Institution: The Institute of Cancer Research

Unit of Assessment: Clinical Medicine

Title of case study: Endocrine therapy in breast cancer treatment

Period when the underpinning research was undertaken: 2005 to 2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Judith Bliss	ICR Team Leader	01/10/1985–Present
Dr Maggie Cheang	ICR Team Leader	28/10/2013–Present
Professor Mitch Dowsett	ICR Honorary Faculty	01/06/1993–Present
Professor Stephen Johnston	ICR Honorary Faculty	01/09/2004–Present
Professor Nicholas Turner	ICR Team Leader	01/09/2008–Present

Period when the claimed impact occurred: 2013 to 2020

Is this case study continued from a case study submitted in 2014? No. The ICR submitted a case study on aromatase inhibitors in breast cancer treatment in REF 2014 which overlaps with some aspects of this case study. However, this REF 2021 case study does not meet the criteria for a continued case study because it is not restricted to aromatase inhibitors and includes new underpinning research and impact.

1. Summary of the impact

Researchers at The Institute of Cancer Research (ICR) led translational and clinical research to improve outcomes for breast cancer patients treated with endocrine therapy. This work led to the following impacts:

- **Policy.** Data from our research underpinned the 2018 National Institute for Health and Care Excellence (NICE) recommendation of 3 prognostic tests in early stage breast cancer: EndoPredict (EPclin score), Oncotype DX, and PAM50/ROR (Prosigna).
- **Patients.** These tests provide accurate predictions of risk and are used to determine who should be offered chemotherapy after surgery, thereby sparing some women unnecessary treatment that affects their quality of life. The Oncotype DX test has been used to guide treatment decisions for more than 1,000,000 cancer patients worldwide.
- **Commercial.** Revenue from the Oncotype DX tests was USD299,400,000 in 2018 which was an increase of 18% from 2017.
- **New therapies to overcome endocrine treatment resistance.** As a result of the PALOMA-3 study, led by Professor Nicholas Turner, palbociclib combined with fulvestrant is being used internationally to treat advanced oestrogen-receptor positive (ER+) breast cancer patients who had progression or relapse during previous endocrine therapy.

2. Underpinning research

Background. Approximately 80% of breast cancers are ER+ and are at least partly dependent on oestrogens for their growth. These cancers are treated with endocrine therapy, such as (a) aromatase inhibitors (AIs), a treatment that blocks the synthesis of oestrogen, (b) tamoxifen, which blocks oestrogen binding to its receptor and (c) fulvestrant, which promotes ER degradation.

Clinical benefit of aromatase inhibitors. The ICR and our hospital partner, The Royal Marsden NHS Foundation Trust (RM), played a key role in the ATAC (anastrozole, tamoxifen, alone or in combination) phase 3 clinical trial. Professor Mitch Dowsett, ICR Professor and Honorary Faculty, was part of the core group involved in developing the protocol for this study and analysing the results alongside Mike Baum (ICR Team Leader 1990–1996), Professor Jack Cuzick (Queen Mary University of London), and Professor Jeff Tobias (University College London). The ATAC study showed that in early post-menopausal breast cancer, anastrozole, an

AI, was superior to tamoxifen alone in preventing recurrence and distant recurrence of breast cancer **(Ref. 1)**.

Translational research for ATAC trial. Professor Dowsett led the translational research committee for the ATAC trial (TransATAC), and his team created the tissue collection of >2,000 tumour blocks from the trial. This material formed the basis of important translational research to determine biomarker profiles to identify endocrine therapy-treated patients who could avoid cytotoxic chemotherapy. Oncotype DX Breast Recurrence Score (hereafter referred to as Oncotype DX) is designed to quantify the 10-year risk of distant recurrence and predict relative treatment effects for chemotherapy. The performance of the Oncotype DX had not been previously evaluated in patients treated with an AI. Using the TransATAC samples the Dowsett team demonstrated for the first time that Oncotype DX can independently predict distant recurrence in ER+ patients treated with anastrozole **(Ref. 2)**. These data was utilised for the NICE and NHS England approvals (see *Section 4*).

Predicting risk of distant recurrence after endocrine therapy. While conducting this work, the team, working with Professor Cuzick, created a much simpler IHC4 immunohistochemical test which provides more information than Oncotype DX at approximately 10% of the cost **(Ref. 3)**. Meanwhile, an independent approach emerged, which uses a risk of recurrence (ROR) score generated from the 50-gene PAM50 test (Prosigna). Professor Dowsett's team, using TransATAC samples, then showed that PAM50/ROR provides more prognostic information in endocrine-treated patients with ER+, node-negative disease than Oncotype DX. They also found that the ROR score provides at least as much information as IHC4 and may provide more information in the node-negative/human epidermal growth factor receptor 2 (HER2)-negative group **(Ref. 4)**. The team went on to show that another test, Endopredict, also provided more prognostic information than Oncotype DX.

