MINDACT  
(Microarray In Node negative Disease may Avoid ChemoTherapy)

A prospective, randomised study comparing the 70-gene expression signature with common clinical-pathological criteria in selecting patients for adjuvant chemotherapy in node-negative breast cancer. (EORTC Protocol 10041 – BIG 3-04)

In the last 20 years, little progress has been made with respect to assisting oncologists in treatment decision making for node-negative breast cancer patients. Great uncertainty persists in selecting those node-negative women who need adjuvant chemotherapy and those who could safely be spared this aggressive treatment. At present oncologists decide whether to prescribe chemotherapy based on common clinical and biological criteria (age, tumour grade, stage and hormone receptor expression). These criteria are used on the basis of guidelines such as the St Gallen and NIH consensus documents, or are organized into specific prognostic tools such as the Nottingham Prognostic Index or Adjuvant! Online.

Limitations of current clinical prognostic tools
There is currently no widespread consensus or proof as to which of these clinical indices is the most useful. The individual prognostic tools are not standardized and have difficulties identifying clinically relevant cut offs. New molecular markers (e.g., HER2, vascular invasion of the primary tumour and expression levels of hormone receptors) are starting to be incorporated, but this is being done in a piecemeal way and there is no clear agreement on the importance of individual molecular markers or their clinically relevant levels. This is further complicated by the fact that the clinical impact of most molecular markers does not follow linear scales.

Recent improvements in our understanding of breast cancer biology and a parallel increase in possible treatment options have led to improvements in treatment; however, we have yet to fully translate our increased understanding into improved outcome for this very heterogeneous disease. Oncologists still have significant difficulty in tailoring treatment strategies to the molecular characteristics of an individual’s disease. This is partly due to the limitations of current prognostic tools. Given the almost 100% death rate from metastatic breast cancer, existing guidelines aim to avoid under-treatment of affected women, assigning only about 15-20% of them to a “low/minimal risk” subset for which no adjuvant treatment (or only adjuvant endocrine treatment) will be considered. Consequently, many women with early breast cancer are probably over-treated, resulting in decreased quality of life for these patients as well as an increased economic burden of this disease on society.

Development of a new molecular prognostic tool
In an attempt to better understand tumour biology and to find new clinically relevant molecular markers, scientists at the Netherlands Cancer Institute looked at global molecular expression levels in 78 tumour samples from untreated node-negative breast cancer patients using microarray technology. They were able to identify a molecular signature that was associated with “poor” clinical prognosis and an associated signature linked to “good” clinical prognosis. This gene expression signature can be used to predict Distant Metastasis Free Survival (DMFS) (1). They went on to validate the prognostic power of this unique set of genes on 295 patients and confirmed that this gene signature outperforms all of the traditional prognostic factors and clearly separates a group with an excellent prognosis at 10 years from a group with a high risk of recurrence (2). An external, independent retrospective validation of these
Clinical validation of the molecular prognostic tool

The MINDACT (Microarray In Node negative Disease may Avoid ChemoTherapy) trial is a multicentre, prospective, phase III randomised study comparing the 70-gene expression signature with a common clinical-pathological prognostic tool (Adjuvant! Online) in selecting patients for adjuvant chemotherapy in node-negative breast cancer. Each patient will be offered those randomisations for which she is eligible, as shown below.

Trial objectives

The primary objective of the MINDACT trial is to confirm that patients with a “low risk” molecular prognosis and “high risk” clinical prognosis can be safely spared chemotherapy without affecting DMFS (Randomisation-Treatment decision). The two other main objectives of the study address questions related to adjuvant treatment of breast cancer. MINDACT will compare anthracycline-based chemotherapy regimens to a docetaxel-capecitabine regimen, which is possibly associated with increased efficacy and reduced long-term toxicities (Randomisation-Chemotherapy). MINDACT will also investigate the efficacy and safety of 7 years single agent Letrozole to the sequential strategy of 2 years of Tamoxifen followed by 5 years of Letrozole (Randomisation-Endocrine therapy).

