Institution: The Institute of Cancer Research

Unit of Assessment: UoA1

Title of case study: Aromatase inhibitors in breast cancer treatment

1. Summary of the impact

The Institute of Cancer Research (ICR) conducted pioneering translational research into the use of aromatase inhibitors (AIs) in breast cancer. Novel assays were developed that enabled the effects of AIs to be measured accurately and facilitated their rapid entry into large scale clinical trials and subsequent widespread availability. The ICR showed how AIs should be used clinically and helped to establish international guidelines; in some indications AIs are now the accepted standard of care. Research at the ICR has also led to the evaluation and development of novel predictive tests to determine the prognosis of patients on these drugs.

2. Underpinning research

70-80% of breast cancers are oestrogen receptor positive and are dependent on oestrogens for their growth. AIs block the production of oestrogen and are an important endocrine therapy in breast cancer treatment.

In 1993, the first specific AI (Formestane (Lentaron)) was licensed. In the 1990s, the second generation AIs, anastrozole and letrozole, were developed by AstraZeneca and Novartis, respectively. Since 1993, the ICR, with its clinical partner the Royal Marsden NHS Foundation Trust (RM), played a key role in assessing these novel drugs in the clinic. Pharmacological research assessments in the first Phase I studies of anastrozole were led by Professor Mitch Dowsett (ICR Honorary Faculty), who devised a novel oestradiol testing methodology. He demonstrated that oestradiol levels were effectively suppressed in the Phase I studies, and on that basis anastrozole proceeded into Phase III trials (Ref 1). The ICR and the RM conducted similar trials of letrozole, enabling Novartis to move letrozole directly from Phase I to Phase III trials.

The ICR and the RM played a key role in the ATAC (anastrozole, tamoxifen, alone or in combination) Phase III clinical trial. Dowsett, together with Professor Michael Baum (ICR Faculty, 1990-1996), initiated the idea for the ATAC study and then formed a core group to develop the protocol. This group also included Professor Jack Cuzick of Queen Mary and Professor Jeff Tobias of University College London; this team, together with Cancer Research Campaign, enlisted the support of AstraZeneca. The study design started in 1994, and the trial began in 1996. The ATAC trial ran in 21 countries and showed that in early post-menopausal breast cancer, AIs were superior to tamoxifen alone (Ref 2, 3). This significant research study had a major impact on standard therapy for early stage breast cancer.

During the late 1990s, Professor Dowsett initiated and chaired the translational research committee for the ATAC trial (TransATAC), and his team created a tissue collection of over 2,000 tumour blocks from the trial. This formed the basis of a translational research study. Dowsett's team used this resource to carry out research to determine biomarker profiles to identify endocrine therapy treated patients who could avoid cytotoxic chemotherapy. The team, with its US collaborators, showed that the 21-gene Oncotype-Dx test could be used as a prognostic biomarker of clinical outcome, and later they also showed that the molecular index, PAM50/ROR, was even more accurate. But, most importantly, while conducting this work, the team created a much simpler and less expensive test, the IHC4 immunohistochemical test, that could be employed in most centres throughout the world (Ref 4). This test provides more information than Oncotype-Dx and gives similar information to PAM50/ROR.

Other translational research studies by the Dowsett team, working with a team led by Professor Ian Smith (ICR Honorary Faculty), have involved Ki67, a cellular marker for proliferation. They investigated Ki67 as a "surrogate" endpoint in clinical trials of neoadjuvant treatment, which comprises systemic therapy prior to surgery. By correlating these data with recurrence-free survival, they demonstrated that Ki67 is a valid intermediate endpoint for evaluating the efficacy of

endocrine therapies (Ref 5). This approach allows the acceleration of clinical development of breast cancer drugs.

The ICR has also been involved in the analysis and evaluation of the AI exemestane, which has different pharmacological properties to anastrozole and letrozole. Professor Judith Bliss (ICR Faculty) coordinated and led the statistical analysis for the Intergroup Exemestane Study (Ref 6). This work has resulted in recommendations for how this drug should be used in the clinic.

