ and the ypT0/is ypN0/+) almost confirmed the results of univariate analyses. Treatment was an independent predictor for achievement of pCR in the breast adjusted for stratification factors as well as adjusted for predefined covariates. Among the predefined covariates in the multivariate logistic regression analysis, pCR in the breast improvements were observed for subtype, tumor size, and tumor grade, in the univariate logistic regression analysis for sTILs.

Both treatment arms did not differ with respect to the percentage of the different types of surgery (p=0.701). Breast conservation rates were similar in both treatment arms overall (EnPC treatment: 67.0%, dtEC-dtD treatment: 68.8%) as well as in subgroups. According to univariate analyses, treatment was not predictive for breast conservation overall (OR EnPC vs dtEC-dtD: 0.92 [95% CI: 0.65-1.30; p=0.637]) or in any of the subgroups analyzed. The results of the multivariate logistic regression analysis of the secondary efficacy parameter breast conservation revealed that treatment was not an independent predictor for breast conservation adjusted for stratification factors or predefined covariates. Among the predefined covariates in the multivariate logistic regression analysis, improvements in breast conservation rates were observed for subtype, tumor size, and sTILs.

Safety Results:

The therapy with EnPC and dtEC-dtD showed to be acceptable for the majority of the patients. There was no difference between the treatment arms in terms of overall dose reductions and overall treatment discontinuations. Dose delays and interruptions were significantly more frequent in patients treated with EnPC. This can be explained by the fact that the protocol of the GAIN-2 study provided guidelines on modifications of single doses in the dtEC-dtD arm depending on individual toxicities.

All treatment was completed by 88.1% of patients in the EnPC and in the dtEC-dtD arm. Dose reductions due to any reason were performed in 46.3% in the EnPC arm and in 43.3% in the dtEC-dtD arm. The chemotherapy dose was delayed in 955 patients (66.8%) in the EnPC arm compared with 839 (58.8%) in the dtEC-dtD arm (p<0.001) and interrupted in 40 patients (2.8%) in the EnPC arm compared with 6 (0.4%) in the dtEC-dtD arm (p<0.001). The most prominent reasons for dose delays were the category's "organizational reason" and "hematological toxicity" in both treatment groups.

Overall, there were few treatment interruptions of trastuzumab and pertuzumab treatment and those did not differ between treatment arms.

In the overall safety population 99.9% of patients experienced at least one AE of any grade during treatment in both arms. No significant differences were seen in terms of any high-grade AEs (EnPC: 99.2%, dtEC-dtD: 98.5%, p=0.078), any grade (EnPC: 99.8%, dtEC-dtD: 99.7%, p=0.726) and high-grade hematological (EnPC: 98.4%, dtEC-dtD: 97.4%, p=0.069) and any grade non-hematological AEs (EnPC: 99.8%, dtEC-dtD: 99.9%, p=0.625). High-grade non-hematological AEs were significantly more frequent in the EnPC compared to the dtEC-dtD arm (50.8% vs 45.1%, respectively, p=0.002). Any grade AEs reported as free text were less

frequent in the EnPC compared to the dtEC-dtD arm (93.4% vs 95.9%, respectively, p=0.005), high-grade AEs reported as free text did not significantly differ between the treatment arms (EnPC: 29.9%, dtEC-dtD: 27.5%, p=0.148).

In both arms, anemia (EnPC: 98.6%, dtEC-dtD: 98.7%), leukopenia (EnPC: 98.7%, dtEC-dtD: 98.2%), lymphopenia (EnPC: 97.1%, dtEC-dtD: 97.3%) and neutropenia (EnPC: 94.4%, dtEC-dtD: 91.7%, p=0.004) of any grade were the most frequent hematological AEs. The most frequent non-hematological AEs of any grade were alopecia (EnPC: 91.8%, dtEC-dtD: 92.4%), fatigue (EnPC: 84.6%, dtEC-dtD: 85.5%), and nausea (EnPC: 73.9%, dtEC-dtD: 73.9%).

Rates of high-grade toxic treatment effects such as leukopenia (EnPC: 93.1%, dtEC-dtD: 87.9%, p<0.001), neutropenia (EnPC: 89.2%, dtEC-dtD: 83.7%, p<0.001), febrile neutropenia (EnPC: 12.2%, dtEC-dtD: 5.1%, p<0.001), arthralgia (EnPC: 5.8%, dtEC-dtD: 2.2%, p<0.001), and peripheral sensory neuropathy (EnPC: 11.5%, dtEC-dtD: 3.6%, p<0.001) were all significantly higher in patients treated with EnPC. High-grade hypersensitivity was more common in patients treated with dtEC-dtD (EnPC: 0.3%, dtEC-dtD: 1.3%, p=0.001).

