



Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Selecting Breast Cancer Patients for Chemotherapy: The Opening of the UK OPTIMA Trial

J. Bartlett^{*}, P. Canney[†], A. Campbell[‡], D. Cameron[§], J. Donovan[¶], J. Dunn[‡], H. Earl^{||}, A. Francis^{**}, P. Hall^{††}, V. Harmer^{‡‡}, H. Higgins[‡], L. Hillier[‡], C. Hulme^{††}, L. Hughes-Davies^{||}, A. Makris^{§§}, A. Morgan^{¶¶}, C. McCabe^{||||}, S. Pinder^{***}, C. Poole^{†††}, D. Rea^{†††}, N. Stallard^{§§§}, R. Stein^{¶¶¶}

^{*} Ontario Institute for Cancer Research, Toronto, Ontario, Canada

[†] Department of Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK

[‡] Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK

[§] Department of Medical Oncology, Edinburgh University and NHS Lothian, Edinburgh, UK

[¶] School of Social and Community Medicine, University of Bristol, Bristol, UK

^{||} Department of Oncology, Addenbrookes Hospital, Cambridge, UK

^{**} Department of Breast Surgical Oncology, University Hospitals Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK

^{††} Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

^{‡‡} St Mary's Hospital, London, UK

^{§§} Department of Clinical Oncology, Mount Vernon Hospital, Northwood, UK

^{¶¶} Independent Cancer Patients Voice, London, UK

^{||||} Department of Emergency Medicine Research, Edmonton, Canada

^{***} Division of Cancer Studies, Kings College London, Guy's Hospital, London, UK

^{†††} Arden Cancer Centre, University Hospitals Coventry and Warwickshire, Coventry, UK

^{§§§} School of Cancer Sciences, University of Birmingham, Edgbaston, Birmingham, UK

^{¶¶¶} Warwick Medical School, University of Warwick, Coventry, UK

^{¶¶¶} Department of Oncology, UCL Hospitals, London, UK

^{|||||} UCLH/UCL NIHR Biomedical Research Centre, London, UK

Received 15 August 2012; received in revised form 19 September 2012; accepted 19 October 2012

Abstract

The mortality from breast cancer has improved steadily over the past two decades, in part because of the increased use of more effective adjuvant therapies. Thousands of women are routinely treated with intensive chemotherapy, which can be unpleasant, is expensive and is occasionally hazardous. Oncologists have long known that some of these women may not need treatment, either because they have a low risk of relapse or because they have tumour biology that makes them less sensitive to chemotherapy and more suitable for early adjuvant endocrine therapy. There is an urgent need to improve patient selection so that chemotherapy is restricted to those patients who will benefit from it. Here we review the emerging technologies that are available for improving patient selection for chemotherapy. We describe the OPTIMA trial, which has just opened to recruitment in the UK, is the latest addition to trials in this area, and is the first to focus on the relative cost-effectiveness of alternate predictive assays.

© 2012 Published by Elsevier Ltd on behalf of The Royal College of Radiologists.

Key words: Adjuvant; breast; chemotherapy; predictive

Statement of Search Strategies Used and Sources of Information

Author for correspondence: R. Stein, Department of Oncology, UCL Hospitals, 1st Floor Central, 250 Euston Road, London NW1 2PG, UK.
Tel: +44-20-3447-4430; Fax: +44-20-3447-9055.

E-mail address: rstein@ucl.ac.uk (R. Stein).

Pubmed searches were carried out with Oncotype Dx, PAM50, Mammostrat, Mammaprint, TAILORx, adjuvant breast cancer chemotherapy.

0936-6555/\$36.00 © 2012 Published by Elsevier Ltd on behalf of The Royal College of Radiologists.

<http://dx.doi.org/10.1016/j.clon.2012.10.005>

Please cite this article in press as: Bartlett J, et al., Selecting Breast Cancer Patients for Chemotherapy: The Opening of the UK OPTIMA Trial, Clinical Oncology (2012), <http://dx.doi.org/10.1016/j.clon.2012.10.005>

Introduction

Since chemotherapy was introduced as an adjuvant treatment for breast cancer [1–3], oncologists have recognised that it benefits only some of the patients who receive it, depending on their risk of recurrence. Over the past 10 years, there has been extensive research into improving patient selection for chemotherapy, using either multiparametric gene expression assays or extended immunohistochemical (IHC) tests.

