

Prospective comparison of Recurrence Score and different definitions of luminal subtypes by central pathology assessment of single markers in early breast cancer: results from the Phase III WSG-planB Trial.

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Background: Routine use of multigene RT-PCR based assays e.g. Recurrence Score® (RS) panel vs. single markers (grade, uPA/PAI-1, ER/PR, HER2, Ki-67) is controversially discussed in early BC. Several definitions of luminal A/B subtypes have been proposed by the St. Gallen guidelines and individual researchers (by grade 1/2 vs. 3, Ki-67 cut-offs 14 or 20%). Recently, integration of PR>20% was proposed into an immunohistochemical luminal A subtype definition (Ki-67<14%). Here, we present the final WSG-planB trial correlation analysis of risk assessment tools and the first prospective comparison of central and local pathology IHC/FISH assessment, RT-PCR for single markers and impact of central and local grade regarding allocation of patients to luminal A/B subtypes.

Methods: Plan B trial (04/09 to 11/11: n=2,449 randomized for 6xTC vs. 4xEC-4xDOC in locally HER2- BC; n=3197 registered; n=3072 available for central tumor bank). RS was used as selection criterion for chemotherapy (CTx) omission in HR+ invasive BC (if $RS \leq 11$ in pN0 or pN1). Risk assessment by grade, ER/PR, HER2 (IHC/FISH), Ki-67 was evaluated locally and centrally by the independent trial pathologist in all tumors. Clinical risk was estimated using AdjuvantOnline 8.0 (cut-off of 88% of breast cancer specific survival after 10 years without therapy in HR+ disease)

Results: RS distribution in 2569 HR+ tumors: 0-11 (18%), 12-25 (60%), >25 (22%). (RS_{18} 53%/34%/13%). Luminal A subtype based on Ki-67 cut-off of <14%/<20%: 50.4%/68.8%. If PR>20% was included in the luminal A/Ki-67<14% definition: 37.6%. Luminal A/B based on local/central grade: 79%/21%; 67.9%/32.1%. In 354 pN0-1 patients, CTx was omitted based on low risk RS (88% compliance). In this group, 62% were high-risk by clinical-pathological criteria; luminal B subtype: 30% by Ki-67₁₄, 16% by Ki-67₂₀, 44% by Ki-67_{14/PR>20%}, 20% by central grade (HR+/G3). Allocation to luminal A/B subtypes based on local and central grade varied substantially: overall concordance was 72%, but 40% of locally luminal B (HR+/G3) were luminal A (HR+/G1/2) by central and 60% of centrally luminal B were locally luminal A. Moderate correlations were found between RS and both central grade (Spearman correlation $rs=0.317$; $p<0.001$), local grade ($rs=0.321$; $p<0.001$), and Ki-67 ($rs=0.374$; $p<0.001$), particularly due to poor correlations in the RS group <26. Correlations between groups were as follows: RS_{12} and luminal A/B Ki-67₁₄ ($rs=0.26$; $p<0.001$). Inclusion of PR>20% moderately improved the correlation to $rs=0.34$. Data on allocation to luminal subtypes by local vs. central Ki-67 will be presented at the meeting.

Conclusions: Our results represent the first prospective correlation of different luminal A/B definitions vs. a guideline mentioned gene signature (Recurrence Score assay). High Recurrence Score result usually implies high grade and luminal B classification but the converse is not true. There is substantial heterogeneity in risk assessment by luminal A/B classification and grade in low/intermediate Recurrence Score groups. The concordance for central and local assessment of grade and luminal A/B status was limited. The clinical significance of these findings will be addressed by further follow up of the WSG-planB trial.