Institution: University of Nottingham		
Unit of Assessment: UoA1		
Title of case study: Fulvestrant: the development and clinical advancement of a novel anti-oestrogen used to treat breast cancer worldwide		
Period when the underpinning research was undertaken: 2001 – 2016		
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 John Robertson	Professor of Surgery	1989 – present
Period when the claimed impact occurred: 2014 – present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

As part of a thirty year partnership with AstraZeneca, Professor John Robertson has made a significant and consistent contribution to the development of fulvestrant (Faslodex®), an endocrine agent licensed for the treatment of breast cancer [redacted]. Fulvestrant has been one of AstraZeneca's highest grossing oncology drugs between 2014 and 2018, with sales of USD1,028,000,000 in 2018. Since 2010, fulvestrant has been the endorsed standard of care for second line endocrine therapy. In 2017 fulvestrant became the treatment of choice for first line and combined endocrine therapy, resulting in improved treatment outcomes and greater survival for patients. Professor Robertson has been instrumental in the global uptake of fulvestrant; his advice, expertise and professional training of clinicians has resulted in significant changes to clinical practice in adopting and using endocrine therapies.

2. Underpinning research

Background: the initial development of fulvestrant

Breast cancer is the most common cancer in women in the United Kingdom (UK): one in every eight females will be diagnosed in their lifetime. The most common subtype is called 'hormone sensitive' as it expresses oestrogen receptors (ER) &/or progesterone receptors (PR): this accounts for 70% to 80% of breast cancers. Endocrine (anti-hormone) therapy has been a major component of 'hormone sensitive' breast cancer treatment for over one hundred years. Two key approaches have emerged as the most effective for post-menopausal patients with ER/PR-positive tumours: drugs which block the ER (anti-oestrogens), or drugs which lower serum oestradiol, the ligand that binds to ER (i.e. aromatase inhibitors). Tamoxifen was the first anti-oestrogen approved in 1997, and is known as a Selective Estrogen Receptor Modulator (SERM). It has an antagonist action, which blocks the growth of the tumour, but also a partial agonist action on other organs/tissues in the body (e.g. uterus), and in some patients this agonistic action can stimulate growth of the cancer.

Fulvestrant, known by its brand name as Faslodex®, is a pure-anti-oestrogen with only antagonistic properties. Like tamoxifen, it binds to and blocks the ER but in addition degrades the ER. With this unique mode of action, fulvestrant became the first-in-class of what is called a Selective Estrogen Receptor Degrader (SERD). As part of a thirty year partnership with AstraZeneca, Professor John Robertson has made a significant and leading contribution to the development of fulvestrant which is the only new endocrine agent approved for breast cancer in the last 22 years. Between 1990-2000 Professor Robertson was involved in two early phase 2 trials that, between them, identified that fulvestrant 250mg had activity against tumours resistant to prior endocrine therapy and might be effective as a treatment for postmenopausal women with advanced breast cancer.

Development of 250mg and 500mg dose of fulvestrant as second line therapy

In **2001** Professor Robertson was the Chief Investigator (CI) of the first randomised pre-surgical study of the biological effects of three different doses of fulvestrant (50mg, 125mg and 250mg) on human breast cancer - a study which was critical in terms of determining the final dose of the drug **[1]**. In **2002** he was a leading investigator in one of the two Phase 3 trials which demonstrated fulvestrant at the 250mg dose was equivalent to anastrazole, an aromatase inhibitor which was the standard of care **[2]**. Both Phase 3 studies also assessed the 125mg dose which was deemed less efficacious. These studies facilitated registration (in 2002 in the United States of America (USA) and 2004 in the EU) of the 250mg dose.

In **2004**, Robertson was an investigator in another Phase 3 study concluding that fulvestrant 250mg was as effective as tamoxifen in the first line endocrine therapy setting. In **2001-2011**,

Professor Robertson was CI of an investigator-initiated study, which showed that even after long-term treatment with fulvestrant 250mg in tumours which showed objective response, a reduced level of ER was still detectable: data were available and presented earlier followed by the final publication in **2016 [3]**.

