Prognostic impact of 21-Gene Recurrence Score, IHC4, and central grade in high-risk HR+/HER2- early breast cancer (EBC): 5-year results of the prospective Phase III WSG PlanB trial

Gluz O[1,2], Nitz U[1,2], Christgen M[3,], Kates RE[1], Clemens M[4], Kraemer S[5], Nuding B[6], Reimer T[7], Aktas B[8], Kuemmel S[9], Just M[10], Stefek A[11], Lorenz-Salehi F[12], Krabisch P[13], Liedtke C[1,14], Shak S[15], Svedman C[15], Wuerstlein R[1,16], Kreipe HH[3], and Harbeck N[1,16].

[1] West German Study Group, Moenchengladbach, Germany; [2] Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany; [3] Medical School Hannover, Institute of Pathology, Hannover, Germany; [4] Mutterhaus der Borromäerinnen, Breast Center, Trier, Germany; [5] University Clinics Cologne, Breast Center, Cologne, Germany; [6] Department of Obstetrics & Gynecology, Evangelical Hospital Bergisch Gladbach, Bergisch Gladbach, Germany [7] Clinics Suedstadt, Department of Gynecology and Obstetrics, Rostock, Germany [8] University Clinics Essen, Women Clinics, Essen, Germany; [9]Clinics Essen-Mitte, Breast Center, Essen, Germany; [10] Oncologic Practice, Bielefeld, Germany [9] Clinics Suedstadt, Department of Oncology, Rostock, Germany; [11] Johanniter Clinics, Breast Center, Genthin-Stendal, Germany; [12] Dr. Horst-Schmidt Clinics, Women Clinics, Wiesbaden, Germany; [13] Klinikum Chemnitz, Chemnitz, Germany; [14] University Clinics Schleswig-Holstein/Campus Luebeck, Women Clinics, Luebeck, Germany; [15] Genomic Health Inc, USA [16] Breast Center of the University of Munich (LMU), Munich, Germany.

Background

Over the last decades, adjuvant clinical trials in early breast cancer (EBC) have addressed all patients, independent of tumor biology and usually tested a new compound vs. standard. Since molecular biology has demonstrated substantial heterogeneity of EBC, a second generation of trials has been designed focusing on which patient should receive which drug. Plan B is one of the first trials of this new generation testing anthracycline-free chemotherapy in HER2- EBC and aiming to reduce overtreatment by chemotherapy (CT) by introducing the Onco*type* DX assay as a decision tool in HR+ HER2- tumors with limited nodal involvement .

Methods

The WSG-PlanB trial randomized candidates for chemotherapy with HER2- EBC, according to national guidelines, to adjuvant CT with 6x Docetaxel (Doc) + Cyclophosphamide (C) vs. 4x Epirubicin + Cyclophosphamide (EC) - 4 x Doc .

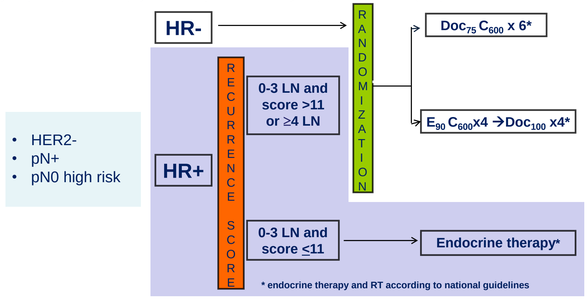


Fig. 1: Trial Design WSG-PlanB

Inclusion criteria:

- female patients (18-75 years) with histologically confirmed unilateral primary invasive breast carcinoma; adequate surgical treatment (R0, complete resection)
- T1-T4c, HER2 negative and estrogen and/or progesterone receptor analysis performed on the primary tumor prior to randomization;
- node-positive disease or node-negative disease with at least one other risk factor (tumor size >2 cm, grade ≥2, ER and PR negative, age <35 years old, high uPA/PAI-1 levels);
- no evidence of distant metastasis (M0) after conventional staging; performance status ECOG ≤1 or Ki67≥80%;
- HR positive patients must also meet all of the following clinical inclusion criteria: patient willingness to participate in adjuvant chemotherapy PlanB trial if score >11 and indication for chemotherapy given, provided either ≥4 involved lymph nodes or score >11 in 1-3 lymph nodes or N0 disease.

Primary trial endpoint is disease-free survival (DFS, events: relapse, second malignancy, death) in two chemotherapy arms.
Secondary endpoints include toxicity and overall survival (OS).
Within the **translational research program**, classical decisional tools like central grade, IHC (HR, HER2, Ki67) were assessed locally and centrally by an independent trial pathologist. Since an early amendment (August 2009), Onco*type* DX® was available within the trial for all HR+ tumors.

