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

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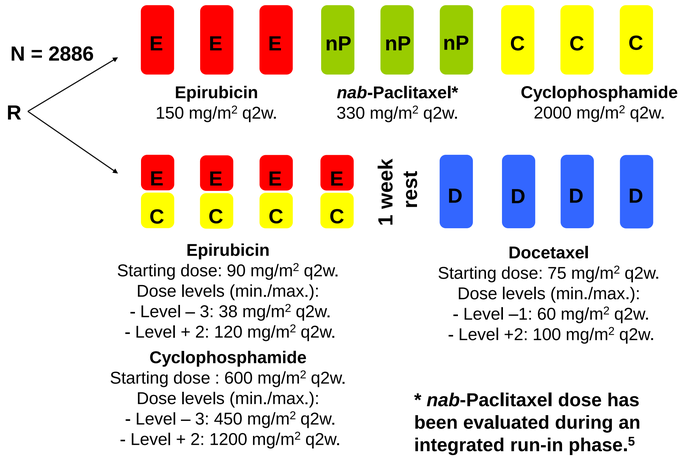
P1-13-05

Background

- Sequential administration of single-agent therapies allows high doses and dose-dense intervals. Such intense dose-dense (idd) regimen (q2w) significantly improved recurrence-free and overall survival compared to conventional dosed chemotherapy (q3w)[1,2,3].
- *nab*-Paclitaxel provides a better toxicity profile and higher efficacy compared to solvent-based taxanes and might therefore be preferred in an idd regimen[4].
- GAIN-2 compares efficacy and safety of a predefined idd regimen (EnPC) vs a dose-dense regimen where single doses are adjusted depending on individual hematological and non-hematological toxicities (dtEC-dtD). A substudy compares the administration of trastuzumab s.c. to the abdominal wall vs thigh.

Figure 1: GAIN-2 study design



Main inclusion criteria:
Women (≥18 and biologically ≤65years) with histologically confirmed high-risk breast cancer defined as

- HER2-pos or TNBC irrespective of N status
- Luminal B-like tumors with Ki-67 >20%
- Luminal A-like tumors with Ki-67 ≤20% and ≥4 N involved

Pegfilgrastim s.c. as primary prophylaxis on day 2 and **Erythropoiesis stimulating factors + 200mg Fe²⁺** daily (starting if Hb <10g/dl and until Hb ≥11g/dl) is recommended .

Objectives

Primary Objective:

Invasive disease-free survival (IDFS) after adjuvant chemotherapy with iddEnPC or dtEC-dtD.

Secondary Objectives:

- Overall, distant disease-free, locoregional relapse-free, local relapse-free, regional relapse-free and brain metastasis free survival (in subgroup TNBC and HER2+) between study arms.
- Therapy adherence and safety (incl. time to resolve neuropathy to grade 1)
- Side-effects of taxanes
- Treatment effects by intrinsic subtypes; by 0-3, 4-9 or 10+ involved nodes; and by Ki-67 between the arms

Translational objectives:

Prognostic and predictive factors, e.g. SPARC, tumor- or stroma-infiltrating lymphocytes, OncotypeDX®, uPA/PAI-1 etc., and correlation with treatment effect.

Materials and Methods

GAIN-2 (NCT01690702) is a multicenter, prospective, randomized, open-label phase III trial that compares adjuvant iddEnPC vs dtEC-dtD in node-positive or high-risk node-negative early breast cancer.

Patients are randomized in a 1:1 ratio to iddEnPC or dtEC-dtD stratified by biological subtype (HR, HER2 and Ki67) and nodal status.

Statistical methods:

Efficacy analyses are planned 60 months after end of accrual, assuming that dtEC-dtD will achieve 5-year IDFS of 75% and iddEnPC will improve IDFS to 79% (HR 0.819) with 80% power (α=0.05, ß=0.2).

Here we report the results of the second safety interim analysis (900 patients).

