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.

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Background: The 21-gene Recurrence Score (RS) assay, nodal status, grade, and ER, PR, Ki67, or IHC4 are recommended for chemotherapy (CT) decision making in HR+/HER2- EBC. The phase III PlanB trial prospectively used RS to define a low-risk subset of pN0-1 EBC patients who could be treated by adjuvant endocrine therapy (ET) alone. Here, we report for the first time a comparison of the prognostic impact of RS, central grade, and IHC4 regarding long-term 5-year outcome. Methods: A central tumor bank was prospectively established within PlanB. Following an early amendment, HR+, pN0-1 patients with RS ≤ 11 were recommended to omit CT. Patients with RS > 12 or pN2-3 or HR-/HER2- BC were randomized to CT: 6xTC vs. 4xEC-4xDoc. Primary endpoint of the study is disease-free survival (DFS), defined here as any relapse, secondary malignancy, or death. Results: From 2009 to 2011, PlanB enrolled 3198 patients (central tumor bank n = 3073); median age was 56 years; 41.1% had pN+ and 32.5% G3 EBC. In 348/404 patients (15.3%), CT was omitted based on RS ≤ 11. After 55 months median follow-up, 5-year DFS in ET-treated patients with RS ≤ 11 was estimated as 94% (in both pN0 and pN1) vs. 94% (RS 12-25) and 84% (RS > 25) in CT-treated patients ($p < 0.001$); 5-year overall survival (OS) was 99% vs. 97% vs. 93% ($p < 0.001$), respectively. Nodal status, central and local grade, tumor size, continuous Ki-67, PR, IHC4, and RS were univariate prognostic factors for 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 Ki-67 were independent adverse factors. If RS is excluded, then IHC4 or both Ki-67 and PR enter the model. Conclusions: RS seems to provide stronger prognostic impact in addition to clinical-pathological markers (local and central grade, tumor size, and nodal status) vs. IHC4 or Ki-67 in our prospective WSG PlanB trial. The excellent 5-year DFS of 94% and OS of 99% in pN0 and pN1 EBC patients who did not receive adjuvant CT based on RS ≤ 11 support the use of well-validated genomic assays such as RS combined with standardized pathology for adjuvant treatment decisions in HR+ HER2- EBC. Clinical trial information: NCT01049425