ADAPT - Adjuvant Dynamic marker-Adjusted Personalized Therapy trial optimizing risk assessment and therapy response prediction in early breast cancer

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Background: Appropriate indication for chemotherapy (CTx) in patients with hormone receptor (HR) positive breast cancer (BC), prediction of CTx response, and addition of novel targeted therapies are the most important questions in adjuvant therapy of early BC. Few well evaluated prognostic tests identify patients (pts) with a low-risk profile resulting in a low enough CTx benefit to justify omission of CTx. Several clinical trials with results still pending have already addressed this question such as TAILORx, MINDACT, NNBC-3, WSG-planB. However, proliferation seems to be a key part of all prognostic genomic signatures. Moreover, dynamic changes of proliferation (as a result of endocrine, cytotoxic, and targeted therapy) during therapy have been shown to be most important for outcome prediction in patients with pathological complete response to neoadjuvant chemotherapy in distinct BC subtypes (luminal B, TNBC, HER2+).
Trial design: ADAPT is one of the first new generation adjuvant trials dealing with individualization of adjuvant decision-making in early BC. The WSG-ADAPT trial combines static assessment of prognosis of patients by a genomic signature (Recurrence Score® panel in HR+ disease) and conventional prognostic markers (nodal status) with dynamic measurement of proliferation/apoptosis changes during a short course of preoperative therapy. ADAPT will establish early predictive molecular surrogate markers for outcome by assessing response to a short 3-week induction treatment, using a baseline diagnostic core biopsy and a second biopsy after induction treatment. ADAPT consists of an umbrella trial and four different sub-protocols (HR+/HER2-, HR-/HER2-, HR+/HER2+, HR-/HER2+) and is set up as a prospective, multi-center, controlled, non-blinded, randomized phase II/III trial.
Eligibility criteria: Pre-/postmenopausal women with histologically confirmed unilateral primary invasive early BC. Women identified to require chemo- or targeted (anti-HER2) therapy must have adequate laboratory values and organ function. Pts must have no contraindications for the planned treatment.
Specific aims: Primary endpoints will include evaluation of the dynamic test for outcome prediction and prospective comparison of 5yr EFS in HR+/HER2- patients with intermediate Recurrence Score results by Onco*type* DX® assay (RS 12-25) and good response to short-term endocrine therapy, and HER2+/triple negative (TN) pts with pCR) with the 5 year EFS of HR+/HER2- N0-1 pts with low Recurrence Score results (RS≤11) (control group). Secondary endpoints will include overall survival.
Statistical methods: Assumption across sub-protocols is that adjuvant CTx can be spared in HR+/HER2- BC or pCR be achieved in HER2+/TN in expected 1120 (HR+/HER2-) or 170 (HER2+/TN) pts respectively within the main phase. Their outcome will be compared to the control group (expected n=640 HR+/HER2- pts: low risk (by RS) and thus no CTx). Assuming 94% 5yr survival in control group, one-sided test of non-inferiority at 95% CI will have 80% power for a survival non-inferiority margin corresponding to 3.2% (i.e. 90.8% survival).
Present and target accrual: By June 2012, 11 of 12 initial sites have been initiated, and 7 pts recruited. Target accrual for run-in phase is 400 pts (4000 for run-in and main phase).