According to protocol, patients with 0-3 involved nodes and with recurrence score (RS) ≤11 could opt for endocrine therapy alone. **Primary endpoint of the translational research sub-study** was to assess correlations between a multigene signature (Onco*type* DX) and independent central pathology review. In the translational research program, exploratory DFS analysis was planned after 3 and 5 years of follow-up. Tissue micro arrays (TMA; diameter=1.4 mm) were constructed during the first slide review by choosing one morphologically representative region from each tumor sample. Slides were stained for ER (rabbit (SP1), Meomarkers), PR (mouse monoclonal PgR636, DAKO), Ki67 (clone 30-9 rabbit monoclonal, Ventana), HER2 (4B5 mouse monoclonal, Ventana) according to a standard protocol. Tumors were classified as ER or PR positive if immunostaining was present in >1% of tumor nuclei. Ki67 was evaluated by two experienced breast pathologists with special expertise in Ki67 evaluation (M.C., H.K.) on at least 100 tumor cells at the area with the highest density. IHC4 was calculated according to IHC4=94.7x(-0.100*ER10-0.079 *PgR10+0.240 ln(1+10x Ki67)) according do modified criteria of the ER H Score.

Results

From April 2009 to December 2011, 3198 patients were recruited; of these, 2449 were randomized to CT. Locally HR+ cases from the central tumor bank population reported here included n=2642 (HR- n=429). In 97,4%, local HR+ status was centrally confirmed.
RS was available in 2568 locally HR+ cases (n=2553 from tumor bank).
A substantial 34% discordance for histological grade was observed between central and local pathology in HR+ tumors (12% in HR-). 55% of centrally G3 tumors were assessed as G1-2 by local pathology. Within the pN0-1 post-amendment group (n=2274) with RS 0-11 (n=404, 18%), CT was omitted in 348 patients (86%).

Table 1: Baseline characteristics in locally HR+ patients

Characteristic	N = 2642
Age, years	
Median	56
Tumor size, mm	
Median	19
Nodal status, N (%)	
pN0	1554 (58.8)
pN1	930 (35.2)
pN2	122 (4.6)
pN3	36 (1.4)
Therapy, N (%)	
Endocrine	348 (13.0)
Chemotherapy randomization	1970 (74.6)
Out of study	324 (12.4)
Recurrence Score result, N (%)	
≤11	459 (17.4)
12--25	1544 (58.4)
>25	550 (20.8)
Unknown	89 (3.4)
Central grade	
G1	134 (5.1
G2	1636 (61.9)
G3	825 (31.2)
Unknown	47 (1.8)
Median Ki-67 (%)	15

Compliance with treatment recommendations within PlanB was 94% in pN0 and 75% in pN1 patients. 25% of pN0 patients with RS 12-25 discontinued the study (15% of pN1), particularly within the large group of RS 12-18 (30% of all cases).
Survival analysis: After 55 months of median follow-up, 5-year DFS was estimated as 94% for RS 0-11 (in all patients and in patients treated by ET only), 94% for RS 12-25 (95% in pN0 and 94% in pN1) and 84% for the RS >25 patients (88% in pN0 and 84% on pN1).

5 year DFS was estimated as 94% in the RS 0-11, 95% in the RS 12-25 and 88% in the RS>25 groups in patients with pN0 disease, respectively. Patients with pN1 BC had 5 year DFS of 94%, 94% and 84% in the RS 0-11; RS 12-25 and RS >25 subgroups respectively.

Figure 2: DFS by RS subgroups

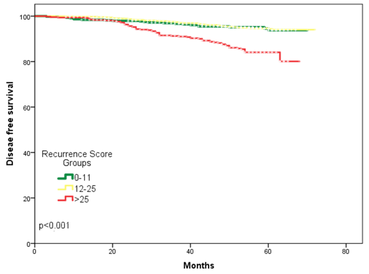


Figure 3: DFS by RS and nodal status subgroups

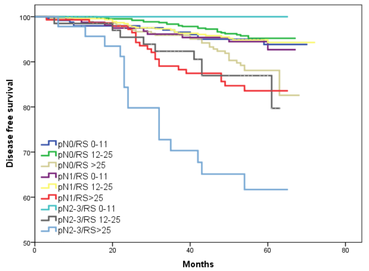
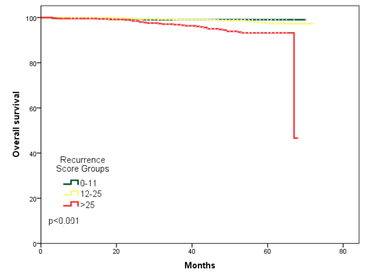


Figure 3: OS by Recurrence Score



Patients with pN2-3 disease and RS>25 had very poor 5 year DFS of 62% (compared to 100% in pN2-3 and RS<12 and 87% in pN2-3 and RS 12-25) (Fig. 2)