870 SAEs were reported for patients treated with EnPC, 594 SAEs were reported for patients treated with dtEC-dtD, resulting in a total of 1464 SAEs. Relevant higher frequencies of SAEs by SOC were documented in the EnPC arm for blood and lymphatic system disorders, nervous system disorders, vascular disorders, gastrointestinal disorders and general disorders and administration site conditions. Respiratory, thoracic and mediastinal disorders were more frequently reported in the dtEC-dtD arm. Frequencies of SAEs by SOC were: Infections and infestations (EnPC: 84 SAEs, dtEC-dtD: 88 SAEs), neoplasms benign and malignant (including cysts and polyps) (EnPC: 2 SAEs, dtEC-dtD: 1 SAE), blood and the lymphatic system disorders (EnPC: 389 SAEs, dtEC-dtD: 167 SAEs), immune system disorders (EnPC: 2 SAEs, dtEC-dtD: 3 SAEs), metabolism and nutrition (EnPC: 2 SAEs, dtEC-dtD: 4 SAEs), psychiatric disorders (EnPC: 7 SAEs, dtEC-dtD: 9 SAEs), nervous system disorders (EnPC: 31 SAEs, dtEC-dtD: 12 SAEs), eye disorders (EnPC: 2 SAEs, dtEC-dtD: 1 SAE), ear and labyrinth disorders (EnPC: 8 SAEs, dtEC-dtD: 6 SAEs), cardiac disorders (EnPC: 13 SAEs, dtEC-dtD: 15 SAEs), vascular disorders (EnPC: 32 SAEs, dtEC-dtD: 21 SAEs), respiratory, thoracic and mediastinal disorders (EnPC: 14 SAEs, dtEC-dtD: 18 SAEs), gastrointestinal disorders (EnPC: 91 SAEs, dtEC-dtD: 68 SAEs), hepato-biliary disorders (EnPC: 2 SAEs, dtEC-dtD: 7 SAEs), skin and subcutaneous tissue disorders (EnPC: 2 SAEs, dtEC-dtD: 16 SAEs), musculoskeletal, connective tissue and bone disorders (EnPC: 15 SAEs, dtEC-dtD: 17 SAEs), renal and urinary disorders (EnPC: 6 SAEs, dtEC-dtD: 4 SAEs), reproductive system and breast disorders (EnPC: 1 SAE, dtEC-dtD: 1 SAE), general disorders and administration site conditions (EnPC: 155 SAEs, dtEC-dtD: 126 SAEs), investigations (EnPC: 6 SAEs, dtEC-dtD: 3 SAEs), injury, poisoning and procedural complications (EnPC: 3 SAEs, dtEC-dtD: 4 SAEs), surgical and medical procedures (EnPC: 2 SAEs, dtEC-dtD: 3 SAEs), product issues (EnPC: 1 SAE, dtEC-dtD: 0 SAEs).

Among all 26 AESIs recorded for the overall safety population, all predefined AESIs (anaphylaxis [EnPC: 3 AESIs, dtEC-dtD: 5 AESIs], any AE affecting cranial nerves [EnPC: 4 AESIs, dtEC-dtD: 9 AESIs] and macula edema [EnPC: 2 AESIs, dtEC-dtD: 3 AESIs]) were more common in the dtEC-dtD arm.

A total of 6 therapy related deaths occurred. Two deaths occurred during dtEC-dtD treatment due to acute respiratory distress and sudden death. Four deaths in the dtEC-dtD arm occurred after completion of all treatment cycles.

Quality of Life Results:

Quality of life, assessed using the FACT taxance questionaires, was not markedly different between patients receiving EnPC and dtEC-dtD**.**

Trastuzumab s.c. Substudy Results:

A total of 219 of the 226 randomized patients started treatment, being either treated with s.c. trastuzumab to the thigh (110 patients) or to the abdominal wall (109 patients). Patient demographics and tumor specific baseline characteristics in the s.c. trastuzumab substudy were well balanced between the treatment groups with respect to almost all parameters analyzed.

Overall, 182 patients replied to the question of the preference to s.c. or i.v. trastuzumab treatment. 23 of these patients had no preference to s.c. or i.v. treatment. Only 7 out of 159 patients preferred i.v. trastuzumab treatment. As a secondary objective, the descriptive analysis of all items in patient interview (PINT) 1 and PINT 2 stratified by treatment arm was conducted. PINT 1 was conducted at baseline and showed no relevant differences between treatment arms. Among patients who replied to PINT 2, 80.2% had no problems with irritations on the injection site but significantly more patients in the thigh arm reported problems with irritations on the injection site (thigh: 26.9% abdominal wall: 12.4%, p=0.033). However, the s.c. administrations were generally described as acceptable by the majority of patients.