It is notable that current trials evaluating these technologies are all single assay studies that have not been designed to compare competing assays or to test their cost-effectiveness. They are committed to a specific assay from the outset and can only provide information about, and justification for, the use of that assay. There is an urgent need to cross-compare competing tests and evaluate their cost-effectiveness.

Here we briefly discuss this emerging research and describe the OPTIMA-prelim trial, which is opening at 25 centres in the UK. This is the latest addition to trials in this area, and the first to compare alternative tests. OPTIMA has an adaptive design. It has two parts. Initially, in OPTIMA-prelim, a preliminary concordance and cost-effectiveness analysis of multiple different assays will be carried out, in order to identify the most cost-effective tests for a larger efficacy trial, OPTIMA-main. OPTIMA is therefore not only a comparison of different assays, but also, in the main trial, a test of whether biomarker-directed therapy is better or worse than standard care, which includes chemotherapy.

Defining Adjuvant Therapy

Oncologists define adjuvant therapy as ‘treatment for presumed microscopic disease’ [4,5], to reduce the subsequent risk of relapse and death. Microscopic disease can be locoregional, in which case radiotherapy is used, or systemic, in which case it can be treated with chemotherapy, endocrine therapy or targeted treatments such as trastuzumab. In recent years there has been a marked expansion in the use of adjuvant chemotherapy, especially for postmenopausal women [6].

In the UK it has become standard practice to offer chemotherapy to most postmenopausal women with axillary node involvement [7]. This expansion in the use of chemotherapy is continuing, with recent research showing the efficacy of chemotherapy for older women (aged over 70 years) [8]. Elderly patients are now being offered treatment that would not have been considered even 5 years ago [9].

Although undoubtedly highly effective for some women, chemotherapy is associated with a small risk of death and is at best unpleasant and at worst life changing. About one in six patients require admission to hospital with serious complications and it is associated with anxiety, fatigue, depression and sometimes symptoms of post-traumatic stress disorder, which severely affects quality of life for months or even years afterwards [10,11]. There is also

a small long-term risk of treatment-induced leukaemia and cardiomyopathy [12,13].

Chemotherapy is also expensive. Adjuvant chemotherapy treatment for breast cancer alone imposes a financial burden of more than £150m every year on the National Health Service, and also requires a substantial additional investment in delivery infrastructure.

For both of these reasons, it is important to target chemotherapy to those patients who would probably benefit. The major challenge facing oncologists recommending adjuvant therapy is that it is given for presumed microscopic disease. This microscopic disease cannot currently be routinely detected or imaged. A second challenge is that there seems to be considerable inter-patient variation in response to chemotherapy [14,15]. This means that many of the women who are presumed to be at risk of relapse receive an unpleasant and costly treatment that does not benefit them and may well harm them. Although decision support tools (for example www.adjuvantonline.com) have been developed to improve patient selection, the number needed to treat to save one life with chemotherapy can vary between five and 30, depending on the patient’s individual baseline risk as computed with these support tools. There is therefore an urgent need to improve patient selection: to identify those with a high rather than a very low risk of microscopic disease, and particularly those with disease that is sensitive rather than insensitive to chemotherapy. Although the Oxford Overview analyses have not identified a chemotherapy insensitive subgroup, the amount of pathological information available for these analyses was limited, and the existence of such a subgroup has not been excluded [6]. The identification of chemotherapy sensitive and insensitive subpopulations among these patients would allow adjuvant treatment to be optimised with improved outcomes and reduced overall treatment morbidity.

New Assays for Patient Selection

In the past 10 years new diagnostic assays have emerged that promise to allow the identification of some women with invasive breast cancer who are at low risk of recurrence and for whom chemotherapy offers toxicity without a clinically meaningful benefit (see Table 1). These assays can be grouped into two methodologies: (1) multiparametric gene expression measurements and (2) extended IHC testing.

The first and still probably the most influential of the multiparametric classifications of breast cancer [16,17] divided breast cancers into ‘intrinsic subtypes’: luminal A, luminal B, HER2, basal and normal-like.

