Institution: The University of Manchester

Unit of Assessment: 1

Title of case study:
Improving outcomes of women diagnosed with and at increased risk of breast cancer: the results of translational research and national and international clinical trials

1. Summary of the impact

Researchers at the University of Manchester (UoM) have made a significant impact internationally on improving outcomes for women diagnosed with breast cancer (>49,000 pa in the UK) and on preventing the disease. The changes in clinical practice based on our research are now national guidelines and have helped set international treatment standards. These new approaches have: increased the duration of survival of women with advanced breast cancer; reduced relapse rates and improved survival after surgery for early breast cancer; and prevented disease in women at high risk. The revised treatment has benefited >1.5m women worldwide annually who develop breast cancer and sales of anastrozole, which has replaced tamoxifen as the major endocrine therapy, have grossed over $1bn p.a.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

Key UoM researchers:

- **Anthony Howell** (Senior Lecturer, 1980-1997; Professor of Medical Oncology, 1997-2007; Professor of Breast Oncology, 2007-date)
- **Nigel Bundred** (Senior Lecturer, 1991-1996; Reader, 1996-2001; Professor of Surgical Oncology, 2001- date)

Breast cancer is the commonest tumour in women and the leading cause of death in middle-aged women. Survival is improved by early detection and the use of systemic therapy given after surgery. Both endocrine therapy (e.g. tamoxifen, developed in Manchester in the 1970s) and chemotherapy prevent relapse and improve survival. These treatments are also used to extend the duration of survival after systemic relapse.

The key contribution of the UoM group has been the development of new approaches to endocrine therapy. We led the translational development of the so-called 'pure anti-oestrogen' fulvestrant (ICI182780), which blocks oestrogen. We conducted clinical trials of this drug and the aromatase inhibitor anastrozole, which lowers oestrogen concentrations in postmenopausal women.

Key findings:

1. We demonstrated that, *in vitro*, fulvestrant was a more effective endocrine therapy than tamoxifen. Preoperative studies demonstrated that fulvestrant completely downregulated the oestrogen receptor (1) and, in a trial in women with advanced breast cancer, was active after women became resistant to treatment with tamoxifen (2). Later we led randomised trials in advanced disease which indicated that fulvestrant was equivalent to anastrozole and tamoxifen (3). More recent studies (performed by others) at higher doses of fulvestrant indicate that it is the most active endocrine therapy for breast cancer.

2. In collaboration with colleagues at AstraZeneca, we improved on the reduction of oestrogen caused by the old drugs aminoglutethimide and megestrol acetate. We used anastrozole, a newly synthesised inhibitor of the enzyme aromatase (which converts the adrenal oestrogen precursor, androstenedione, to oestrogen in peripheral tissues). In a randomised trial, anastrozole gave a longer duration of remission than megestrol acetate in women with advanced breast cancer. At that time the standard treatment after surgery for breast cancer was 'adjuvant' tamoxifen. In a trial of tamoxifen versus anastrozole in over 6,000 women worldwide, it was shown that anastrozole prevented relapse of breast cancer to a greater degree than tamoxifen (4).

3. UoM researchers demonstrated that treatment for five years with tamoxifen prevents about 40% of breast cancers in women at high risk of developing breast cancer (5). In a second international randomised trial we demonstrated that anastrozole prevents 50-60% of breast cancers (6).

3. References to the research

1. DeFriend DJ, **Howell A**, Nicholson RI, Anderson E, Dowsett M, Mansel RE, Blamey RW, **Bundred NJ**, Robertson JF, Saunders C, Baum M, Walton P, Sutcliffe F, Wakeling AE. Investigation of a New Pure Antiestrogen (ICI 182780) in Women with Primary Breast Cancer. *Cancer Research*. 1994;54(2):408-14. *Available from UoM on request.*

2. **Howell A,** DeFriend DJ, Blamey RW, Robertson JF, Walton P. Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer. *Lancet*. 1995;345(8941):29-30. DOI: 10.1016/S0140-6736(95)91156-1

