Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Improved Life Expectancy with Fewer Side-Effects in Breast Cancer Using an Innovative Switching Strategy

1. Summary of the impact (indicative maximum 100 words)

Laboratory research at Imperial College supported the concept of switching adjuvant treatment of breast cancer (i.e. tamoxifen for 2-3 years to exemestane for 2-3 years) which has now been shown in Imperial-led clinical trials to improve overall survival of breast cancer patients for at least 5 years post-switching. In association with this, the effects of switching on endometrial, skeletal and joint function have shown few long-term deleterious effects. This way of treating breast cancer has now gained acceptance worldwide, as being more efficacious and resulting in fewer longterm, serious side effects. It is the recommended treatment in international guidelines.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor R Charles Coombes, Professor of Medical Oncology (1990-present)
Professor Simak Ali, Professor of Molecular Endocrine Oncology (1992-present)
Dr Justine Reise, Senior Clinical Trials Manager (2005-present)

There are two commonly used strategies for reducing the effects of estrogens and hence treating an estrogen dependent tumour such as breast cancer. The first uses a drug such as tamoxifen which is a selective estrogen receptor modulator and binds to one of the active regions of the estrogen receptor. The other is to use an aromatase inhibitor (AI). This enzyme converts androgens into estrogens and is irreversibly inhibited when bound by the drug. The concept of aromatase inhibition to treat breast cancer by reducing estrogen synthesis has been around for several decades. Following the first specific AI, 4-hydroxy-androstenedione, being shown to be clinically effective, a more potent orally-available AI, termed exemestane, was produced by Pharmacia. Research by Professor Coombes and colleagues at Imperial from 2000 showed that, on responding and then becoming resistant to tamoxifen, breast cancer cells then die if deprived of estrogen (1, 2).

Professor Coombes and colleagues hypothesised, on the basis of this laboratory research, that an improvement in overall survival would be achieved by 'switching' to exemestane after 2 years of tamoxifen treatment, since this is the length of time that cancer cells take to become resistant to tamoxifen (1, 2). Professor Coombes designed the trial concept with the statistician, Judith Bliss (Institute of Cancer Research) and coined the term 'The Switch Strategy". The greater mechanistic understanding, together with the good effectiveness and tolerability in earlier clinical trials, paved the way for the application of exemestane using a switching strategy in early breast cancer, in the 'adjuvant' setting, i.e. in early breast cancer, after primary surgery. Up to this point, adjuvant endocrine therapy in breast cancer was limited to either oophorectomy (removal of the ovaries) or tamoxifen, the latter being administered as a single agent for 5 years. Patients were entered into the switching trial between 1998 and 2003.

It was found that by using the strategy of 'switching' treatment recurrences could be substantially delayed and disease-free survival of patients improved (3, 4). This also reduced the death rate and improved overall survival (3, 4). Thus, the protective effect of switching to exemestane compared with continuing on tamoxifen on risk of relapse or death was maintained for at least 5 years post-treatment and was associated with a continuing beneficial impact on overall survival.

Professor Coombes and colleagues also demonstrated that the 'switching strategy' is better tolerated by patients. Although AI treatment leads to a mild loss of bone mineral density, this is more than compensated for by the beneficial 'calcium-sparing' effects of the prior tamoxifen

therapy (5). In addition, following treatment withdrawal, the differences in bone mineral density observed between the two endocrine strategies were partially reversed.

It was also shown that both endometrial cancer and deep venous thrombosis is reduced after 'switching' (6). Endometrial thickness is a surrogate measure for endometrial problems due to tamoxifen: two years after randomisation, the proportion of patients with abnormal endometrial thickness was significantly lower in the exemestane compared with tamoxifen arm (36% versus 62%, respectively). Therefore, switching from tamoxifen to exemestane significantly reverses endometrial thickening associated with continued tamoxifen (6).

3. References to the research (indicative maximum of six references)

(1) Chen, D., Riedl, T., Washbrook, E., Pace, P.E., Coombes, R.C., Egly, J.M., & Ali, S. (2000). Activation of estrogen receptor alpha by S118 phosphorylation involves a ligand-dependent interaction with TFIIH and participation of CDK7. *Molecular Cell,* 6 (1), 127-137. DOI. Times cited: 153 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 15.28

(2) Chen, D., Washbrook, E., Sarwar, N., Bates, G.J., Pace, P.E., Thirunuvakkarasu, V., Taylor, J., Epstein, R.J., Fuller-Pace, F.V., Egly, J.M., Coombes, R.C., & Ali ,S. (2002). Phosphorylation of human estrogen receptor alpha at serine 118 by two distinct signal transduction pathways revealed by phosphorylation-specific antisera. *Oncogene*, 21 (32), 4921-4931. DOI. Times cited: 119 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 7.35

(3) Coombes, R.C., Hall, E., Gibson, L.J., Paridaens, R., Jassem, J., Delozier, T., Jones, S.E., et al. (2004). A randomised trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *New England Journal of Medicine*, 350, 1081-1092. DOI. Times cited: 1019 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 51.65