MINDACT has several secondary objectives including the identification and validation of novel gene expression signatures predicting clinical response to therapies used (chemotherapy and endocrine therapy). An estimation of the efficacy of chemotherapy in terms of Disease Free Survival (DFS), DMFS and Overall Survival (OS) in the two subgroups where the clinical-pathological prognosis and the molecular prognosis are discordant will also be performed. Overall estimates of efficacy (endpoints DFS, DMFS, OS) for each treatment strategy according to clinical-pathological prognosis and according to the 70-gene signature prognosis will be calculated, as will an estimate of the percentage of patients receiving chemotherapy per each prognostic method. The project also aims to set up several tissue bank resources (RNA, tumour tissue, serum) for future translational research studies in both genomics and proteomics.
Chemotherapy: comparison of anthracycline-based treatments to a docetaxel-capecitabine regimen

Of concern to women with a medium rather than a high risk of relapse are two possible long-term toxicities of anthracycline-based therapy: secondary leukaemia and cardiotoxicity. The MINDACT study will investigate whether a docetaxel-capecitabine regimen is more effective and safe than an anthracycline-based one. This combination (TC) has been evaluated in the metastatic setting and showed a survival gain when compared to Docetaxel alone (3). Of the trials attempting to delineate the role of taxanes in the adjuvant treatment of breast cancer, the use of a non-anthacycline combination has only been addressed by one trial, an American study (N=1016) which compared TC (docetaxel + cyclophosphamide) to AC (doxorubicin + cyclophosphamide); while the follow-up is still insufficient to draw conclusions, preliminary reports have shown TC to be at least as effective as AC (4).

Endocrine treatment: comparison of 2 years of Tamoxifen followed by 5 years of Letrozole with 7 years of Letrozole

Recent large clinical trials have demonstrated the advantage of Aromatase Inhibitor (AI) over Tamoxifen for the adjuvant treatment of breast cancer (5,6). One trial in particular has demonstrated that starting AI upfront was better than Tamoxifen upfront in terms of DFS (7). Which drug should be used as well as the best sequence of treatment (AI alone vs sequence of AI/Tamoxifen) is still a matter of debate. It is highly probable that only a subgroup of patients will benefit from starting AI upfront (those patients at high risk of recurrence within the first two years) while for other patients selecting a switching strategy (e.g. 2 years of Tamoxifen followed by an AI) is safe, cost-effective and possibly superior in the long term. MINDACT will attempt to answer this question while being in a unique position to identify which may be the subgroup of patients who need to start AI therapy upfront, given its unique prospective collection of biological material.

Translational research opportunities

Tumour tissue, serum and RNA will be stored for all 6000 participants, creating a unique resource for future research. Given the storage of RNA from all tumours it will be possible to study gene expression profiles for women receiving anthracycline-based chemotherapy or docetaxel-capecitabine and to search for a correlation of gene expression with success or failure of the adjuvant chemotherapy regimen. MINDACT also offers a unique opportunity to look for a “signature” of hormonal treatment success or failure in the adjuvant setting, as RNA from all hormone receptor positive women will be available. A major translational research objective is the validation of previously discovered gene expression profiles and/or the identification of novel signatures, in the MINDACT population.

Potential benefits for patients and society

One of the primary objectives of this trial is to better select patients for adjuvant chemotherapy and hopefully thereby reduce the number of patients exposed to short and long term side effects of unnecessary cytotoxic treatments. This positive outcome could also translate into a reduced economic burden of this disease on society.