3. References to the research

All ICR authors are in bold and ICR team leaders/Faculty are in bold and underlined.

1. Plourde PV, Dyroff M, **Dowsett M**, Demers L, Yates R, Webster A. 1995, ARIMIDEX: A new oral, once-a-day aromatase inhibitor, J Steroid Biochem Mol Biol. 53 (1-6), 175-179. (http://dx.doi.org/10.1016/0960-0760(95)00045-2)
2. 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)
3. Cuzick J, Sestak I, **Baum M**, Buzdar A, Howell A, **Dowsett M,** Forbes JF. 2010, Effect of anastrozole and tamoxifen as adjuvant treatment for early stage breast cancer: 10-year analysis of the ATAC trial, Lancet Oncol, 11 (12), 1135-1141. (http://dx.doi.org/10.1016/S1470-2045(10)70257-6).
4. 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)
5. **Dowsett M**, **Smith IE**, Ebbs SR, Dixon JM, Skene A, **A'Hern R**, **Salter J**, Detre S, Hills M, Walsh G; IMPACT trialists Group. 2007, Prognostic Value of Ki67 Expression After Short-Term Presurgical Endocrine Therapy for Primary Breast Cancer, JNCI J Natl Cancer Inst. 99 (2), 167-170. (http://dx.doi.org/10.1093/jnci/djk020)
6. Coombes RC, **Kilburn LS**, Snowdon CF, Paridaens R, Coleman RE, Jones SE, Jassem J, Van de Velde CJH, Delozier T, Alvarez I, Del Mastro L, Ortmann O, Diedrich K, Coates AS, Bajetta E, Holmberg SB, Dodwell D, Mickiewicz E, Andersen J, Lønning PE, Cocconi G, Forbes J, Castiglione M, Stuart N, Stewart A, Fallowfield LJ, Bertelli G, **Hall E**, Bogle RG, Carpentieri M, Colajori E, Subar M, **Ireland E, Bliss JM**, on behalf of the Intergroup Exemestane Study. 2007, Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial, Lancet. 369 (9561), 559-570. (http://dx.doi.org/10.1016/S0140-6736(07)60200-1)

Selected research grant support

1. Bliss – 'POETIC: Trial of Perioperative endocrine therapy – individualising care', Cancer Research UK, 2007-2016, £1,054,191
2. Dowsett – 'Integration of 2 week Ki67 with IHC4 in the POETIC trial', Cancer Research UK, 2013-2014, £191,855

4. Details of the impact

The studies at the ICR, in collaboration with others, on the use of AIs in breast cancer have made a vitally important contribution to how these drugs are used clinically. As such, they had a very significant impact on patient survival outcomes and wellbeing, and substantially improved the control of this disease. The ICR's research into the use of AIs has also had impacts on commerce.

Impacts on health

Impact on patient survival and treatment outcomes came from the demonstration, by the collaborative team involving ICR, of the superiority of AIs to tamoxifen in preventing disease recurrence in early post-menopausal breast cancer patients. This led to a rapid change in the choice of therapy in clinical practice. Clinical guidance for these patients was changed to AI treatment in 2004 in the US, followed in 2006 in the UK through changes to NICE guidelines [1]. These guidelines remain in place, illustrating that the ICR research has continued to make an impact on patient health throughout the assessment period. AIs are now the international standard of care in early breast cancer in post-menopausal women. In 2012, approximately 470,000 breast cancer patients in the USA, Europe and Japan initiated treatment with an AI [2]. In the UK, in 2012, an estimated 33,000 patients commenced adjuvant AI treatment for resectable breast cancer (about 70% of newly diagnosed resectable patients), with a further 6,000 patients receiving AI treatment for advanced and metastatic breast cancer [2].

The ICR Clinicial Trials and Statistics Unit, led by Bliss, was instrumental in the exemestane AI study, thereby influencing the recommended change in clinical practice; an impact that continues [1].