Building on this significant work, Professor Dowsett worked with individuals from the relevant companies to compare the performance of the 6 prognostic signatures for ER+ breast cancer: Oncotype DX, PAM50/ROR, Breast Cancer Index (BCI), EndoPredict, Clinical Treatment Score, and IHC4 immunohistochemical test. The Dowsett team showed that all signatures performed similarly during the first 5 years of follow-up, however, for women with node-negative disease, the PAM50/ROR, BCI and EPclin tests were significantly more prognostic than the other tests in years 5 to 10, a period of time when decisions are made with regard to extending endocrine treatment **(Ref. 5)**.

CDK4/6 inhibition in ER+ breast cancer. Resistance to endocrine therapies remains a significant clinical challenge in metastatic breast cancer, and there is a need for therapeutic strategies that overcome this resistance and potentially prolong patient survival. Based on preclinical data from ICR researchers, ICR Team Leader Professor Nicholas Turner, designed and led PALOMA-3, a randomised phase 3 study of palbociclib sponsored by Pfizer. Palbociclib is a selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6, which complex with cyclin D to allow cell cycle progression. This phase 3 study showed that women taking palbociclib with hormone therapy lived for 34.9 months on average, 6.9 months longer than those on hormone treatment alone. The drug's benefit was stronger in women who had previously responded to hormone therapy—who lived 10 months longer with the combination treatment (39.7 months versus 29.7 months). The group of women given the combination treatment also saw a longer delay until the start of chemotherapy **(Ref. 6** and **Ref. 7)**.

Ongoing work to improve outcomes for ER+ breast cancer. Building on our previous prognostic and therapeutic research, the ICR's Clinical Trials and Statistics Unit, directed by Professor Judith Bliss are conducting the POETIC, PALLET and POETIC-A trials. Professor Dowsett and Professor Bliss conducted the POETIC trial in 4,480 patients across the UK who received two weeks perioperative aromatase inhibitor or no perioperative therapy. This study showed that measuring Ki67 levels at surgery and two weeks after starting AI treatment segregated patients into groups with high or low risk of recurrence. Measuring Ki67 levels is a simple and cost-effective test and it could be incorporated into routine practice on the NHS.

Moreover, the ICR-led PALLET trial (Chief Investigator: Professor Stephen Johnston) showed neo-adjuvant treatment with palbociclib and letrozole, an AI, in early breast cancer significantly enhanced the suppression of cancer cell proliferation, yet did not increase tumour shrinkage as determined by clinical ultrasound. The findings from the POETIC trial are continuing to drive national research with the team's launch of the UK-wide POETIC-A trial in which patients with high Ki67 on AI treatment will be randomised to the addition of a CDK4/6 inhibitor or not, stratified by a biomarker test, building on PAM50 work by Professor Dowsett and Dr Maggie Cheang (Co-inventor of Prosigna).

3. References to the research

Key: **ICR employed staff** at the time of publication, **ICR Team Leaders (including Honorary Faculty)** at the time of publication.

1. Howell A, Cuzick J, Baum M, Buzdar A, **Dowsett M**, Forbes JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS; ATAC Trialists' Group. 2005, Results of the ATAC Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer, Lancet. 365 (9453), 60-62. (http://dx.doi.org/10.1016/S0140-6736(04)17666-6). *Times cited: 1,679 (WOS).*
2. **Dowsett M**, Cuzick J, Wale C, Forbes J, Mallon EA, Salter J, Quinn E, Dunbier A, Baum M, Buzdar A, Howell A, Bugarini R, Baehner FL, Shak S. 2010. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J Clin Oncol. 2010 Apr 10;28(11):1829-34. (http://dx.doi.org/10.1200/JCO.2009.24.4798). *Times cited: 448 (WOS).*
3. Cuzick J, **Dowsett M**, Pineda S, Wale C, Salter J, Quinn E, Zabaglo L, Mallon E, Green AR, Ellis IO, Howell A, Buzdar AU, Forbes JF. 2011, 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. 29 (32), 4273-4278. (http://dx.doi.org/10.1200/JCO.2010.31.2835). *Times cited: 446 (WOS).*
4. **Dowsett M**, Sestak I, Lopez-Knowles E, Sidhu K, Dunbier AK, Cowens JW, Ferree S, Storhoff J, Schaper C, Cuzick J. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. J Clin Oncol. 2013 Aug 1;31(22):2783-90. (http://dx.doi.org/10.1200/JCO.2012.46.1558). *Times cited: 363 (WOS).*
5. Sestak I, **Buus R**, Cuzick J, Dubsky P, Kronenwett R, Denkert C, Ferree S, Sgroi D, Schnabel C, Baehner FL, Mallon E, **Dowsett M**. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2018 Apr 1;4(4):545-553. (http://dx.doi.org/10.1001/jamaoncol.2017.5524). *Times cited: 104 (WOS).*
6. **Turner NC**, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, Huang Bartlett C, Zhang K, Giorgetti C, Randolph S, Koehler M, Cristofanilli M; PALOMA3 Study Group. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015 Jul 16;373(3):209-19. (http://dx.doi.org/10.1056/NEJMoa1505270). *Times cited: 743 (WOS).*
7. **Turner NC**, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, Colleoni M, DeMichele A, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, André F, Puyana Theall K, Huang X, Giorgetti C, Huang Bartlett C, Cristofanilli M. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2018 Nov 15;379(20):1926-1936. (http://dx.doi.org/10.1056/NEJMoa1810527). *Times cited: 264 (WOS).*