The early research into subtyping used complex microarray analysis and frozen tissue samples, (as does the version of the MammaPrint assay being tested in the MINDACT trial). The expression of thousands of genes within each breast cancer was analysed simultaneously. More recent work in tissue from 2000 breast cancers has added a further layer of complexity, using DNA-based

Table 1
Emerging tests for prognostication in breast cancer

	Assay (investigators or company)	Details of multiparametric assay	Test material	Test output
Gene-based Assays	Perou and Sorlie (academic)	Original intrinsic classification (495 genes)	Fresh/frozen	Category
	Oncotype DX (Genomic Health Inc.)	21 gene qRT-PCR expression assay (16 cancer related and 5 normalisation genes)	FFPE	Risk score
	MammaPrint (Agendia)	70 gene microarray-based expression signature.	Fresh/frozen FFPE	Risk score
	Rotterdam signature (Academic)	A 76 gene microarray-based expression signature; not commercially available.	Fresh/frozen	Risk score
	PAM50 (ARUP Laboratories & nanoString Technologies)	A 50 gene expression assay using RT-PCR or the nanoString system.	FFPE	Subtyping
	Breast Cancer Index (bioTheranostics)	A 7 gene qRT-PCR expression assay HOXB13; IL17BR; BUB1B, CENPA, NEK2, RACGAP1, RRM2	FFPE	Breast cancer index, 10 point
	Blueprint (Agendia)	A microarray-based assay used in conjunction with MammaPrint for subtyping	Fresh/frozen FFPE	Subtyping
Immuno-based assays	MAPQUANT-Dx Genomic Grade (Ipsogen)	A 97 gene microarray-based expression signature.	Fresh/frozen FFPE	Risk score
	Breast Cancer Array (Randox)	A 23 gene assay using bio-chip technology	Fresh/frozen FFPE±	Subtyping
	IHC4 (HistoRx & non-proprietary)	Quantitative immunohistochemical assay for ER, PgR, Her2, Ki67	FFPE	Risk score
	Mammostrat (GE Healthcare)	A 5 gene immunohistochemical assay p53, HTF9C, CEACAM5, NDRG1 and SLC7A5.	FFPE	Risk score
	NPI plus	A 10 gene immunohistochemical assay. ER, PgR, HER2, CK5/6, CK7/8, EGFR, HER3, HER4, p53; MUC1)	FFPE	Risk score
	Ki67/BCL2	A 2 gene immunohistochemical assay	FFPE	Three risk groups
	German Breast Group	uPA/PAI-1	Fresh	Low or high risk

qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; FFPE, formalin-fixed paraffin-embedded; FFPE±, FFPE method in development; ER, oestrogen receptor; PgR, progesterone receptor.

analysis on fresh frozen tissue, and suggested a molecular subtyping approach, which identified 10 subgroups of breast cancer [18].

Research in this area is very active, with ongoing analyses through the International Cancer Genome Consortium and The Cancer Genome Atlas carrying out whole genome sequencing, copy number variation and expression analysis. There will probably be further rapid progress in the classification of breast cancers over the next 5–10 years. However, these research tools are frequently complex and potentially subject to inter-assay variability, or restrictions regarding sample requirements, which make them unlikely candidates for routine biomarker assays. There has therefore been a parallel effort to develop these research approaches into robust assays that can be used in routine pathology laboratories. For example, the PAM50 assay, which involves measuring the expression of 50 genes in formalin-fixed paraffin-embedded material (which is the standard tissue handling protocol for routine laboratories) to assess the molecular subtypes using either quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) methods or the nanoString system has recently been described, but is not yet in routine clinical use [19–21].

Although a number of the novel multiparametric assays require further validation and remain experimental, a few

have significant evidence to support their clinical utility, particularly in oestrogen receptor-positive tumours. Some assays have been developed commercially, making them available to the clinical community, and have been marketed for clinical use (Table 1), and those that are widely available and can be accessed, often by sending samples internationally, are being considered as candidates for the OPTIMA trial.

Oncotype DX

Oncotype DX is a PCR-based expression assay testing 21 genes. The initial study [22] developed the 21 gene signature assay from an expression array analysis of tamoxifen-treated cancers and translated this into a multiplex PCR diagnostic assay with an associated 'recurrence score' estimating the risk of recurrence after tamoxifen treatment in node-negative breast cancers. The test is carried out centrally in a single US laboratory. Currently each assay costs £2580.