Dowsett's team initiated a translational research study to identify and validate biomarkers of patient prognosis on AI treatment using a tissue collection of over 2,000 tumour blocks from the ATAC trial. This research has had a significant clinical benefit to patients by sparing endocrine therapy-responders from further cytotoxic chemotherapy, improving their wellbeing. In the USA, for example, there has been a substantial fall in the number of patients receiving cytotoxic chemotherapy based on the use of the Oncotype-Dx test validated by the Dowsett team, and this impact continues: 37% of treatment decisions have changed because of the employment of this test [3].

The IHC4 biomarker test that the Dowsett team developed is at least as accurate as Oncotype-Dx and is also simpler and less expensive (Research Ref 4 above). The details of the IHC4 test have been openly published and, with appropriate standardisation of local testing practices, can be employed worldwide. The ICR ensured that it retained access to the intellectual property developed during its work on Oncotype-Dx and was therefore both able to demonstrate the comparative value of the IHC4 test and to make it widely available. In countries with lower budget healthcare systems the IHC4 is a highly attractive proposition.

Further development of biomarkers for AI responsiveness by the Dowsett and Smith teams has focussed on Ki67 as a surrogate marker of treatment effectiveness (Research Ref 5 above). Use of this marker enables swifter trials and therefore a patient benefit with earlier access to new drugs. This has reach beyond the use of AIs, as Ki67 is used in the commercial testing of targeted therapies such as EGF receptor antagonists. Professor Dowsett created and chairs the International Working Party on Ki67 in Breast Cancer that has published guidelines for method harmonisation [4]; these guidelines help pharmaceutical companies worldwide to measure Ki67 and deliver the consequent patient benefit of earlier access to new drugs.

Impacts on commerce

The Dowsett team at the ICR developed and validated plasma oestradiol assays as a marker of the effectiveness of AIs, enabling the team to play a central role in the selection of AIs and their dosages for full clinical development by pharmaceutical companies. Measuring plasma oestradiol in Phase I clinical trials of the AIs anastrozole and letrozole enabled AstraZeneca and Novartis, respectively, to gain regulatory authority to take these drugs directly from Phase I to Phase III

clinical trials and to get to market quickly. Together, these two drugs therefore captured the majority of the market share for AIs, to the considerable commercial benefit of the companies involved. This impact was still seen in the period 2008 to 2013. In 2012, across the major markets of USA, Europe and Japan, anastrozole and letrozole respectively secured approximately 48% and 36% of AI patient share [2] generating $6.6 billion [5] and $5.3 billion [6,7] in revenue within the REF period.

Dowsett's work on the Oncotype-DX test has had commercial impact benefiting the developers of the test (Genomic Health Inc.). Its revenues from the test totalled over $230million in 2012, with even further growth anticipated in 2013 [8].

The development of the IHC4 test has also had commercial impact, as it is currently being marketed by Genoptix [9].

The work of the Dowsett and Smith teams on Ki67 as a surrogate marker of treatment effectiveness (Research Ref 6 above) enables swifter trials and therefore a commercial benefit from reduced trial costs.

5. Sources to corroborate the impact

[1] NICE Guideline TA112 (http://publications.nice.org.uk/hormonal-therapies-for-the-adjuvant-treatment-of-early-oestrogen-receptor-positive-breast-cancer-ta112)

[2] Therapy Leader, Oncology, Decision Resources (Identifier 1)

[3] http://www.oncotypedx.com/en-GB/Breast/HealthcareProfessional/ClinicalSummary.aspx#b6

[4] Dowsett M et al. 2011, Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst, 103 (22), 1656-1664 (http://dx.doi.org/10.1093/jnci/djr393)

[5] AstraZeneca annual report 2012 (http://www.astrazeneca-annualreports.com/2012/download_centre)

[6] Novartis annual report 2012 (http://www.novartis.com/newsroom/corporate-publications/annual-report-2012.shtml)

[7] Chugai Pharmaceuticals revenue by product (http://www.chugai-pharm.co.jp/hc/ss/english/ir/finance/revenue_product.html)

[8] http://files.shareholder.com/downloads/GHDX/2761879700x0x683953/57935EC6-E76A-47F8-A583-D7E8FA24EA35/Q2_13_corporate_presentation_8_8_13.pdf

[9] www.genoptix.com/nexcourse_breast_IHC4.php