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The Treat CTC trial – a new approach targeting circulating tumor cells (CTC) in early breast cancer (EBC)

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Background

The presence of CTC in metastatic BC is associated with an impaired prognosis. Recent data have shown a reduced disease-free survival and increased risk of death in the presence of CTC in EBC. Patients with persisting CTC after (neo)adjuvant chemotherapy are at increased risk of relapse and might benefit from additional systemic treatment. Recent data have reinforced the hypothesis that trastuzumab can eliminate tumor cells by antibody dependent cell cytotoxicity (ADCC) or other immune mechanisms. Preclinical data have provided evidence that the benefit of trastuzumab may be associated with targeting cancer stem cells in a model that does not require HER2 amplification (Ithimakin et al Cancer Res 2013). In a single center phase 2 study trastuzumab eliminated CTC, irrespective of the HER2 status of the primary tumor and of CTC and this was associated with reduced relapses (Georgoulias et al Ann Oncol 2012).

Methods

15 mL of blood will be processed using the CellSearchTM System. The sample will be enriched for cells expressing the epithelial-cell adhesion molecule (Epcam) with antibody-coated magnetic beads. Fluorescently labeled monoclonal antibodies specific for leukocytes (CD45) and epithelial cells (cytokeratin 8,18,19) are used. The CTC blood test will be regarded positive with ≥ 1 CTC / 15 mL of blood confirmed by central laboratory review. Additional HER2 phenotyping on CTC by immunocytochemistry will be performed.

The primary test will be a one-sided test with overall α of 0.1 to compare the trastuzumab arm to the observation arm for the CTC detection rate at week 18 (superiority test) in the intention-to-treat population. The odds ratio and its confidence interval will be estimated using a logistic regression model. The comparison of RFI, IDFS, DFS and OS will be done using a two-sided test in a proportional hazards model for cause specific hazard, adjusted for the stratification factors.

Trial Design

Treat CTC trial is a multicenter European randomized phase II trial, sponsored by the EORTC and run under the BIG umbrella. It will assess the efficacy of trastuzumab in eliminating persisting CTC after the completion of (neo)adjuvant chemotherapy and surgery in patients with HER-2-negative EBC. Eligible patients will be randomized in a 1:1 ratio to either 6 cycles of trastuzumab or observation. Patients' peripheral blood will be tested again for CTC after 18 weeks.

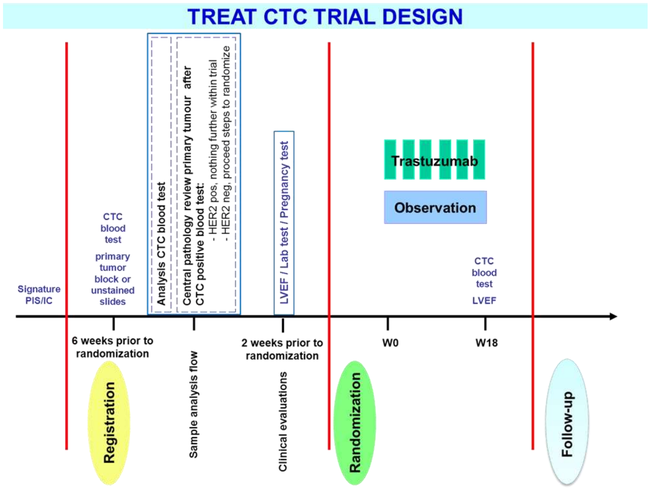

Figure 1: TREAT CTC summary flow chart

Main Eligibility Criteria

- Adequately excised HER2-negative EBC
- ≥1CTC/15mL of blood using the CellSearch technology after completion of (neo)adjuvant chemotherapy
- Completion of adjuvant chemotherapy for node-positive disease or neoadjuvant chemotherapy with residual invasive disease in breast or lymph nodes (no complete pathological response)
- Histological Grade > 1 and primary tumor size > 1 cm

Primary Objective

To evaluate whether trastuzumab decreases the detection rate of CTC in patients with HER2-negative EBC by comparing the trastuzumab treated arm to the observation arm.

Secondary Objectives

To compare clinical outcomes as measured by Recurrence Free Interval (RFI), Invasive Disease Free Survival (IDFS), Disease Free Survival (DFS) and Overall Survival (OS)) between the trastuzumab and observation arms.

Target Accrual and Present Status

Treat CTC started patient screening in April 2013 in Belgium. 28 patients have been screened, 1 patient has been randomized. It is estimated that 2175 women will be screened to include 174 patients eligible for randomization in a 1:1 ratio. Accrual is expected to be completed in 2 years.

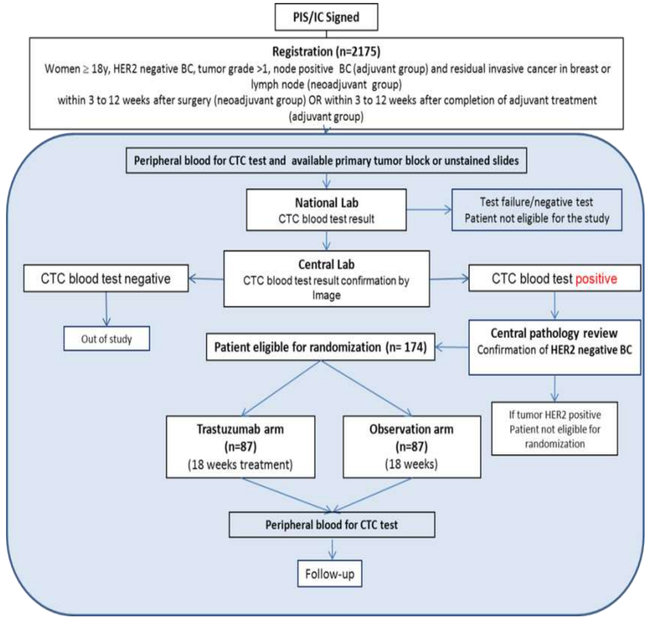

Figure 2: TREAT CTC trial design

Perspectives

Given the prognostic relevance of CTC in BC, the Treat CTC trial will be the first multicenter, randomized trial in which CTC are used to guide treatment decisions in EBC. The results of this trial will help to clarify the clinical utility of CTCs in early disease.