(4) Bliss, J.M., Kilburn, L.S., Coleman, R.E., Forbes, J.F., Coates, A.S., Jones, S.E., Jassem, J., Delozier, T., Andersen, J., Paridaens, R., Van de Velde, C.J., Lønning, P.E., Morden, J., Reise, J., Cisar, L., Menschik, T., Coombes, R.C. (2012). Disease-related outcomes with long-term follow-up: an updated analysis of the intergroup exemestane study. *J Clin Oncology*, 30 (7), 709-717. DOI. Times cited: 15 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 18.03

(5) Coleman, R.E., Banks, L.M., Girgis, S.I., Vrdoljak, E., Fox, J., Cawthorn, S.J., Patel, A., Bliss, J.M., Coombes, R.C., Kilburn, L.S. (2010). Reversal of skeletal effects of endocrine treatments in the Intergroup Exemestane Study. *Breast Cancer Res Treat*, 124 (1), 153-161. DOI. Times cited: 12 (as at 4th November on ISI Web of Science). Journal Impact Factor: 4.49

(6) Bertelli, G., Hall, E., Ireland, E., Snowdon, C.F., Jassem, J., Drosik, K., Karnicka-Mlodkowska, H., Coombes, R.C., Bliss, J.M. (2010). Long-term endometrial effects in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES)--a randomised controlled trial of exemestane versus continued tamoxifen after 2-3 years tamoxifen. *Ann Oncology*, 21 (3), 498-505. DOI. Times cited: 16 (as at 4th November on ISI Web of Science). Journal Impact Factor: 7.38

Key funding:

- Pharmacia Italia (2004-2014; £4483,738), Principal Investigator (PI) C. Coombes, Randomised double blind trial in post-menopausal women with primary breast cancer who have received adjuvant Tamoxifen for 2-3 years comparing subsequent adjuvant Exemestane with further Tamoxifen.
- Cancer Research UK (2007-2012; £328,034), PI C. Coombes, IES Pathology sub-study.
- Pfizer (2008-2011; £156,743), PI C. Coombes, Randomised double blind trial in post-menopausal women with primary breast cancer who have received adjuvant Tamoxifen for 2-3 years comparing subsequent adjuvant Exemestane with further Tamoxifen.

- Pfizer (2008-2010; £31,088), PI C. Coombes, Path IES – Retrospective Pharmacogenomic Study: Correlating Genetic Polymorphisms in Cytochrome P450 2D6 with Tamoxifen Response.

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, public policy and services
Main beneficiaries include: patients, NICE, practitioners, ESMO, NCCN

Breast cancer is the most common cancer diagnosed in women worldwide. The research conducted on 'switching' to exemestane after 2 years of tamoxifen treatment at Imperial College has shown improved overall survival for patients at least 5 years post-switching; improved quality of life and patients have shown few long-term deleterious effects. This research has led to the publication of international guidelines that impact upon the treatment of patients with breast cancer.

The American Society for Clinical Oncology guidelines published in 2010 were developed following the publication of the Imperial-led trial. The guideline committee was specifically looking at what adjuvant therapy should be offered to postmenopausal women with hormone receptor-positive breast cancer. The published recommendation, based upon data from randomised controlled trials (including those described above), was that postmenopausal patients should receive an AI after 2 or 3 years of tamoxifen treatment for a total of 5 years of adjuvant endocrine therapy [1; see page 3789]. The European Society for Medical Oncology (ESMO) clinical practice guidelines also recommend this course of treatment [2; page vi18].

The NICE 2009 guidelines for early and locally advanced breast cancer also recommend the use of exemestane as adjuvant therapy for early estrogen receptor (ER)-positive invasive breast cancer in postmenopausal women [3; see page 17]. The assessment report used to inform the recommendations in these guidelines use the research findings of Professor Coombes and colleagues.

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for exemestane 25 mg (Product Licence number: PL 24668/0260) on 11 January 2011. Their recommendation was that for 'patients with early breast cancer, treatment with exemestane should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by exemestane), or earlier if tumour relapse occurs' [4]. In terms of the durability of these recommendations, the National Comprehensive Cancer Network (NCCN) Guidelines of the USA, dated February 2013, still recommend the switching strategy for adjuvant therapy of breast cancer, as well as single therapy for five years [5].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] Burstein, H.J., Prestrud, A.A., Seidenfeld, J., Anderson, H., et al (2010). American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncology*, 28 (23), 3784-3796 (see page 3789 for recommendation based on Imperial research). DOI.

[2] Aebi, S., Davidson, T., Gruber, G., & Cardoso, F. (2011). Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 22 (supp 6): vi12-vi24. DOI.

[3] NICE Guidelines. Early and Locally Advanced Breast Cancer: Diagnosis and Treatment (2009). http://www.nice.org.uk/nicemedia/pdf/CG80NICEGuideline.pdf. Archived on 4th November 2013.

[4] MHRA Marketing Authorisation (licence). http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con111521.pdf. Archived on 4th November 2013.

[5] The NCCN Guidelines (see page BINV-J): [image removed for publication]