

**[OT3-2-04] ADAPT - Adjuvant Dynamic marker-Adjusted Personalized Therapy trial optimizing risk assessment and therapy response prediction in early breast cancer**

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Background: Early therapy response is currently not regarded for further treatment decisions as standard of care in the treatment of breast cancer (BC). Predictive markers for the success of a certain therapy could support the physician's choice of adequate and beneficial therapies by simultaneous reduction of unnecessary toxicity. Proliferation makers as Ki-67 seem to be a suitable tool, as dynamic changes of proliferation (as result of induction therapy) have been shown to be most important for outcome of neoadjuvant chemotherapy prediction in patients with pCR in distinct BC subtypes (luminal B, TNBC, HER2+).

Methods: Trial design: ADAPT combines early assessment of prognosis by conventional markers (e.g. molecular classification, nodal status) with dynamic measurement of proliferation changes during a 3-week induction therapy, using baseline diagnostic core biopsy and a second biopsy after induction therapy. ADAPT consists of an umbrella trial and five different sub-trials (HR+/HER2-, HR+/HER2+, HR-/HER2+, HR-/HER2-, Elderly) and is set up as prospective, multi-center, controlled, non-blinded, randomized phase II/III trial.

Subtype-specific treatment across the sub-trials is highly innovative and involves the following treatment strategies:

- HR+/HER2-: endocrine therapy (ET) vs. chemotherapy (4xPac q2w – 4xEC q2w vs. 8xNab-Pac q1w – 4xEC q2w) + ET, depending on risk classification/early response.
- HER2+/HR+: T-DM1 vs. T-DM1 + ET vs. trastuzumab + ET.
- HER2+/HR-: Trastuzumab + Pertuzumab ± Paclitaxel q1w.
- TN: Nab-Paclitaxel + Gemcitabine vs. nab-Pac + Carboplatin.
- Elderly: 2xMyocet + Cyclophosphamide q3w, depending on cPR/cCR or NC/toxicity the treatment will be continued for two more cycles or changed to 6xPac q1w.

Adaptation/change in therapy regimens can be made by interim analysis after n=130 in each sub-trial.

Eligibility criteria: Histologically confirmed unilateral primary invasive BC with known HR-/HER2-status (central pathology) for allocation to the respective sub-trial. Pts requiring chemo- or targeted (anti-HER2) therapy must have adequate laboratory values and organ function and must have no contraindications for the planned treatment.

Primary endpoints: Evaluation of dynamic test for outcome prediction/prospective comparison of 5yr EFS in responders (intermediate risk (RS 12-25) / good response to short-term ET in HR+/HER2- or pts

with pCR in HER2+/TN BC) compared to low risk HR+/HER2- (RS≤11, N0-1) pts (control group).

Statistical methods: Assumption across sub-protocols: adjuvant CTx can be spared in HR+/HER2- or pCR be achieved in HER2+/TN in expected 1120 (HR+/HER2-) or 170 (HER2+/TN) pts, respectively. Outcome will be compared to the control group (expected n=640 HR+/HER2- pts: low risk (by RS), i.e. no CTx).

Assuming 94% 5yr survival in control group, one-sided test of non-inferiority at 95% CI will have 80% power for survival non-inferiority margin of 3.2% (i.e. 90.8% survival).

Present and target accrual: By June 2014, 73 active sites have recruited 1820 pts for ADAPT HR+/HER2-. Target accrual is 4000 pts. 190 of 380 pts were successfully randomized for ADAPT HER2+/HR+. ADAPT HER2+/HR- has included 17 of 220 pts and ADAPT Triple Negative has recruited 150 of 336 pts.

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