Multiple additional studies [23–27] in retrospective phase III trials have confirmed the value of Oncotype DX as a predictor of residual risk, extending the original observations to patients with positive lymph nodes and after endocrine therapy, including Aromatase Inhibitors (AIs),

and also to patients with ductal carcinoma *in situ* [27]. Oncotype DX has been shown to provide additional prognostic information to Adjuvant! [28]. Studies have shown that Oncotype Dx leads to changes in decision making in about a third of patients, although these studies involve small sample sizes and often poorly described protocols [29,30]. Thus, there is still considerable uncertainty about its true clinical value.

An American Society of Clinical Oncology Expert Panel reviewed the evidence and recommended the use of Oncotype DX in routine care in 2007 [31], a controversial decision that triggered a debate about the quality of the evidence [32,33]. Although some health economics research has claimed to show that Oncotype Dx is cost-effective [34–36], there are substantial uncertainties about the assumptions in these analyses [37,38]. The results are highly sensitive to the baseline rate of chemotherapy use, recurrence rate, long-term anthracycline-related cardiac toxicity, quality of life, test cost and the time horizon. Estimates of the incremental cost-effectiveness per quality adjusted life year have varied from around £5000 to £26 000 depending on how these variables are set [37,38], confirming the uncertainties about the true clinical value of this assay.

Despite these concerns, the test has quickly become the market leader. It has been carried out over 250 000 times at a cost of nearly a billion dollars to global health care systems in the past 8 years. Although there are numerous retrospective studies that support the value of this assay in assessing residual risk after treatment with endocrine therapy, and some evidence for its utility in selecting patients for chemotherapy, there is no evidence that the Oncotype Dx assay is any more informative than other gene expression assays [39], or indeed cheaper and simpler IHC assays [40]. No prospective studies reporting the effect of Oncotype Dx on long-term outcomes, such as overall survival, have been identified, nor has the test been prospectively trialled against any alternatives. Its success seems to lie in its ready marketability, as it generates a simple and easily understood recurrence score, which is appealing to both patients and their physicians. It was also the first such test on the market and based on more clinical data than any of its competitors.

Mammostrat

Derived after expression array analysis identifying markers of residual risk in early breast cancer, the Mammostrat assay relies on the IHC analysis of five markers (p53, NDRG1, SLC7A5, CEACAM5 and HTF9C) [41,42] and classifies patients into three risk groups. First described in 2006, this assay was validated across multiple retrospective institutional and clinical trial cohorts, including the NSABP B-14 and NSABP B-20 trials [43]. Recent evidence from the TEAM trial suggests that this assay also provides information on residual risk in patients treated with AI [51]. After Federal Drug Administration approval of this test as a marker of residual risk in early breast cancer, the assay is available on a commercial basis within the USA. It costs about £1500 [37]; given the large price discount compared with Oncotype Dx, direct evidence on the comparative performance of the two tests will probably be highly valuable.

IHC4 and Fluorescence IHC4

The IHC4 and fluorescence IHC4 tests are extensions of longstanding evidence on the ability of four conventional IHC markers, oestrogen receptor, progesterone receptor, HER2 and Ki67 [44,45] to select patients at increased residual risk after adjuvant endocrine therapy. These observations have been refined by centralised quantitative analysis of clinical trials of endocrine therapy [46] and the development of fluorescence IHC-based methods with improved reproducibility [46,47]. Algorithms have been developed that have integrated these data into a predictor of risk, which has been claimed to provide information equivalent to that from the more complex and expensive Oncotype DX assay.

PAM50

After the publication of molecular classifiers of breast cancer subtypes [16], the development of a simple molecular assay for clinical determination of these subtypes has been a key objective. The development of the PAM50

Table 2
Summary of biomarker/multiparametric assay trials in breast cancer

Trial name	Trial group	Assay	Date opened	Target accrual	Standard arm
TAILORx	NCI	Oncotype Dx	2006 (completed)	10 000	Node-negative patients with recurrence score of 11–25 randomised to chemotherapy or not
MINDACT	BIG	Mammaprint	2007 (completed)	6700	Randomised to a decision on microarray result or adjuvant online result
RxPONDER	SWOG	Oncotype Dx	2011	9000 1–3 nodes	Node-positive patients with a score <25 randomised to chemotherapy or not
WSG-PLANB	WSG	Oncotype Dx	2009 (completed)	3196 higher risk patients with	RS < 11 no chemotherapy RS ≥ 11 TC6 or ECT chemotherapy randomisation
OPTIMA	NHS/HTA	Adaptive design	2012	1,860 per arm	
NNBC-3	GBG	uPA/PAI-1	2002 (completed)	4149	Randomised to risk evaluation by biomarker or St Gallen clinical
CHEMO-N0	GBG	uPA/PAI-1	1993–1998	647	Low risk patients hormones only; high risk patients had significant benefit from chemotherapy

