Background: Both, the Recurrence Score (RS) multi-gene assay and invasion factors uPA/PAI-1 are included in guidelines (ASCO, AGO) for decision support regarding adjuvant chemotherapy in early breast cancer (BC). Here, we present the first pre-planned WSG-Plan B trial correlation analysis of RS, uPA/PAI-1, and molecular subtypes by protein expression.

Methods: Plan B trial (n=2,448) is evaluating anthracycline-free adjuvant chemotherapy (6x TC) vs. 4x EC4xDOC in HER2-negative BC. RS is used as selection criterion for chemotherapy or hormonal therapy alone; uPA/PAI-1 (by ELISA) is obtained as an optional risk factor. Central and Ki-67-modified grade, and luminal B subtype by 13.25% or 20% Ki-67 cut-offs are evaluated by the independent trial pathologist.

Results: From April 2009 to February 2011, 2380 patients have been recruited and 1860 randomized to the study. In 1106 pts, both RS and central grade, in 592, both Ki-67 and RS, and in 201 uPA/PAI-1 and RS were available. When considered as continuous variables, RS was weakly positively correlated (Pearson's coefficient r1) with PAI-1 (r1=0.21, p<0.00), Ki-67 (r1=-0.336, p<0.001), and central grade (r1=0.336, p<0.001). 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. 29-33% of G3 tumors are allocated to high-risk category. While RS high risk was predictive of high risk by uPA/PAI-1, grade and luminal B subtype, the converse was not true; clinically relevant proportions (between 33-66%) of patients identified by uPA/PAI-1 and Ki-67 as being at high risk have low/intermediate RS.

Discussion: For the first time, risk groups according to RS, Ki-67 and uPA/PAI-1 have been prospectively compared. These preliminary data show that the high-RS group sees predictive of high uPA/PAI-1, aggressive central grade and luminal B subtype, but the converse is not true; these markers do not predict the RS. Further evaluation within the Plan B trial will clarify the clinical significance of these findings.

Objectives

- Subproject of the prospective WSG-Plan B trial.
- Prospective correlation of uPA and PAI-1 levels with Oncotype DX (Recurrence Score®, RS) taking into account nodal subgroups of patients and different RS cut-offs.
- Prospective correlation of uPA and PAI-1 with proliferation marker Ki-67 as a possible determinator of molecular subtypes (luminal A and B) in hormone receptor (HR) positive disease.
- Prospective correlation of uPA and PAI-1 levels with central grade.
- Prospective correlation of uPA and PAI-1 with luminal A/B subtypes determined by Ki-67.
- uPA/PAI-1 is the only prospectively validated biomarker guiding adjuvant chemotherapy decision making in node-negative breast cancer

Methods

- Patients with primary HER2-negative, node-negative and positive breast cancer (BC) are treated with either 6 cycles of chemotherapy with docetaxel (75 mg/m²) and cyclophosphamide (600 mg/m²), q3w (TC) versus docetaxel (75 mg/m²) and cyclophosphamide (600 mg/m²), q3w (TC) versus paclitaxel (80 mg/m²) and doxorubicin (50 mg/m²), q3w (TA).
- Patients are randomized in a 1:1 fashion to either Arm A or Arm B within the WSG-Plan B study.
- Central pathology of all tumor samples for grade, histology, and proliferation marker Ki-67 (MIB-1 antibody, Thermo Scientific) is performed for all patients.
- uPA / PAI-1 tumor levels are measured by standardized ELISA (Femtelle®, American Diagnostica Inc.).
- Availability of Recurrence Score is an inclusion criterion in hormone receptor (HR)+ disease.
- Patients with 0-3 positive lymph nodes and low RS ≤11 should not be randomized to chemotherapy; they will be treated by endocrine therapy alone; follow-up will be obtained.
- Mandatory: Standard radiation after breast conserving surgery and endocrine therapy for HR+ disease.

Conclusions

- Further evidence for prospective correlation between AGO and ASCO recommended prognostic biomarkers uPA/PAI-1 and recurrence score, RS (Oncotype DX), proliferation marker Ki-67 and central grade has been provided.
- Despite of a modest overall correlation between risk groups by both biomarkers and luminal A/B subtypes, there is a strong correlation between the high-risk RS subgroup, uPA/PAI-1 high risk, and luminal B subtype (Ki-67). In their patients, adjuvant chemotherapy would be a guideline-supported standard of care.
- uPA/PAI-1 and luminal A/B subtypes by Ki-67 could potentially identify a subgroup with good prognosis within the large (about 50%) patient subgroup stratified as "intermediate" risk by RS.
- However, there is also a substantial group of patients with high-risk tumors by central grade and luminal B subtype whose tumors have a low RS.
- The high acceptance of risk stratification of uPA/PAI-1 represents its acceptance in clinical routine use.
- These data are preliminary and should be used only for further hypothesis-generating studies.
- Further recruitment and follow-up of the WSG Plan B trial will substantiate the clinical significance of the trial.
- Final data to these prospective comparison will be presented at SABCS 2011.

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