Additional Quality indicators

Prizes:

- 2014 Komen Brinker Award for Scientific Distinction in Clinical Research: Mitch Dowsett
- 2017 American Association for Cancer Research (AACR) Outstanding Investigator Award for Breast Cancer Research: Nicholas Turner

4. Details of the impact

There are approximately 55,000 new breast cancer cases in the UK every year making it the most common cancer in the UK, accounting for 15% of all new cancer cases (2016).

Impact of ATAC trial on breast cancer patients and clinical practice. The results of the ATAC trial **(Ref. 1)** led to a rapid change in practice: receiving full marketing approval from the US Food and Drug Administration (FDA) in 2004 and NICE approval in 2006. AIs have remained the international standard of care for early breast cancer in post-menopausal women since that time (2013 to 2020 inclusive). Five years of an AI reduces 10-year breast cancer mortality rates by approximately 40% compared with 30% with tamoxifen. Anastrozole causes significantly fewer side effects than tamoxifen. Between 2013 and 2017 there were over 13,200,000 prescriptions of anastrazole (Arimidex) in the United States alone showing the huge number of patients benefitting from this therapy **[A]**.

Use of the prognostic tests on the NHS. In September 2013, NICE recommended Oncotype DX as a test for some breast cancer patients in order to predict risk of cancer spread and to determine the need of chemotherapy. This recommendation was based on data from Professor Dowsett's work **(Ref. 3)** and at the time Dr Carole Longson, director of NICE's health technology evaluation centre, said:

> *"Breast cancer patients face significant emotional and psychological strain when considering chemotherapy. A test that can help to predict better the risk of the breast cancer spreading, and therefore the potential likely benefit of additional chemotherapy, represents a significant step forward for patients."* **[B]**

Following the 2013 guidance, NICE also included Oncotype DX in the updated Breast Cancer Quality Standard in June 2016 and their Breast Cancer Pathway in September 2017. As a result, over 95% of NHS trusts have adopted Oncotype DX and helped more than 22,000 patients benefit from making personalised chemotherapy treatment decisions **[C]**.

In 2018, NICE reviewed the available evidence and determined that EndoPredict, Oncotype DX and PAM50/ROR are recommended as options for guiding adjuvant chemotherapy decisions for people with ER+, HER2-negative and lymph node (LN)-negative cancer. The main source of UK evidence was a bespoke analysis of data from the TransATAC study (led by Professor Dowsett). The recommendation of these tests allows more accurate determination of the patients with early breast cancer that have a low risk of distant recurrence by a tumour profiling test and thus could not gain significant benefit from adjuvant chemotherapy. By omitting chemotherapy treatment the associated comorbidities and negative effects on quality of life can be avoided. This recommendation allows people with breast cancer and clinicians to have more confidence that the treatment they are having or recommending is appropriate to the individual **[C]**.

Use of the prognosis tests internationally. Professor Dowsett's validation of the Onctoype DX for both tamoxifen and anastrozole provided evidence for healthcare systems across the world to recognise the value of Oncotype DX, which is incorporated in all major international clinical guidelines such as St. Gallen, the European Society for Medical Oncology and the US National Comprehensive Cancer Network (NCCN) **[D]**. Moreover, in April 2016, the American Society of Clinical Oncology released a clinical practice guideline recommending the use of Oncotype DX, EndoPredict and PAM50/ROR. The study described in **Ref. 3** was one of 12 studies that underpinned these guidelines **[E]**. The Oncotype DX test is currently reimbursed by public healthcare systems in 8 countries in Europe, including the United Kingdom, Germany, Ireland, Spain and Switzerland. More than 900,000 patients in over 90 countries around the world have used the Oncotype DX test to inform their treatment decisions **[D]**.