multiplex PCR assay parallels that of Oncotype DX in that it translates expression array data into a clinically viable diagnostic assay [20,21] using 50 genes to identify molecular subtypes of early breast cancer. The assay also generates a numerical risk score (risk of recurrence), which has been compared with Oncotype Dx in the trans-ATAC cohort [48]. Studies validating the PAM50 signature have been carried out, predominantly using *in silico* validation cohorts

and expression array data [49]. More recently, the assay has been adopted by a commercial partner, NanoString Technologies, and is currently being developed for clinical validation.

As can be seen, there is considerable overlap between the methodology and markers included in these tests, which tend to have in common elements of proliferation, oestrogen and HER2 signalling. None of these assays has been

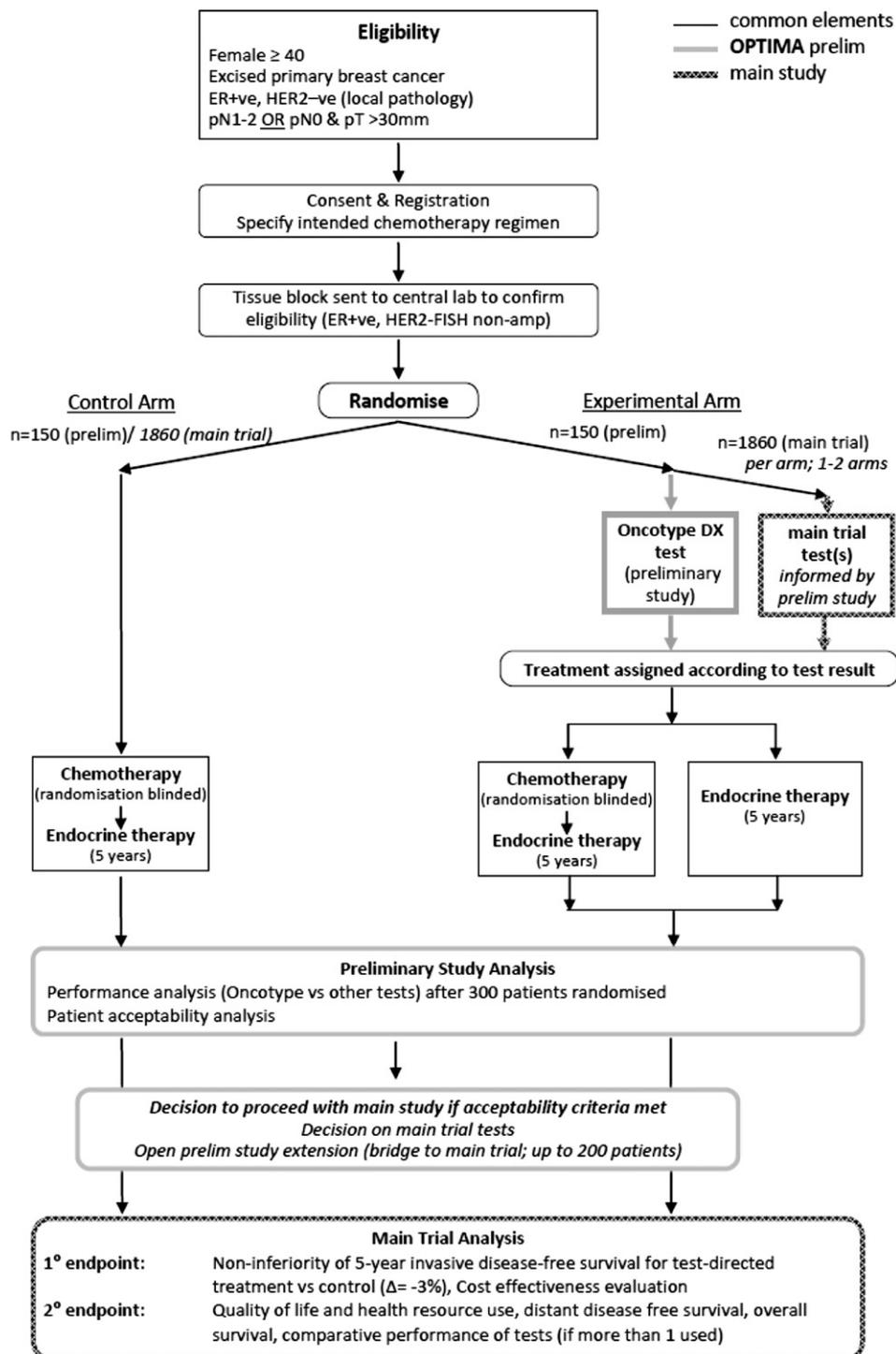


Fig 1. The design of the OPTIMA trial.

tested against best routine pathological practice, or prospectively against each other or against much cheaper tests.

It is certainly conceivable that fewer markers could be assayed with similar value and much better cost-effectiveness, and there is an urgent need for comparative trials of these emerging tests. The cost-effectiveness of Oncotype DX may be more evident in the North American health-care setting, but less so in the National Health Service, where the existence of high-quality histopathology services offers the possibility of rolling out IHC tests such as IHC4 at a fraction of the cost of Oncotype DX. Elaborate multiparametric assays from a single laboratory in the USAs may not be the most cost-effective platform for test-guided chemotherapy in the National Health Service.

Although trials of these new technologies are being carried out (Table 2), it is notable that these are all single assay studies and are not designed to report the comparative effectiveness or cost-effectiveness of competing assays. They are all committed to a specific assay from the outset and can only provide information about and justification for the use of that assay.

The National Health Service/National Institute of Health Research Health Technology Assessment-funded OPTIMA-prelim (Optimal Personalised Treatment of early Breast Cancer using MultiParameter Analysis) trial opened to recruitment in August 2012. This, the preliminary phase of the study, will run in 25 centres across the UK. The target accrual in the first 2 years is 300 patients. Eligible patients have oestrogen receptor-positive and HER2-negative disease and would ordinarily be treated with adjuvant chemotherapy because of tumour stage. The randomisation in OPTIMA is between standard therapy (chemotherapy and endocrine therapy for all patients) and test-directed therapy (chemotherapy given only to patients with high risk scores, with endocrine therapy given to all patients).