These results taken together showed i) a dose dependent downregulation of ER (50, 125, and 250mg, ii) a dose dependent efficacy (125 and 250mg), and iii) persistence of ER expression even after long term treatment with fulvestrant 250mg. These findings raised the question of whether a higher dose of fulvestrant may have greater biological and clinical effects. This was unexpected since no previous endocrine therapy had been shown to be more effective by increasing the dose. Subsequently, 500mg fulvestrant showed greater down-regulation of ER in two independent translational studies, one, an investigator-initiated study led by Professor Robertson, commenced in 2002 and published in 2013 **[4]** in collaboration with Professor Ian Ellis (Oncology, University of Nottingham), and Dr Julia Gee (University of Cardiff) and the other by Dr Irene Kutter (Massachusetts General Hospital) published in 2012. Both were presented at scientific meetings prior to publication in support of the results of the clinical trials of fulvestrant 500mg, and published in a combined paper in **2014 [5]**. The CONFIRM randomised control trial (RCT) (Robertson adviser), led by Professor Angelo di Leo (Italy), showed that 500mg was superior to 250mg in second line endocrine therapy (Di Leo 2010 & 2014). As a result, fulvestrant 500mg was adopted as the standard of care in second line endocrine therapy in 2010.

Fulvestrant as first line of endocrine therapy

In 2006 Professor Robertson was co-CI (with Professor Matthew Ellis at Baylor College of Medicine, Houston) for the Phase II FIRST study sponsored by AstraZeneca. This was an open-label multicentre trial in the first line endocrine therapy setting comparing fulvestrant 500mg versus anastrozole, an aromatase inhibitor (which by this point had replaced tamoxifen as the first line standard of care). The initial publication in **2009 [6]** reported a significant improvement on Progression Free Survival (PFS), (ie duration of control while on fulvestrant treatment). The improved PFS was further confirmed by a subsequent publication in 2012 reporting longer follow up. The mature Overall Survival (OS) data for this study published in **2015** showed fulvestrant 500mg also significantly improved OS in the first line setting **[7]** – as has previously been shown in the second line setting**.**

In **2016** Professor Robertson published the results of the FALCON Phase III double-blind RCT for which he and Professor Matthew Ellis were again Co-Is; a large multi-centre international trial in over 150 countries sponsored by AstraZeneca **[8]**. This study again reported that fulvestrant 500mg gave significantly longer PFS than anastrozole.

3. References to the research

[1] **Robertson JF**, et al. 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. *Cancer Res*. **2001**; 61(18): 6739-46

[2] **Robertson JFR**, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. *Cancer*. **2003**; 98(2): 229-38. DOI: 10.1002/cncr.11468

[3] Agrawal A, **Robertson JFR**, Cheung KL, Gutteridge E, Ellis IO, Nicholson RI, Gee JM. Biological effects of fulvestrant on estrogen receptor positive human breast cancer: short, medium and long-term effects based on sequential biopsies. *International Journal of Cancer*. **2016**; 138(1): 146–159. DOI: 10.1002/ijc.29682

[4] Robertson, JFR, et al. A randomized trial to assess the biological activity of short-term (pre-surgical) fulvestrant 500mg plus anastrazole versus fulvestrant 500mg alone or anastrozole alone on primary breast cancer. *Breast Cancer Research.* **2013**; 15:R18 DOI: 10.1186/bcr3393

[5] **Robertson JFR**, et al. A good drug made better: the fulvestrant dose-response story. *Clin Breast Cancer*. **2014;** 14(6):381-9. DOI: 10.1016/j.clbc.2014.06.005

[6] **Robertson JFR**, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. *Journal of Clinical Oncology*. **2009;** 27(27): 4530-5. DOI: 10.1200/JCO.2008.21.1136

[7] Ellis MJ, Llombart-Cussac A, Feltl D, Dewar JA, Jasiówka M, Hewson N, Rukazenkov Y, **Robertson JFR**. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of

advanced breast cancer: overall survival analysis from the Phase II FIRST study. *Journal of Clinical Oncology*. **2015;** 33(32): 3781-3787. DOI: 10.1200/JCO.2015.61.5831

[8] Robertson JFR, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet.* **2016;** 388(10063): 2997-3005. DOI: 10.1016/S0140-6736(16)32389-3

Grants and investments

[9] Robertson JFR Effects of Faslodex® in primary breast cancers (2001-2005) AstraZeneca GBP126,775

[10] Robertson JFR Faslodex® 9238IL/0057 and primary breast cancer (2003-2009) AstraZeneca GBP340,995

[11] Robertson JFR Biological effects of Faslodex® on breast cancer (2004-2009) AstraZeneca GBP82,036

4. Details of the impact

Background: the initial (pre-2014) worldwide impact of fulvestrant

Research by Professor Robertson assisted AstraZeneca in the development and worldwide registration of both a 250mg dose of fulvestrant (e.g. 2002 in the USA and 2004 in the EU) and a 500mg dose (2010). In 2010, Professor Robertson was AstraZeneca's sole invited expert for discussions between the Scientific Advisory Group-Oncology and the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, when the company pursued a broadened indication for the increased dose. From 2010 to present, fulvestrant has been the recognised and endorsed standard of care for second line endocrine therapy.