The PAM50/ROR test, marketed as the Prosigna Breast Cancer Prognostic Gene Signature Assay by Nanostring, was approved by the FDA in September 2013 with the study in **Ref. 4** quoted in the press release. The Prosigna Assay has been CE-marked in 2012 and is available for use by healthcare professionals in the European Union and other countries that recognize

the CE mark such as Canada, Israel, Australia, Hong Kong and New Zealand **[F]**. (Oncotype DX does not have a CE mark/FDA approval because it is provided as a service by Genomic Health).

Commercial impact. Arimidex (anastrozole) was developed by AstraZeneca and between 2014 and 2019 it totalled USD1,434,000,000 in sales. In December 2019 AstraZeneca agreed to sell the commercial rights to Arimidex in a number of European, African and other countries to Juvisé Pharmaceuticals. Juvisé Pharmaceuticals has made an upfront payment of USD181,000,000 to AstraZeneca and may also make future sales-contingent payments of up to USD17,000,000. Arimidex had lost its compound patent protection in these countries and AstraZeneca already divested the rights to both Arimidex and Casodex in the US in 2017 **[G]**.

Oncotype DX is now marketed by Exact Sciences, who in 2019 acquired Genomic Health, Inc., the company that initially marketed the test. Speaking about the acquisition, Kevin Conroy, chairman and CEO of Exact Sciences stated: *"Genomic Health's Oncotype DX is the global standard of care to inform treatment decisions for women with breast cancer."* **[H]**

Palbociclib and fulvestrant combination in breast cancer. Based on data from the PALOMA-3 study **(Ref. 6)** in February 2016 the FDA approved palbociclib (Ibrance) in combination with fulvestrant for the treatment of ER+, HER2-negative advanced breast cancer in women with disease progression following endocrine therapy. The European Medicines Agency (EMA) approval in this indication followed in November 2016. As of May 2020, palbociclib is approved in more than 95 countries and has been prescribed to more than 300,000 patients globally **[I]**.

Palbociclib has been reviewed for use on the NHS in combination with fulvestrant. Pfizer offered palbociclib free to the NHS for 5 months during the initial review in 2017 under the 'Ibrance Patient Programme'. In July 2019, the Scottish Medicines Consortium announced that palbociclib would be available on the NHS in Scotland in combination with fulvestrant in women who have received prior endocrine therapy and in November 2019, it was approved for use in England via the Cancer Drugs Fund in the same indication **[J]**. Palbocicib has generated significant economic impact for Pfizer. Since palbociclib's first approval it has led to sales of USD14,340,000,000 with its biggest year of sales in 2019 (USD4,961,000,000) **[K]**.

5. Sources to corroborate the impact

A. US prescriptions of anastrozole: https://clincalc.com/DrugStats/Drugs/Anastrozole

B. NICE DX recommendation: https://www.theguardian.com/society/2013/sep/25/women-breast-cancer-test-spares-chemotherapy

C. Oncotype DX test NICE press release: https://www.oncotypeiq.com/-/media/GHI/GHI_PressRoom/PressRelease/NICE%20updated%20guidelines_UK%20press%20release_Final.pdf

D. Oncotype DX test information: https://www.oncotypeiq.com/en-GB/breast-cancer/healthcare-professionals/oncotype-dx-breast-recurrence-score/about-the-test

E. American Society of Clinical Oncology Clinical guideline: https://ascopubs.org/doi/full/10.1200/JCO.2015.65.2289

F. PAM50 FDA approval: https://investors.nanostring.com/news/news-details/2013/NanoString-Technologies-Receives-FDA-510k-Clearance-for-Prosigna-Breast-Cancer-Prognostic-Gene-Signature-Assay/default.aspx

G. AstraZeneca annual reports: https://www.astrazeneca.com/investor-relations/annual-reports.html

H. Exact Sciences and Genomic health to combine: http://investor.exactsciences.com/investor-relations/press-releases/press-release-details/2019/Exact-Sciences-and-Genomic-Health-to-Combine-Creating-Leading-Global-Cancer-Diagnostics-Company/default.aspx

I. Worldwide approvals and patient numbers: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-provides-update-phase-3-pallas-trial-ibrancer

J. Palbociclib on the Cancer Drugs Fund: https://www.nice.org.uk/guidance/ta619

K. Ibrance sales compiled for Pfizer's 2019, 2018, 2017 and 2016 annual reports: https://investors.pfizer.com/financials/annual-reports/default.aspx