54.5% of patients in the thigh arm and 57.8% of patients in the abdominal wall arm completed treatment. The most prominent reason for dose discontinuation was the decision of the investigator to discontinue the treatment due to the fact that the number of usually given 18 cycles of trastuzumab was already achieved together with the trastuzumab i.v. treatment in the main study. No increased toxicity was observed in both treatment groups. No deaths occurred.

The analysis of pharmacokinetic parameters in the s.c. trastuzumab substudy was performed based on the per protocol-set consisting of 30 patients (17 in the thigh and 13 in the abdominal group). Baseline characteristics were well balanced between the groups. The geo-means of Cmax and AUC0-21d were higher in the thigh than in the abdominal group (GMR 1.29 [90 %CI 1.05; 1.58] and GMR 1.29 [90%CI 1.03; 1.63], respectively). Overall delay of s.c. trastuzumab application within the first 7 cycles of the substudy was observed in 19 patients (10 in thigh and 9 in abdominal group) mainly due to organizational reasons, no delay due to toxicity was reported.

Overall 29 patients (96.7%) reported any grade AEs (grades 1-4) and 5 patients (16.7%) high-grade AEs (grades 3-4). The most frequent hematological AEs were leukopenia (80.0%) and anemia (66.7%), and the most common non-hematological AEs of any grade were fatigue (60.0%) and peripheral neuropathy (53.3%).

Pharmacokinetic parameters of the s.c. trastuzumab administered into the thigh were in line with those from previous studies. Bioavailability of the s.c. trastuzumab as reflected by peak drug concentration and total exposure measured in cycle 7 was approximately 30% higher if administered into the thigh than into the abdominal wall.

CONCLUSIONS:

GAIN-2 is a multicenter, prospective, randomized, open-label phase III trial comparing intense dose-dense epirubicin, nab-paclitaxel, and cyclophosphamide (EnPC) and dose-dense, dose-tailored epirubicin/ cyclophosphamide followed by dose-dense, dose-tailored docetaxel (dtEC-dtD) as adjuvant or neoadjuvant chemotherapy for node-positive or high-risk node-negative early breast cancer. The trial addresses the question whether tailored dose-dense dtEC-dtD versus specified intense dose-dense EnPC chemotherapy differ with respect to efficacy and toxicity to define an optimal dose-dense strategy.

The primary study objective was to compare invasive disease-free survival (iDFS) after neo- / adjuvant chemotherapy with EnPC vs. dtEC-dtD. As planned in protocol and statistical analysis plan addendum, a pre-defined efficacy interim analysis was performed with 414 iDFS events, looking for both, high efficacy and futility. Based on the results of this analysis the GAIN-2 trial was stopped early due to fuitility and final analysis of all time-to-event-endpoints was performed. There was no difference in the primary endpoint iDFS, with an identical 4-year iDFS rate in both arms (84.3% [95% CI 82.0% to 86.4%]). The hazard ratio was 1.01, 95% CI 0.83-1.23 (p=0.9102) for EnPC vs dtEC-dtD. Likewise, all other evaluated time-to-event endpoints were similar between arms. Subgroup analysis for iDFS showed that patients with luminal B/HER2- tumors, might benefit from dtEC-dtD (hazard ratio EnPC vs dtEC-dtD of 1.44, 95% CI 1.02-2.02, p=0.036), but this subgroup advantage was not seen in any of the other secondary time-to-event endpoints. Hence, this potential benefit should be further investigated in future studies.

A total of 593 patients were treated in the neoadjuvant setting and here GAIN-2 shows a statistically

significant difference in terms of pCR rates within the breast for patients receiving intense dose-dense EnPC compared to dtEC-dtD (58.3% vs. 49.7%) as neoadjuvant chemotherapy. Even though further significant differences between treatment groups in pCR rates according to other pCR definitions as well as for the overall breast conservation rate were not found, pCR rates were consistently nummerically higher in the EnPC arm compared to the dtEC-dtD arm for all pCR definitions analyzed. However, the elevated pCR rate did not translate into a superior iDFS. The pCR rate within the breast with intense dose-dense EnPC is comparable with the pCR rate of the EPC arm in the previous Gepar-Octo study. In this GeparOCTO study the pCR in the breast was 54% with an EPC regimen, using a different taxane (paclitaxel in the GeparOCTO study and nab-Paclitaxel in the GAIN-2 study).