3. **Howell A**, Robertson JFR, Abram P, Lichinitser MR, Elledge R, Bajetta E, Watanabe T, Morris C, Webster A, Dimery I, Osborne CK. Comparison of Fulvestrant Versus Tamoxifen for the Treatment of Advanced Breast Cancer in Postmenopausal Women Previously Untreated With Endocrine Therapy: A Multinational, Double-Blind, Randomized Trial. *Journal of Clinical Oncology*. 2004;22(9):1605-13. DOI: 10.1200/JCO.2004.02.112

4. **Howell A**, Cuzick J, Baum M, Buzdar, Dowsett M, Forbes, JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS; ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005;365(9453):60-2. DOI: 10.1016/S0140-6736(04)17666-6

5. Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, **Howell A**. Long-Term Results of Tamoxifen Prophylaxis for Breast Cancer—96-Month Follow-up of the Randomized IBIS-I Trial. *Journal of the National Cancer Institute*. 2007;99(4):272-82. DOI: 10.1093/jnci/djk049

6. Cuzick J, Sestak I, Forbes JF, Cawthorn S, N. Roche, R.E. Mansel, G. von Minckwitz, B. Bonanni, T. Palva, A **Howell A**. First results of the International Breast cancer Intervention Study II: a multicentre prevention trial of anastrozole versus placebo in postmenopausal women at increased risk of developing breast cancer. *Lancet.* December 2013, in press. *Available from UoM upon request.*

4. Details of the impact

See section 5 for corroborating sources S1-S9.

Context

Approximately 70% of breast cancers express oestrogen receptors (ER). Endocrine response is obtained by blocking the ER and/or by reducing exposure of the tumour to oestrogen. Endocrine therapy increases survival by reducing the growth of advanced metastatic breast cancer. It also cures approximately one third of women after surgery for breast cancer by eliminating occult metastatic disease. In the early 1990s, tamoxifen (developed in the early 1970s by Cole and Todd at the Christie Hospital in Manchester) was used to block the ER. Oestrogen was lowered by blocking adrenal steroid biosynthesis with the relatively toxic agents amonoglutethimide and megestrol acetate. With colleagues at AstraZeneca UoM researchers have successfully improved on these treatments so that more women presenting with early breast cancer are cured, remissions in advanced disease last longer and survival is prolonged. Furthermore, we have demonstrated that approximately half of breast cancer is preventable.

Pathways to impact

Howell devised the laboratory and translational research strategy to bring fulvestrant to the clinic in collaboration with **Bundred** (Surgeon) and DeFriend (Research Fellow). Laboratory work on

tumours was followed by a phase I preoperative study (1), followed by a phase II trial (2) and an international phase III study also led by **Howell.**

After phase III trials in advanced breast cancer, anastrozole was introduced into adjuvant therapy in a multicentre international study with **Howell** as one-time chairman of the trial steering committee (4). In order to establish tamoxifen and, later, anastrozole for prevention, two international randomised controlled trials were performed with Cuzick and **Howell** as joint principle investigators (5, 6).

Reach and significance of the impact

The studies outlined above have been instrumental in changing the endocrine treatment and prevention of breast cancer to the benefit of the more than 1.5 million women annually who develop breast cancer worldwide.

As a result of these studies, anastrozole was approved by the FDA for the first line treatment of advanced breast cancer in 2000 and for the adjuvant treatment of breast cancer in 2005 (S1). These approvals have been followed by anastrozole becoming the first line treatment for both early and advanced breast cancer. The presentation of the comparison of anastrozole with tamoxifen in 2005 (4) as adjuvant therapy caused considerable impact worldwide. It resulted in a steep increase in anastrozole use. Called a 'blockbuster' by AZ, it has grossed over $1 billion per year, indicating the extent of its use and replacement of tamoxifen as the major endocrine therapy (S2). The chief of the Division of Medical Oncology and Hematology at the Harbor-UCLA Medical Center emphasises the importance of **Howell's** work on the ATAC trial for breast cancer patients: 'In the 8 years since that initial *Lancet* report, anastrozole has maintained its leadership position as the most commonly prescribed adjuvant breast cancer therapy for postmenopausal women with hormone receptor positive disease in Europe and United States. The development and implementation of this new hormone therapy intervention has resulted in tens of thousands of women with early stage breast cancer remaining free of breast cancer recurrence' (S3).

