The TAILORx[188] and MINDACT[187] trials aim to address the gaps in the literature (clinical utility data).

Anticipated data from TAILORx and MINDACT

TAILORx and MINDACT were recently initiated to prospectively evaluate the clinical utility (i.e. provide direct evidence that these tests in breast cancer patients lead to improvement in outcomes) of OncotypeDX and MammaPrint respectively. Definitive high-quality evidence of the effect of these tests on patient outcomes and their ability to predict treatment response is expected. TAILORx will provide information on the appropriate RS threshold for recommending adjuvant chemotherapy, and will not directly assess the effect of clinical decision-making with and without the test (as all patients will receive the test). The data generated may allow indirect inferences to be made. MINDACT will allow more direct inferences about the clinical utility as it will be compared directly with the use of a conventional risk index. For both trials, patient health outcomes will be end points.

TAILORx

This multicentre, partially randomised trial aims to assess whether hormone therapy alone or hormone therapy with combination chemotherapy is better for women who have a RS of 11–25 (an intermediate risk score) when tested using OncotypeDX.[91] The trial will also allow for the generation of new data on patients with very low RSs. Patients at the low end of the RS spectrum will be compared with a prespecified target of 95% recurrence-free survival.[91] It should be noted that the cut-off values used in the TAILORx trial are different from those delineated in other studies of OncotypeDX.[32]

Population

Patients with ER+ and/or PR+, HER2/neu-negative tumours who are LN– (and who will be treated with tamoxifen) are eligible for inclusion.

Key aspects of the study design

- Patients showing low RSs (≤10) by OncotypeDX testing will receive endocrine therapy alone.
- Patients with high RSs (≥26) by OncotypeDX testing will receive endocrine therapy and adjuvant chemotherapy.
- Patients with mid-range RSs (11–25) by OncotypeDX will receive endocrine therapy and be randomly assigned to chemotherapy or no chemotherapy.

After completion of the study treatment, patients will be followed up for up to 20 years.

Objectives

The primary objective is to assess whether or not women with an intermediate OncotypeDX score have better outcomes (DFS, DMFS, RFI and OS) when treated with either hormone therapy alone or hormone therapy with combination chemotherapy.

The secondary objectives include assessing whether or not low-risk patients (score ≤10) can safely be treated with hormone therapy alone (expect 95% to have DFS); to determine the DFS, DRFI, RFI and OS of patients with OncotypeDX RSs of ≤10; to compare the outcomes projected

at 10 years using classical pathological information with those made by the OncotypeDX test; to estimate failure rates as a function of OncotypeDX RS separately in patients treated with combination chemotherapy and in patients treated with no chemotherapy; to determine the prognostic significance of the OncotypeDX RS and of the individual RS gene groups (proliferation gene group, HER2 gene group, ER gene group, invasion gene group and other genes) in patients treated with these regimens.[91]

This study will not provide direct evidence for the value of OncotypeDX but will indicate whether or not adjuvant chemotherapy is of value within the trial's intermediate RS range. This will provide better estimates of the degree of benefit gained by using the test, but cannot ascertain what therapeutic choices would have been made and what clinical outcomes would have occurred if only standard risk prediction methods were used. Information about what choices would have been made could be inferred by applying other prognostic methods retrospectively.[33]

Completion

TAILORx commenced in April 2006.The trial is currently still recruiting and has a primary completion date of April 2014. The target for recruitment is 11,248 participants and the study currently has 280 centres recruiting in the USA, Canada, Australia and Peru.

MINDACT

A partially randomised trial, MINDACT[194] has recently been activated. The multicentre, prospective, phase III randomised trial will compare two different ways of assessing the risk of cancer recurrence and making therapeutic decisions: a 'traditional method' using Adjuvant! Online and the MammaPrint assay. The rationale for this study is that many women who actually have low-risk tumours are currently classified as average or high risk and therefore are recommended to receive adjuvant chemotherapy that ultimately may be of no benefit.

Population

Patients with histologically confirmed unilateral invasive breast cancer with T1–T3 operable disease, up to three positive lymph nodes and no distant metastases are eligible for inclusion. It situ tumours were allowed. Patients must have undergone breast-conserving surgery or a mastectomy with a sentinel node procedure or full axillary clearance, and appropriate radiotherapy.

Key aspects of the study design

- Patients at low risk by both MammaPrint and standard clinicopathological criteria will not receive chemotherapy.
- Patients at high risk by both criteria receive chemotherapy.
- Patients with discordant criteria, in which the clinicopathological prognosis using Adjuvant! Online is different to the gene expression prognosis using the 70-gene signature (which is estimated to be the case for 1920 patients), will be randomised to use either MammaPrint only or standard criteria to decide treatment. This is achieved by randomising patients to either receive or not receive chemotherapy. This will directly test whether or not the choice of chemotherapy guided by MammaPrint provides benefit over that guided by the Adjuvant! Online criteria.
- All those who go on to have chemotherapy (i.e. those at high risk by both prognostic tests, as well as those with discordant criteria who went on to receive chemotherapy) are then eligible for further randomisation to treatment with anthracycline-based chemotherapy or docetaxel/capecitabine-based chemotherapy.

- All hormone receptor-positive patients, regardless of previous randomisations and risk categorisations, are eligible for randomisation to two different endocrine treatment regimens, namely letrozole only or tamoxifen followed by letrozole.
- Patients will be followed up for DMFS at 5 years and DFS. Follow-up will be for a minimum of 15 years after completion of the study treatment.

Objectives

The main objective of the trial is to confirm that patients with low-risk molecular prognosis and high-risk clinical prognosis can be safely spared chemotherapy without affecting DMFS and to demonstrate the superiority of the molecular profiling approach over the usual clinical assessment in assigning risk categories.

The trial has two further main objectives: (1) a comparison of docetaxel and capecitabine regimens (which are possibly associated with increased efficacy and reduced long-term toxicities) with existing commonly used anthracycline-based chemotherapy regimens and (2) to determine the best endocrine treatment strategy between a single-agent upfront aromatase inhibitor (letrozole) for 7 years and the sequential endocrine strategy of 2 years of tamoxifen followed by 5 years of letrozole.

Completion

The trial is currently still recruiting and has a primary completion date of March 2019. The target for recruitment was recently increased from 6000 to 6600 participants and the projected proportion of patients who will fall into the discordant group is 32%.

Comparative summary of the design and characteristics of the TAILORx and MINDACT trials

Variable	TAILORx	MINDACT
Trial	Hormone therapy with or without combination chemotherapy in treating women who have undergone surgery for LN– breast cancer	A prospective, randomised study comparing the 70-gene expression signature with common clinicopathological criteria in selecting patients for adjuvant chemotherapy in LN– breast cancer (EORTC Protocol 10041 – BIG 3–04)
Trial type	Prospective, controlled, partially randomised	Prospective, controlled, partially randomised, open label
	Clinical utility	Clinical utility
	Non-inferiority design	
Test	OncotypeDX	MammaPrint
Gene signature	21-gene	70-gene
Tissue sample type	FFPE	Fresh tissue
Non-molecular clinical profiling technique/prognostic tool (comparator)	Adjuvant! Online	Adjuvant! Online
Sponsor	NCI (co-ordinated by ECOG)	EORTC/TRANSBIG
Countries participating	USA and Canada	Europe
Target for recruitment	11,248 [7887 recruited to date, 4500 randomised (45%?)]	6600 [2100 (32%) randomised]
Date of trial start/activation	April 2006	September 2006
		Estimated accrual time of 3 years and a total duration of 6 years