[P4-11-01] Prognostic impact of discordance between different risk assessment tools in early breast cancer (recurrence score, central grade, Ki67): Early outcome analysis from the prospective phase III WSG-PlanB trial

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Background: In early HR+, HER2-negative breast cancer (BC), the 2013 St. Gallen Consensus recommends adjuvant chemotherapy (CT) for patients with nodal involvement, Recurrence Score (RS) >25, grade G3, or high Ki67. However, risk assessment by these factors may be discordant; e.g., in PlanB, about 60% of centrally G3 tumors did not have RS >25. Here, we present first cumulative outcome data from PlanB for evaluation of different risk assessment tools.
Methods: The WSG-PlanB trial was designed to evaluate anthracyline-free adjuvant CT, 6 x TC vs. 4 x EC - 4 x Doc in HER2-negative BC. Since an early amendment (August, 2009), HR+ patients with 0-3 involved nodes and RS≤11 were selected to omit CT, receiving only adjuvant endocrine therapy. The primary trial endpoint is event-free survival (EFS, events: relapse, second malignancy, death); secondary endpoints include relapse-free (RFS) and overall survival (OS). Central grade and luminal B classification were centrally assessed by an independent trial pathologist.
Results: From April 2009 to December 2011, 3198 patients were recruited; of these, 2449 were randomized to chemotherapy. Median age was 56 years; 84.1% were HR+ by local pathology, 60.8% node-negative. The central tumor bank population reported here included 3071 cases. RS was available in 2566/2741 cases registered as HR+; of these, 18% had Recurrence Score of 0-11, 60.4% RS 12-25, and 11.6% RS >25. In 343 patients (14.1% of pN0-1 patients after amendment), CT was omitted based on RS ≤11.
By central assessment, in HR+ disease, grade was distributed as follows: G1/G2/G3: 5.3%/62.6%/32.1%; only 43.5% of central G3 tumors were locally G3; overall concordance between central and local grade was 65.6%. 41.7% of (central) HR+ patients, had "luminal B" tumors (central Ki67≥20% and/or PR≤20%). After 35 months median follow-up, 131 events, including 103 relapses, have been documented; 3-year EFS and RFS in the no-chemotherapy group were 98.4% and 99.0%, respectively.
In the central HR+ population, EFS was substantially poorer in patients with RS >25 than in others (3y EFS: 92% vs. 98% in both RS 12-25 and RS 0-11; p<.001) (n.b.: all patients with RS ≥12 received CT). RFS was lower in luminal B than in luminal A patients (3y RFS: 96% to 99%, p=.03); EFS did not differ significantly. Involved lymph nodes, Ki67, central grade, tumor size, and RS were univariate prognostic factors for EFS. In multivariate analysis (EFS) in central HR+ disease including these factors, tumor size (fractionally ranked), central G3 (vs. G1 or G2), lymph nodes (≥2 vs. <2), and RS (fractionally ranked) were all significant predictors for poor EFS.
Discussion: In spite of receiving no adjuvant CT, patients with RS 0-11 (HR+ HER2- pN0-1) had excellent 3y-EFS. The excellent outcome of patients with RS 12-25 receiving CT suggests potential CT

overtreatment in a subgroup. The ongoing WSG-ADAPT trial addresses this issue. Early results of WSG-PlanB suggest that quality-assured pathology together with Oncotype DX® are essential in identifying high-risk patients to avoid undertreatment.