Institution: University of Nottingham

Unit of Assessment: UoA1

Title of case study:
The development and introduction to worldwide clinical use of a new anti-oestrogen, fulvestrant, in the treatment of breast cancer

1. Summary of the impact

As part of a 20 year partnership with AstraZeneca, Professor John Robertson, University of Nottingham, has made the largest and most consistent contribution by a clinical academic to the development of the most recent endocrine agent licensed for breast cancer, fulvestrant (Faslodex®). [text removed for publication]. Since 2008, fulvestrant 250mg has continued to be registered and launched in a number of countries based on Robertson's work, and Robertson has enhanced the clinical uptake of fulvestrant 250mg through training. His research has also been instrumental in the development and uptake of the more efficacious fulvestrant 500mg, including registration in 2010.

2. Underpinning research

Breast cancer (BC) is the most common female cancer in the world. Between 650,000 and 780,000 cases of hormone receptor positive tumours in postmenopausal women account for 50-60% of all new breast cancer cases diagnosed each year. Professor John Robertson has been involved in 13 clinical trials of fulvestrant since 1992 to present day: 9 as Chief Investigator (CI), of which 7 were multi-centre RCTs (3/7 UK and 4/7 international).

Development of 250mg dose: The first Phase II clinical study (performed at Manchester and Nottingham) demonstrated in 1995 that fulvestrant 250mg had substantial activity against tumours resistant to prior endocrine therapy[1]. A translational biology study confirmed AstraZeneca's initial laboratory findings on fulvestrant's distinct mode of action in BC patients (Robertson; CI). It also provided pharmacokinetic (PK) data showing dose response up to the highest (250mg) dose studied[2]. In the subsequent clinical programme in postmenopausal patients with advanced BC, Robertson was an Investigator in one of the two pivotal Phase III trials[3] and primary author of the published combined analysis[4]. Of five PK studies, Robertson was involved in four (two as CI). These included the study which confirmed the unique mechanism of action of fulvestrant[2], the two pivotal Phase III trials[4] and a study on a split dose (2x125mg) for data required to meet USA guidelines. The latter study bridged the two Phase III clinical trials. Robertson's study showed that a 2 x 2.5mls (125mg) injection regimen (USA schedule) was equivalent pharmacokinetically to the single 5ml (250mg) dose used in the rest of the world [Cancer Chemother Pharmacol. 2003; 52: 346-348]. This facilitated registration of the 250mg dose by showing the bioavailability equivalence of the two regimens.

Development of 500mg dose: In 2004, Robertson was an investigator in a Phase III study concluding that fulvestrant 250mg was as effective as tamoxifen (but not superior) in the first line endocrine therapy setting[5]. Collaboration with Professor Robert Nicholson and Dr Julie Gee (both at the Tenovus Institute, Cardiff) had shown previously that, while 250mg down-regulated oestrogen receptor (ER) significantly more than tamoxifen in the short term, it did not deplete ER completely[2]. In 2004, this collaboration showed that even after long-term treatment with 250mg in tumours which showed objective response, a reduced level of ER was still detectable. Subsequently, 500mg fulvestrant showed greater down-regulation of ER in independent translational studies, one from Nottingham, in collaboration with Professor Ian Ellis (Oncology, University of Nottingham), and the other by Dr Irene Kutter (Massachusetts General Hospital). The CONFIRM RCT (Robertson adviser) showed that 500mg was superior to 250mg in second line endocrine therapy, and the FIRST RCT (Robertson CI) showed that 500mg was superior to an aromatase inhibitor (AI) in the first line endocrine setting[6]. Both trials reported no increase in side-effects using the 500mg dose.

Combination of fulvestrant and other targeted therapies: Other research has investigated targeted therapies that might prevent or delay the onset of resistance to fulvestrant. An international RCT (Robertson, CI) demonstrated that anti-IGFR therapy produced by AMGEN did not delay onset of resistance to fulvestrant and, unexpectedly, was detrimental to patient outcome[7]. Critically, this work highlighted the importance to patient care of biologically based and statistically robust clinical trials.

Fulvestrant in premenopausal patients: Robertson was also CI of a pivotal study concluding that fulvestrant 250mg had no biological activity on markers of the ER pathway in premenopausal BC [Eur J Cancer 2007; 43: 64-70].

3. References to the research (Overall 38 publications on fulvestrant)

1) Response to a specific antioestrogen (ICI 182,780) in tamoxifen-resistant breast cancer. Howell A, DeFriend D, **Robertson JFR**, et al. Lancet 1995;345: 29-30 **[IF: 39.06] (Scopus citations = 274)**
http://dx.doi.org/10.1016/S0140-6736(95)91156-1

2) Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5,(10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. **Robertson JFR**, Nicholson RI, Bundred NJ, et al. Cancer Res. 2001; 61: 6739-6746 **[IF:8.65] (SC = 121)** (pdf available on request).

3) Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. Howell A, **Robertson JFR**, Quaresma Albano J, et al. J Clin Oncol. 2002; 20: 3396-3403 **[IF: 18.04] (SC = 356)**
http://dx.doi.org/10.1200/JCO.2002.10.057

4) Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. **Robertson JFR,** Osborne CK, Howell A, et al. Cancer. 2003; 98: 229-238 **[IF: 5.20] (SC = 189)**
http://dx.doi.org/10.1002/cncr.11468

5) 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 Howell A, **Robertson JFR**, Abram P, et al. J Clin Oncol. 2004; 22:1605-1613 **[IF: 18.04] (SC=191)**
http://dx.doi.org/10.1200/JCO.2004.02.112

6) Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced cancer: the results from the FIRST study **Robertson JFR**, Llombart-Cussac A, Rolski J, et al. J Clin Oncol. 2009: 27:4530-4535. **[IF: 18.04] (SC=69)**
http://dx.doi.org/10.1200/JCO.2008.21.1136

7) Ganitumab with either exemestane or fulvestrant for postmenopausal women with advanced, hormone receptor-positive breast cancer: a randomised, controlled, double-blind, phase 2 trial **Robertson JFR**, Ferrero J-M, Bourgeois H, et al. Lancet Oncology 2013; 14: 228-235 **[IF: 25.11]**
http://dx.doi.org/10.1016/S1470-2045(13)70026-3

Funding sources include:
Since 1993, Robertson's research on fulvestrant has been funded primarily by AZ, but also by AMGEN and Novartis looking at fulvestrant in combination with their drugs. The funding support has been for clinical, translational and basic biological studies. Some of the clinical studies have been Investigator Initiated Studies and others RCTs by the companies.
Total funding was £1.2 - £1.5 million.

4. Details of the impact

Fulvestrant: Development and introduction into worldwide use
[text removed for publication] [a] [b] [c]. Since registration in 2010, fulvestrant 500mg has become the treatment of choice for second-line endocrine therapy in post-menopausal women, and it is now used as the standard arm in new, on-going Phase III registration studies (e.g. FGFR inhibitor [AZD4547 AstraZeneca], Pi3K inhibitor [BKM120, Novartis], CDK4/6 inhibitor [Palbociclib, Pfizer]) [d].

[text removed for publication] [a].

Improving treatment for breast cancer patients: [text removed for publication] [b]. Fulvestrant has not only provided another therapeutic option to keep BC controlled for longer, but the 500mg dose is also better than current options, providing improved treatment outcomes in the second line setting – both in terms of disease progression (HR=0.80; P=0.006) and overall survival (HR=0.81; p=0.016) [e]. [text removed for publication] [a] [f] [g]

[text removed for publication] [a] [b] [g]

In summary, translational research at the University of Nottingham, combined with a long-term commercial partnership, has changed clinical practice and the standard of care and is improving outcomes for hundreds of thousands of breast cancer patients worldwide. The impact is also increasing year on year (shown by commercial sales) and is expected to further increase based on the FALCON trial.

5. Sources to corroborate the impact

[a] Letter from Dr Elizabeth Stott, Vice President, Global Medicines Development, AstraZeneca.

[b] Letter from Larry Norton, Professor of Medicine, Weill Medical College of Cornell University and Deputy Physician-in-Chief, for Breast Cancer Programs, Medical Director, Evelyn Lauder Breast Cancer Center, Memorial Sloan Kettering Cancer Center, New York (Past President of ASCO).

[c] Email correspondence from Gary Nunn, Global Products Manager, AstraZeneca.

[d] Trials in which fulvestrant 500mg is the standard arm:
http://clinicaltrials.gov/show/NCT01202591
http://clinicaltrials.gov/show/NCT01610284
http://clinicaltrials.gov/ct2/show/study/NCT01437566

[e] Di Leo A, Jerusalem G, Petruzelka L, et al. 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. J Clin Oncol 2010; 28:4594-4600.
http://dx.doi.org/10.1200/JCO.2010.28.8415

[f] Letter from Sandra Swain, Professor of Medicine, Georgetown University and Medical Director, Washington Cancer Institute, MedStar Washington Hospital Center (Immediate Past President of ASCO).

[g] Letter from John Forbes, Professor of Surgical Oncology, University of Newcastle, Director, Department of Surgical Oncology, Calvary Mater Newcastle Hospital, Newcastle, Australia and Director of Research and a member of Board of the Australia and New Zealand Breast Cancer Trials Group (ANZBCTG).