Both treatment arms did not differ with respect to the percentage of the different types of surgery. Breast conservation rates were similar in both treatment arms overall (EnPC treatment: 67.0%, dtEC-dtD treatment: 68.8%) as well as in subgroups. This is comparable to previous results in early breast cancer.

The safety profile for EnPC and dtEC-dtD observed in the GAIN-2 trial is in line with observations derived from other trials investigating intense, respectively dose-dense regimens, namely the GeparSIXTO and the GeparOCTO study. Since the tailored dose-dense regimen adjusts the dose based on individual toxicity, it is not suprising that the tailored regimen has a better toxicity profile. No new safety concerns have emerged from the GAIN-2 trial. Considering the safety/benefit ratio, the use of intense dose-dense regimen (EnPC) and dose-dense regimen with modification of single doses depending on individual toxicities (dtEC-dtD) appears feasible in this patient population.

Co-primary endpoint of the Trastuzumab s.c. substudy was patient preference for previous iv administration versus sc injection (thigh/abdominal wall) and pharmacokinetic profiles of trastuzumab sc (thigh/abdominal wall). Overall 83.5% of patients preferred administration of trastuzumab sc. No increased toxicity was observed and the study compliance was comparable (thigh/ abdominal wall). Trastuzumab sc injections were generally described as acceptable by the majority of patients. These results are in line with the results of the PREFHER study. Pharmacokinetic parameters of the s.c. trastuzumab administered into the thigh were in line with those from previous studies. Bioavailability of the s.c. trastuzumab as reflected by peak drug concentration and total exposure measured in cycle 7 was approximately 30% higher if administered into the thigh than into the abdominal wall.

In summary, in high-risk early-stage breast cancer patients, there was no difference in the 4-year iDFS rate in both arms. The GAIN-2 trial shows a statistically significant difference in terms of pCR rates within the breast for patients receiving intense dose-dense EnPC compared to dtEC-dtD as neoadjuvant chemotherapy and consistently nummerically higher pCR rates in the EnPC arm. However, the elevated pCR rates did not translate into a superior iDFS. Toxicity was significant but manageable with both regimens and no new safety concerns were reported in comparison to other published dose-dense trials. If an indication for chemotherapy is given, EnPC could be considered as one of the effective dose-dense regimens for high-risk early breast cancer patients either in the adjuvant or neoadjuvant setting.

With regard to the Trastuzumab substudy it could be confirmed, as allready shown in the PREFHER study, that the s.c. regimen is preferred by the patients. However, due to higher bioavailability, the s.c. trastuzumab should further be injected into the thigh rather than into the abdomen, with the latter being easier for the patients but resulting in a lower drug concentration.

Date of the Report:

June 23, 2020

Annex 1

The original study protocol (Version 10.07.2012) was amended three times.

Amendment 1

The study protocol was amended to implement a change in the inclusion criteria. The definition of high risk breast cancer was expanded to also include patients with luminal A like tumors and 4 or more involved lymph nodes.

Amendment 2

The study protocol and informed consent form (ICF) were amended to implement changes in the design of the run-in phase. The number of patients additionally recruited into each dose-level to avoid interruption of accrual was increased from 10 to 20.

Also, the number of recruiting centers was increased from 100 to 120 to speed up accrual.

The study protocol was additionally amended to adapt stratification factors according to the changes in amendment 1. Thus, the stratification factor subtype was changed to include the patients with 4 or more involved lymph nodes.

Amendment 2 also introduced the Trastuzumab s.c. study for comparison of subcutaneous injection of trastuzumab into the thigh vs. the abdominal wall in patients with HER2-positive primary breast cancer. The protocol was amended accordingly to clarify study design and all pertinent information on the study drug and application.

Amendment 3

Amendment 3 was a substantial amendment of the study protocol and ICF to open GAIN-2 for the neoadjuvant setting due to slow accrual. While endpoints of the study remained unchanged, an additional stratification factor was added (neoadjuvant vs adjuvant chemotherapy) and HER2-positive patients were now allowed to receive double anti-HER2-blockade (Pertuzumab + Trastuzumab). Corresponding changes were implemented in all parts of the protocol.

Addendum Statistical Analysis Plan (SAP)

The SAP was amended to describe the statistical methods for the preplanned interim analysis for efficacy. It was planned in the protocol 65 months after start of randomization when it was expected that 50% of the events (total number of events: 797) have occurred and was initially planned for high efficacy. In agreement with the IDMC of the study the analysis considered the futility as well as the high efficacy: “In case of high efficacy as well as in case of the futility the final time to event analysis will be done as described in the main SAP and published. In case of no high efficacy and no futility only the results of the primary endpoint will be reported now and the final analysis will be performed 45 months after the end of the accrual period when it is expected that 797 events have occurred.”