International impact on clinical practice (post-2014)

Following the FIRST-Phase II (2015) and then FALCON-Phase III (2016) trials, fulvestrant 500mg has become the standard of care for first line endocrine therapy for post-menopausal women with advanced breast cancer across the world. Former President of the American Society of Clinical Oncology (ASCO, 2016-2017) states that Professor Robertson's research '*demonstrated that, at the proper dose, it [fulvestrant] is more effective than the previously existing standard of care…this is a remarkable set of accomplishments…His [Professor Robertson's] work has clearly changed practice*', Furthermore, '*Fulvestrant 500mg/month has become the backbone endocrine agent of choice for combination with other non-endocrine treatments*' **[A]** and is also used as the control arm in ongoing studies, thus confirming its status as the standard of care **[B]**.

The use of fulvestrant 500mg as monotherapy for the treatment of hormone-receptor positive (HR+), locally-advanced or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy (i.e. as first-line therapy) was approved by the European Commission (EC) in July **2017 [C, p.8-9]** and by the US Food and Drug Administration (FDA) in August **2017 [D]**. [Redacted]

Improvement in breast cancer patient treatment

Fulvestrant 500mg dose has been shown to be better than other current options by providing improved treatment outcomes in both the second and first line setting, both in terms of Progression-Free Survival (PFS) and Overall Survival (OS). The Phase II FIRST study (randomised, open-label trial with 205 patients) reported '*improved OS with fulvestrant 500 mg treatment compared with anastrozole in the first-line setting for ER-positive advanced breast cancer, with an approximately 30% reduction in mortality risk*' and '*an improvement in OS of approximately 6 months with fulvestrant 500 mg (54.1 months) compared with anastrozole (48.4 months)*' **[7, pp.3783-4]**. This represents, to the authors knowledge, the first time an endocrine monotherapy has demonstrated improved efficacy compared with a third-generation aromatase inhibitors. The FALCON trial (phase 3, randomised, double-blind trial with 462 patients) further confirmed the superior efficacy of fulvestrant, with '*patients receiving fulvestrant having a significantly longer progression-free survival than patients receiving anastrozole*' **[8, p.3002]**. Taken together these trial results indicate significant health benefits for breast cancer patients receiving fulvestrant [redacted].

Fulvestrant is the only new endocrine therapy registered in the last eighteen years, and the only endocrine therapy to show a Progression Free Survival (PFS) and Overall Survival (OS) advantage in both the second line (Di Leo 2014) and first line settings **[7, 8]**. Former President of the ASCO (2012-2013) says "*I can affirm that [it] is very important to have fulvestrant available as a hormonal therapy that is easy to administer and non-toxic…I would conclude with high praise for the life-long and focused work of Professor John Robertson that has clearly resulted in*

not only a survival benefit but quality of life improvement for patients with advanced breast cancer" **[F]**. Former President of the ASCO (2016-2017) states fulvestrant is "*now considered the most efficacious endocrine agent for ER positive metastatic breast cancer…its very existence as such an efficacious agent was made possible through the efforts and research work of Professor Robertson*" **[A]**.

Increasing commercial impact

Fulvestrant (under the brand name FASLODEX®) has been AstraZeneca's highest (2016) and second highest (between 2014 and 2015, and 2017 and 2018) grossing oncology drug **[G(a) p. 182, G(b) p. 149]**. In 2018, fulvestrant sales generated revenue of **USD1,028,000,000 [G(a) p. 182]**. Despite going off patent in the USA in 2019, it has remained the **fourth highest grossing oncology drug sold** by the company and continues to have clinical impact **[G(a) p. 182]**.

[Redacted]

In addition to his research role, Professor Robertson also played a significant role in the commercial impact of fulvestrant. Between **2014** and **2019**, Professor Robertson acted as AstraZeneca's principal expert in the patent litigation which took place in the USA and Europe against a group of generic companies who were contesting the 2011-21 patent for fulvestrant. The Chief Patent Litigator confirmed that '*the legal team relied on Dr. Robertson's expertise to support these important inventions*' and his '*role in the cases was critical to the overall, overwhelming success of these litigations for AstraZeneca*' **[H]**. In particular, they highlighted that '*Robertson did significant research in the course of the drug's development*' and '*[t]hat research was what enabled him to give detailed testimony with the credibility that comes with having been a leader in use of the drug'* **[H]**. This success for AstraZeneca in the patent litigation protected their markets in the US and Europe contributing to the continued commercial success of fulvestrant for the company.