To be eligible for the MINDACT trial patients will have to comply with the following main eligibility criteria:

- In consenting to participate in the trial, patients agree that if their prognosis is discordant when assessed by clinical and molecular methods they will be randomised for prognostic tool used to determine treatment.
- Women with cytologically or histologically proven operable invasive breast cancer who have a negative sentinel node or a negative axillary clearance.
- Tumour T1, T2 or operable T3.
- The breast cancer must be unilateral. DCIS or LCIS is allowed, provided invasive cancer is present.
- Authorised surgery options are breast conserving surgery or mastectomy combined with either a sentinel node procedure or full axillary clearance.
- Availability of a frozen tumour tissue sample (not fixation in formalin) and permission for microarray analysis are mandatory for the patient to be eligible for the trial.
- Age between 18 and 70 years at registration.
- WHO performance status 0 or 1.
- No previous chemotherapy or radiotherapy (at the time of entry into the trial).

**Statistical design**

**Primary test:** In the group of patients who have a low risk gene prognosis signature and high risk clinical-pathological criteria, and who were randomized (R-Treatment decision) to use the 70-gene risk and thus receive no chemotherapy, a null hypothesis of a 5-year DMFS of 92% will be tested. With 6000 patients accrued overall, this group has an expected size of 672 patients. With an accrual of 3 years, and a total duration of 6 years (so 3 to 6 years follow up for each patient), a one-sided test at 97.5% confidence level has 80% power to reject this hypothesis if the true 5-year DMFS is 95%. In the setting of the first randomization (R-T) several other tests, comparing overall efficacy and chemotherapy assignment probabilities between the two prognosis methods, as well as within specific subgroups of discordant prognosis, will be important in assessing the value of prognosis according to the 70-gene signature.

**Test of chemotherapy randomisation (R-C):** Assuming a 5-year DFS of 86% in the anthracycline arm, with an expected 4000 patients randomized for type of chemotherapy (R-Chemotherapy), there is 80% power to detect a hazard ratio of 0.76 (or 89% experimental 5-year DFS) at the time of the primary analysis.

**Test of endocrine treatment randomisation (R-E):** With an expected 3500 patients being randomized into this question, and assuming a DFS rate at 5 years of 86% on the control arm (Tamoxifen-Letrozole), there is 80% power to detect a hazard ratio of 0.75 at the time of the primary analysis (i.e. a 5-year DFS of 86% vs. 89.3%).

**Trial management**

The EORTC will act as the legal sponsor and coordinating group for the MINDACT trial, which is the first project to be run under the TRANSBIG consortium. TRANSBIG is a translational research Network of Excellence created by the Breast International Group (BIG), a non-profit academic network for breast cancer clinical trials (www.breastinternationalgroup.org). TRANSBIG and MINDACT are partially funded by the European Commission’s Framework Research Programme VI, the Breast Cancer Research Foundation, the Jacqueline Seroussi Memorial Foundation and the Prix Mois du Cancer du Sein. Additional funding specifically for MINDACT will come from three pharmaceutical industry partners, Novartis, F. Hoffmann La Roche, and Sanofi-Aventis and from Agendia (providers of the genomic prognostic test). All data generated by MINDACT will be governed by the EORTC and the TRANSBIG Steering Committee (members of which are listed on the MINDACT web site), who are developing policies for access to the biological material resources for future translational research.

**Timelines and practical details**

The protocol outline was accepted on the 10th May 2005 by the EORTC Protocol Review Committee and the full protocol approved on the 23rd January 2006. The trial activation process has started and we hope to be able to include the first patient in September 2006. A network of National Coordinating Centres/Groups (NCC/NCG) has been set up and the next contact will either be from the EORTC directly, or from your NCC/NCG depending on the structure existing in your country.

**Contact details:**

**MINDACT@EORTC.be**

**EORTC**

European Organisation for Research and Treatment of Cancer, AISBL-IVZW

Avenue E. Mounier, 83/11

B-1200 Brussels,

Belgium

**TRANSBIG@bordet.be**

Breast International Group (BIG)-aisbl

Institut Jules Bordet, 7th Floor

Blvd de Waterloo, 121

B-1000 Brussels,

Belgium

www.mindact.org

Final version  18.07.06
References