Overall survival (OS) by RS result
5-year OS was estimated as 99% in RS 0-11 patients (in all and in the no-CT patients with either pN0 or pN1 disease), 97% in RS 12-25 (98% in pN0, 96% in pN1) and 93% in RS>25 patients (97% in pN0 and 93% in pN1).
Prognostic impact of Ki67 in HR+ disease was assessed in 3 subgroups (0-10, 15-35 and >35%). 5-year DFS of 95% was significantly better in the low Ki67 group (79% CT-treated) compared to 91%; (86% CT treated) and 73% (97% CT treated) (p<0.001) in the other Ki67 groups, respectively. For comparison 5 year DFS in triple-negative cohort was 81%. (Figure 4).
Of note, only 8.6% of patients with low Ki67 (0-10%) had high RS (>25) and only 4% of patients with high Ki67>35% had low RS (<12).
Univariate and multivariate analysis
Nodal status (pN1-3 vs. pN0; pN2-3 vs. pN0-1 and pN2-3 vs. pN3 vs. pN0-2), both central and local grade 3, tumor size >2 cm, continuous fractionally ranked Ki67, PR, IHC4, and RS were univariate prognostic factors for poor DFS.
In multivariate analysis including all univariate prognostic markers, only pN2-3, both central and local grade 3, tumor size>2cm, and RS, but not IHC4 or Ki67 were independent factors for poor outcome.
Of note, if RS is excluded, then IHC4 or both Ki67 and PR enter the model.

Figure 4: DFS by Ki67 in HR+ vs. HR-/HER2- population

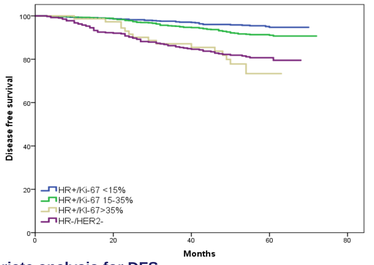


Table 3: Multivariate analysis for DFS

Factor	Coding	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Recurrence Score	Fractionally ranked* (75th to 25th percentile)	2.44 (1.80-3.30)	<.001	1.83 (1.27-2.62)	0.001
Nodal status					
	pN1-3 *v* pN0	1.55 (1.12-2.16)	0.01	n.s.	
	pN2-3 *v* pN0-1	3.13(2.03-4.82)	<.001	2.23 (1.27-3.94)	0.006
	pN3 *v* pN0-2	5.77 (2.93-11.33)	<.001	2.33 (1.25-4.37)	0.005
Tumor stage	pT2-4 *v* pT1	1.62 (1.02-2.58)	.04	1.48 (1.02-2.13)	0.04
Local grade	G3 *v* G1/2	2.37 (1.69-3.31)	<.001	1.64 (1.1-2.44)	0.02
Central grade	G3 *v* G1/2	2.49 (1.78-3.46)	<.000	1.72 (1.27-2.62)	0.01
Ki-67 (%) semi-quantitative	Fractionally ranked (75th to 25th percentile)	2.64 (1.87-3.74)	<.001	n.s.	
ER (%)	Fractionally ranked (75th to 25th percentile)	0.75 (0.53-1.06)	0.11	n.s.	
PR (%)	Fractionally ranked (75th to 25th percentile)	0.53 (0.39-0.72)	<0.001	n.s.	
IHC4	Fractionally ranked (75th to 25th percentile)	2.06 (1.49-2.85)	<0.001	n.s.	

Conclusions

- Substantial discordance in grade assessment and lack of standardization in Ki67 measurement complicate treatment decisions in HR+ HER2- breast cancer
- The excellent 5-year DFS of 94% and OS of 99% from the prospective PlanB trial in pN0 and pN1 EBC patients without adjuvant CT based on RS≤11 support the use of well-validated multigene assays such as RS combined with standardized pathology for adjuvant treatment decisions in HR+ HER2- EBC.
- IHC markers measured by an experienced central pathology lab (Ki67, PR and/or IHC4) provide independent prognostic impact regarding DFS only if RS is not available.
- Based on our results, conventional markers such as grade, nodal status, tumor size should be used together with RS, and Ki-67 is useful as a selection criterion for multigene testing (e.g. Ki67>10% and<35%), but not as sole prognostic marker for adjuvant CT decision.
- Our PlanB prospective 5-year DFS for both pN0 and pN1 patients are similar to the TAILORx results for pN0 disease.
- The impact of adjuvant CT in genomically intermediate-risk EBC is still uncertain and currently evaluated in prospective trials (TailorX, RxPonder, WSG-ADAPT HR+/HER2-).

West German Study Group, Ludwig-Weber-Str. 15b, 41061 Moenchengladbach, Germany; *oleg.gluz@wsg-online.com*