UoM studies led to the approval of fulvestrant by the FDA for the treatment of advanced breast cancer in 2002 and the new dosing was approved in 2010 (S4). The early studies indicated that 500mg of fulvestrant was the dose which maximally down-regulated the oestrogen receptor. However because of perceived problems of administration of 500mg (it requires two intramuscular injections), the 250mg dose was used which was shown to be equivalent to other endocrine therapies such as tamoxifen and the aromatase inhibitor, exemestane. However the 500mg has now been introduced clinically and recent studies (conducted outside UoM) indicate that, at this dose, it is the most active endocrine therapy for breast cancer (S5, S6).

As a result of prevention trials with tamoxifen, NICE (June 2013) has now indicated that this drug and a similar selective oestrogen receptor modulator (raloxifene) can be prescribed for prevention of breast cancer in women at increased risk of the disease (S7, S8). **Howell** presented the background on BBC Breakfast Television on the day of the guideline launch (21st June 2013). The Director of Research for the Australia and New Zealand Breast Cancer Trials Group affirms the importance of **Howell**'s contribution to the research (6) driving the new recommendations. He writes that **Howell** was 'heavily involved in the trial of tamoxifen for prevention (IBIS I). The recent recommendation by [NICE] for tamoxifen to be offered as a standard of care to women at increased risk of breast cancer was substantially influenced by the IBIS I trial results.' (S9). We now have the results of effectiveness of anastrozole as a preventive agent indicating its superiority to tamoxifen (6).

5. Sources to corroborate the impact

S1. Drugs@FDA: FDA Approved Drug Products. Record for Arimidex. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Arimidex Gains Full FDA Approval for Adjuvant Treatment of Hormone Receptor-positive Early

Breast Cancer in Postmenopausal Women. *Medical News Today*. 21 September 2005. http://www.medicalnewstoday.com/releases/30932.php

S2. GenericsWeb, Drug In Focus August 2010 : Anastrozole For the year 2009 *Arimidex sales* generated approximately US$1.9 billion worldwide. www.genericsweb.com/druginfocus/Anastrozole

S3. Letter from Professor of Medicine, David Geffen School of Medicine at UCLA and Chief, Division of Medical Oncology and Hematology, Harbor-UCLA Medical Center, USA.

S4. Drugs@FDA: FDA Approved Drug Products. Record for Faslodex. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

S5. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, Verhoeven D, Pedrini JL, Smirnova I, Lichinitser MR, Pendergrass K, Garnett S, Lindemann JPO, Sapunar F, Martin M. Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor–Positive Advanced Breast Cancer. *Journal of Clinical Oncology*. 2010;28(30):4594-600. DOI: 10.1200/JCO.2010.28.8415

S6. Robertson JF, Lindemann JP, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Emerson L, Dean A, Ellis MJ. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. *Breast Cancer Research and Treatment*. 2012;136(2):503-11. DOI: 10.1007/s10549-012-2192-4.

S7. NICE. Clinical Guideline 164: Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. (2013). http://www.nice.org.uk/nicemedia/live/14188/64204/64204.pdf

S8. Howell A, Evans DG. Breast cancer prevention: SERMs come of age. *Lancet*. 2013;381(9880):1795-7. DOI: 10.1016/S0140-6736(13)60443-2

S9. Letter from Professor of Surgical Oncology, University of Newcastle (Australia) and Director of Research, Australia and New Zealand Breast Cancer Trials Group.