Results

- Between 09/2012 and 05/2015 a total of 1473 patients have been randomized (iddEnPC n=734; dtEC-dtD n=739). Among those, 84 patients have been included in the trastuzumab s.c. substudy. No safety data are currently available for the substudy. Baseline characteristics of patients included in the second safety interim analysis are shown in Table 1.
- High grade hematological toxicities were significantly increased in the iddEnPC arm (Table 2). As for non-hematological side effects, alkaline phosphatase (59 vs 40%), ALAT (69 vs 59%), peripheral sensory neuropathy (83 vs 68%), arthralgia (63 vs 49%), myalgia (48 vs 41%) and bone pain (25 vs 17%) were significantly increased in the iddEnPC arm, whereas epistaxis (10 vs 25%), edema (13 vs 26%) and hand-foot syndrome (12 vs 28%) were more common in the dtEC-dtD arm.
- There were no differences between the treatment arms for the toxicities of special interest (cranial nerves, anaphylaxis, macula edema). Two treatment related deaths (1 acute respiratory distress syndrome, 1 pneumonia) occured in the dtEC-dtD arm.
- More patients required dose-reductions due to hematological toxicities in the iddEnPC arm (30 vs 10%, p<0.001). EC could be escalated to the maximum dose in 34%, docetaxel in 44% of patients, while only 7% and 9% required a dose reduction in the 4th cycle, respectively.

Table 1: Baseline characteristics

Baseline parameter	iddEnPC (N=452) N (valid %)	dtEC-dtD (N=449) N (valid %)	Overall (N=901) N (valid %)	p-value
Age, years (median, range)	52 (18-71)	51 (22-73)	52 (18-73)	n.s.
pT1	168 (37.2)	159 (35.4)	327 (36.3)	**.004***
pT2	233 (51.5)	219 (48.8)	452 (50.2)	
pT3	41 (9.1)	69 (15.4)	110 (12.2)	
pT4	10 (2.2)	2 (0.4)	12 (1.3)	
pN0	131 (29.0)	100 (22.3)	53 (26.5)	**.043***
pN1	98 (21.7)	128 (28.5)	226 (25.1)	
pN2	151 (33.4)	149 (33.2)	300 (33.3)	
pN3	72 (15.9)	72 (16.0)	144 (16.0)	
both ER, PgR neg	151 (33.4)	149 (33.2)	300 (33.3)	n.s.
HER2 pos	114 (25.2)	118 (26.3)	232 (25.7)	n.s.
Grade 1	15 (3.3)	6 (1.3)	21 (2.3)	n.s.
Grade 2	172 (38.1)	183 (40.8)	355 (39.4)	
Grade 3	265 (58.6)	260 (57.9)	525 (58.3)	
Ductal invasive	351 (77.7)	371 (82.6)	722 (80.1)	n.s.
Lobular invasive	43 (9.5)	41 (9.1)	84 (9.3)	
Ki67 ≤20%	125 (27.7)	118 (26.3)	243 (27.0)	n.s.

*Chi² test of baseline parameters between arms

Table 2: Hematological toxicity according to chemotherapy

Adverse Event	Grade	iddEnPC (N=452) N (valid %)	dtEC-dtD (N=449) N (valid %)	Overall (N=901) N (valid %)	p-value
Leukopenia	any	447 (99.1)	438 (98.0)	885 (98.6)	n.s.
	3-4	425 (94.2)	403 (90.2)	828 (92.2)	**.025**
Neutropenia	any	427 (94.7)	410 (91.7)	837 (93.2)	n.s.
	3-4	406 (90.0)	376 (84.1)	782 (87.1)	**.010**
Febrile neutropenia	3-4	54 (12.0)	34 (7.6)	88 (9.8)	**.033**
Lymphopenia	any	437 (96.9)	435 (97.3)	872 (97.41)	n.s.
	3-4	375 (83.1)	347 (77.6)	722 (80.4)	**.043**
Thrombocytopenia	any	397 (88.0)	315 (70.5)	712 (79.3)	**<.001**
	3-4	55 (12.2)	20 (4.5)	75 (8.4)	**<.001**

Conclusions

The second interim analysis showed no additional or unexpected safety signals in the iddEnPC or dtEC-dtD arm and the study will be continued without changes.

References

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Presented at: San Antonio Breast Cancer Symposium - December 8-12, 2015

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