Importantly, OPTIMA differs from all other studies (Table 2) that use only a single assay. It is the first and only one of the new technology trials to include multiple different assays. OPTIMA has an adaptive trial design, as summarised in Figure 1, and will be run in two phases. The initial study of 300 patients (OPTIMA-prelim) will be an evaluation of the performance and comparison of multiple different assays. The goal of this initial phase of the trial is to identify a candidate for the simplest and most cost-effective method to define women with higher risk oestrogen receptor-positive HER2-normal primary breast cancer who would probably benefit or not benefit from chemotherapy. Selection of the assay will be driven by a combination of health economic analysis and concordance between the competing tests and Oncotype Dx. The selected assays will then be assessed in the main trial. OPTIMA-prelim is also designed to evaluate the acceptability of the test-directed chemotherapy to patients. In the North American TAILORx trial there was a 15% non-compliance rate with the assigned treatment (J. Sparano, personal communication) and the OPTIMA-prelim study includes a strong qualitative research programme to examine attitudes of patients to randomisation and possible reasons for non-compliance and

obstacles to recruitment before the full OPTIMA trial opens. From the beginning, there has been extensive patient engagement in the design of the trial, predominantly through the Independent Cancer Patients Voice [50].

In this overview we have seen how oncologists have long realised that adjuvant chemotherapy treatments expose too many women to an unpleasant, expensive and sometimes hazardous treatment that they may not need. A leading priority in breast cancer research has been to improve patient selection for chemotherapy. We have discussed how technologies to do this have emerged over the past decade and have reviewed the differing assays and their readiness for clinical use. We have described the OPTIMA trial, which is currently opening in the UK and which is designed to compare multiple competing assays in order to determine which is the most appropriate for use in the National Health Service. We believe that this research will continue to gather pace and that the goal of accurate patient selection will be achieved over the next decade, through trials such as OPTIMA.

Conflict of Interest

J. Bartlett, D. Cameron, A. Francis, A. Makris, C. Poole, D. Rae and R. Stein have received advisory board honoraria, speaking honoraria or hospitality from Genomic Health (manufacturer of Oncotype Dx); P. Hall has attended an advisory board for Clariant (manufacturer of Mammostrat); J. Bartlett has consultancies from Genoptix and GE Healthcare and research support from HistoRx.

