

Prospective comparison of risk assessment tools in early breast cancer (Recurrence Score, uPA/PAI-1, central grade, and luminal subtypes): final correlation analysis from the phase III WSG-Plan B trial

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Background: Both, the Recurrence Score (RS) multi-gene assay and invasion factors uPA/PAI-1 are recommended by guidelines (ASCO, AGO) for decision support regarding adjuvant chemotherapy in early breast cancer (BC). Central grade 3 and high Ki-67 levels have been shown by our WSG-AGO EC-DOC trial as independent predictive markers for enhanced benefit of taxane-based chemotherapy in intermediate risk breast cancer.

Here, we present the final WSG-Plan B trial correlation analysis of these risk assessment tools.

Methods: Plan B trial (evaluating anthracycline-free adjuvant chemotherapy, 6x TC, vs. 4xEC-4xDOC in HER2-negative BC; n=2,448 to be randomized for chemotherapy). RS has been used as the selection criterion for chemotherapy vs. endocrine therapy alone in HR+ BC (if $RS \leq 11$ in pN0 or 1-3 lymph nodes) since an amendment in August 2009. uPA/PAI-1 (by ELISA) is obtained as an optional risk factor. Evaluation of central grade and luminal B subtype (using 13.25% or 20% Ki-67 cut-offs) are performed by the independent trial pathologist in all HR+ tumors.

Results: From April 2009 to June 2011, 3037 patients have been recruited and 2290 randomized. The study will be completed by August 2011. Data on RS are available in 2361 patients with HR+ tumors: RS is distributed as follows: 0-11 (18%), 12-25 (61%), >25 (21%). In 257 patients with 0-3 involved LN, chemotherapy was omitted based on RS results (12.3% of patients after amendment).

By the last interim analysis in February 2011, data on central grade are available in 1509 patients and Ki-67 in 592 patients. An only moderate positive correlation was observed between Ki-67 and RS (Spearman's coefficient $rs=0.336$; $p<0.001$) as continuous variables and between RS and central grade ($rs=0.498$, $p<0.001$). High RS is correlated with high grade G3 (66% of RS_{25} high risk and 74% of RS_{30} high risk are G3), but within the RS_{11} low-risk group, 33% of tumors were assessed as G3 and within RS_{18} low-risk, 30% were G3. 14% of G3 tumors were classified as RS_{11} low-risk and 40% of G3 tumors as RS_{18} low-risk. When considered as risk categories, there was only a weak concordance between RS and uPA/PAI-1, using either standard RS (18; 30) or PlanB cut-offs (low risk ≤ 11 RS), with 67% of patients having high uPA/PAI-1 within the low/intermediate-RS subgroups. High-risk RS is closely correlated with high-risk by uPA/PAI-1, poor grade and luminal B subtype. However, this close correlation is not seen in the low or intermediate RS groups with clinically relevant proportions (between 33-66%) of patients identified by uPA/PAI-1 or Ki-67 as being at high-risk had low or intermediate RS. Final correlation analyses in all Plan B patients with HR+ tumors ($n>2.500$) will be presented at the meeting.

Discussion: For the first time, risk groups according to RS, Ki-67 and uPA/PAI-1 have been prospectively compared within a phase III trial setting both in node-negative and node-positive early BC. These data show good concordance between high-risk status according to RS and uPA/PAI-1, high grade by central pathology and luminal B subtype. In the low and intermediate risk RS groups, there are still patients considered high-risk according to uPA/PAI-1, Ki-67 or central grade. Further follow-

up of the WSG-Plan B trial will clarify the clinical significance of these findings regarding patient outcome and response to adjuvant chemotherapy.