Acknowledgements

The OPTIMA-prelim trial is funded by the NIHR Health Technology Assessment programme. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Health Technology Assessment programme, NIHR, the National Health Service or the Department of Health.

References

- [1] Fisher B, Carbone P, Economou SG, et al. L-Phenylalanine mustard (L-PAM) in the management of primary breast cancer. A report of early findings. *N Engl J Med* 1975;292(3):117–122.
- [2] Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976;294(8):405–410.
- [3] Early Breast Cancer Trialists Collaborative Group. Review of mortality results in randomized trials in early breast cancer. *Lancet* 1984;2:1205.
- [4] Ellisen L, Haber D. Recent progress in the understanding and treatment of breast cancer. *Nature Medicine* 4, Breast Cancer. Published online: 16 April 2001; <http://dx.doi.org/10.1038/20000257>.
- [5] Kiberstis P, Marshall E. Cancer crusade at 40. *Science* 2011;331(6024):1539.
- [6] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome

- among 100,000 women in 123 randomised trials. *Lancet* 2012;379(9814):432–444.
- [7] National Institute for Clinical Excellence Guideline. Breast cancer (early and locally advanced) (CG80). Available at: <http://www.nice.org.uk/CG80>.
- [8] Ring A, Reed M, Leonard R, et al. The treatment of early breast cancer in women over the age of 70. *Br J Cancer* 2011;105(2):189–193.
- [9] Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13(4):148–160.
- [10] Elklit A, Blum A. Psychological adjustment one year after the diagnosis of breast cancer: a prototype study of delayed post-traumatic stress disorder. *Br J Clin Psychol* 2011;50(4):350–363.
- [11] O'Connor M, Christensen S, Jensen AB, Møller S, Zachariae R. How traumatic is breast cancer? Post-traumatic stress symptoms (PTSS) and risk factors for severe PTSS at 3 and 15 months after surgery in a nationwide cohort of Danish women treated for primary breast cancer. *Br J Cancer* 2011;104(3):419–426.
- [12] Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. *Breast Cancer Res Treat* 2012;135:335–346.
- [13] Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol* 2007;25(25):3808–3815.
- [14] Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 2005;11(16):5678–5685.
- [15] Kim SR, Paik S. Genomics of adjuvant therapy for breast cancer. *Cancer J* 2011;17(6):500–504.
- [16] Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000;406(6797):747–752.
- [17] Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA* 2001;98(19):10869–10874.
- [18] Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* 2012;486(7403):346–352.
- [19] Parker JS, Mullins M, Cheang MC, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol* 2009;27(8):1160–1167.
- [20] Nielsen TO, Parker JS, Leung S, et al. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. *Clin Cancer Res* 2010;16(21):5222–5232.
- [21] Chia SK, Bramwell VH, Tu D, et al. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. *Clin Cancer Res* 2012;18(16):4465–4472.
- [22] Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351(27):2817–2826.
- [23] Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006;24(23):3726–3734.
- [24] Albain KS, Barlow WE, Shak S, et al. Breast Cancer Intergroup of North America. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 2010;11(1):55–65.
- [25] Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol* 2010;28(10):1677–1683.
- [26] Dowsett M, Nielsen TO, A'Hern R, et al. International Ki-67 in Breast Cancer Working Group. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J Natl Cancer Inst* 2011;103(22):1656–1664.
- [27] Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. *Breast Cancer Res Treat* 2011;127(1):133–142.
- [28] Schneider JG, Khalil DN. Why does Oncotype DX recurrence score reduce adjuvant chemotherapy use? *Breast Cancer Res Treat* 2012;134(3):1125–1132.
- [29] Ademuyiwa FO, Miller A, O'Connor T, et al. The effects of Oncotype DX recurrence scores on chemotherapy utilization in a multi-institutional breast cancer cohort. *Breast Cancer Res Treat* 2011;126(3):797–802.
- [30] Albanell J, González A, Ruiz-Borrego M, et al. Prospective transGEICAM study of the impact of the 21-gene Recurrence Score assay and traditional clinicopathological factors on adjuvant clinical decision making in women with estrogen receptor-positive (ER+) node-negative breast cancer. *Ann Oncol* 2012;23(3):625–631.
- [31] Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007;25(33):5287–5312.
- [32] Bernards R. Reaction to American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2008;26(12):2057–2058. author reply 2060–2061.
- [33] Cardoso F, Saghathchian M, Thompson A, Rutgers E. TRANSBIG Consortium Steering Committee. Inconsistent criteria used in American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2008;26(12):2058–2059. author reply 2060–2061.
- [34] Klang SH, Hammerman A, Liebermann N, Efrat N, Doberne J, Hornberger J. Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. *Value Health* 2010;13(4):381–387.
- [35] Kondo M, Hoshi SL, Yamanaka T, Ishiguro H, Toi M. Economic evaluation of the 21-gene signature (Oncotype DX) in lymph node-negative/positive, hormone receptor-positive early-stage breast cancer based on Japanese validation study (JBCRG-TR03). *Breast Cancer Res Treat* 2011;127(3):739–749.
- [36] Lamond NW, Skedgel C, Rayson D, Lethbridge L, Younis T. Cost-utility of the 21-gene recurrence score assay in node-negative and node-positive breast cancer. *Breast Cancer Res Treat* 2012;133(3):1115–1123.
- [37] National Institute for Health and Clinical Excellence Diagnostics Consultation Document. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: MammoPrint, OncotypeDx, IHC4 and Mammostrat. Available at: <http://www.nice.org.uk/nicemedia/live/13283/58040/58040.pdf>.

- [38] Hall PS, McCabe C, Stein RC, Cameron D. Economic evaluation of genomic test-directed chemotherapy for early-stage lymph node-positive breast cancer. *J Natl Cancer Inst* 2012;104(1):56–66.
- [39] Prat A, Parker JS, Fan C, Perou CM. PAM50 assay and the three-gene model for identifying the major and clinically relevant molecular subtypes of breast cancer. *Breast Cancer Res Treat* 2012;135(1):301–306.
- [40] Cuzick J, Dowsett M, Pineda S, et al. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. *J Clin Oncol* 2011;29(32):4273–4278.
- [41] Ring BZ, Seitz RS, Beck R, et al. Novel prognostic immunohistochemical biomarker panel for estrogen receptor-positive breast cancer. *J Clin Oncol* 2006;24(19):3039–3047.
- [42] Bartlett JM, Thomas J, Ross DT, et al. Mammostrat as a tool to stratify breast cancer patients at risk of recurrence during endocrine therapy. *Breast Cancer Res* 2010;12(4):R47.
- [43] Ross DT, Kim CY, Tang G, et al. Chemosensitivity and stratification by a five monoclonal antibody immunohistochemistry test in the NSABP B14 and B20 trials. *Clin Cancer Res* 2008;14(20):6602–6609.
- [44] Bouzubar N, Walker KJ, Griffiths K, et al. Ki67 immunostaining in primary breast cancer: pathological and clinical associations. *Br J Cancer* 1989;59(6):943–947.
- [45] Nicholson RI, Bouzubar N, Walker KJ, et al. Hormone sensitivity in breast cancer: influence of heterogeneity of oestrogen receptor expression and cell proliferation. *Eur J Cancer* 1991;27(7):908–913.
- [46] Dowsett M, Salter J, Zabaglo L, et al. Predictive algorithms for adjuvant therapy: TransATAC. *Steroids* 2011;76(8):777–780.
- [47] Barton S, Zabaglo L, A'Hern R, et al. Assessment of the contribution of the IHC4+C score to decision making in clinical practice in early breast cancer. *Br J Cancer* 2012;106(11):1760–1765.
- [48] Dowsett M, Lopez-Knowles E, Sidhu K, et al. Comparison of PAM50 risk of recurrence (ROR) score with OncotypeDx and IHC4 for predicting residual risk of RFS and distant-(D)RFS after endocrine therapy: a TransATAC study. SABCS 2011 Abstract S4–S5.
- [49] Cheang MC, ChiaSK Voduc D, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst* 2009;101(10):736–750.
- [50] www.independentcancerpatientsvoice.org.uk.
- [51] Bartlett JM, Bloom KJ, Piper T, et al. Mammostrat as an immunohistochemical multigene assay for prediction of early relapse risk in the tamoxifen versus exemestane adjuvant multicenter trial pathology study. *J Clin Oncol* 2012 Oct 8 [Epub ahead of print].