Advanced impact on professional services

Professor Robertson has delivered training, lectures and conference sessions on fulvestrant and endocrine therapies to breast cancer oncologists globally. The training and lectures delivered by Professor Robertson have resulted in improved practitioner confidence and knowledge in the clinical practice of breast cancer endocrine therapy, and in the use of fulvestrant in particular. Former President of the ASCO (2001-2002) stated "*Professor Robertson's acknowledged leadership in the science and clinical use of fulvestrant is demonstrated by the popularity of his lectures, conference participation, and influential publications...All of us in medical oncology—including myself and the teams I lead—must make crucial decisions almost daily regarding dose and scheduling in the care of our patients. We rely on Professor Robertson's' work to inform such decisions"* **[I].**

Professor Robertson delivered over 30 lectures at meeting for clinicians across China between **2013** and **2020**. Professor and Head of the Department of Breast Oncology at the Beijing Cancer Hospital states "*In particular, his work and teaching on fulvestrant is well-known throughout China and has been very important in the adoption of fulvestrant, initially as a second line treatment and, since 2016, as the first line endocrine therapy of choice…*" **[J]**. Professor and Head of Department at Shanghai Cancer Centre states "*Up until 2012-2014, chemotherapy has been the first line treatment of choice for the majority of hormone receptor positive breast cancer, with a paper published in **2014** in the China Medical Journal reporting that over 70% of breast cancer oncologists chose to use chemotherapy in the first-line setting. However, since the publication of the results of the FIRST and FALCON trials, and through Professor Robertson's training and lectures delivered in China, there has been a fundamental and substantial change in favour of endocrine therapy, which is now preferred as the first-line treatment for breast cancer patients*" **[K]**. He became a member of the expert international panel supporting the Chinese Advanced Breast Cancer Guidelines in **2018 [J]** including updating these guidelines on the use of endocrine therapies in autumn **2020 [L]**

Similarly, Professor Robertson has been a regular speaker in Japan since 1995, delivering 4 lectures and training workshops to breast cancer specialists in Kyoto, Osaka, and Tokyo between **2015 and 2020**, including lectures at the Japanese Breast Cancer Society (JBCS) **[M]**. The JBCS changed their practice guidelines based on the evidence from the FIRST and FALCON studies and fulverstrant monotherapy or in combination is now recommended as either first or second line endocrine treatment for post-menopausal patients with metastatic breast cancer. Former President of JBCS (2018-2019) states "*Professor Robertson's contribution to breast cancer management in Japan and worldwide has been excellent and many patients with breast cancer*

have experienced better outcomes because of the SERD…I believe the most important contribution of Professor Roberson's activity to our society was changing our daily practice in Japan" where Professor Robertson was instrumental in educating clinical staff on methods of intramuscular administration of fulvestrant that were not used in routine practice in Japan **[M]**.
Since **2014**, Professor Robertson's research, combined with a long-term commercial partnership with AstraZeneca, has changed clinical practice and the standard of care in breast cancer treatment and is improving outcomes for hundreds of thousands of breast cancer patients worldwide.

5. Sources to corroborate the impact

[A] Testimonial from former President of American Society of Clinical Oncology (ASCO, 2016-2017) and Professor of Breast Cancer Research in Ann Arbor Michigan, U.S.A.

[B] Trials in which fulvestrant is the control/standard arm:

- MONALESSA 3 (Novatis): https://clinicaltrials.gov/ct2/show/NCT02422615
- MONARCH 2 (Eli Lilly): https://clinicaltrials.gov/ct2/show/NCT02107703
- CAPItello-291 (AstraZeneca): https://clinicaltrials.gov/ct2/show/NCT04305496
- Fulvestrant versus letrozole + palbociclib in women >70 years of age with ER positive advanced breast cancer: https://clinicaltrials.gov/ct2/show/NCT03633331
- SERENA-2 (AstraZeneca): https://clinicaltrials.gov/ct2/show/NCT04214288

[C] EC approval of fulvestrant 500mg, EMA Assessment Report for Faslodex® (2017): https://www.ema.europa.eu/en/documents/variation-report/faslodex-h-c-540-ii-0059-epar-assessment-report-variation_en.pdf

[D] US FDA approval of fulvestrant 500mg: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021344Orig1s039lbl.pdf and https://www.cancer.gov/news-events/cancer-currents-blog/2017/fda-fulvestrant-breast-cancer

[E] [Redacted]

[F] Testimonial from former President of American Society of Clinical Oncology (ASCO, 2012-2013) and Professor of Medicine in Washington DC, U.S.A.

[G] (a) AstraZeneca Annual Report 2019 (b) AstraZeneca Annual Report 2016

[H] Testimonial from the Chief Patent Litigator at the legal company which defended AstraZeneca's patents for fulvestrant in the USA.

[I] Testimonial from former President of American Society of Clinical Oncology (ASCO, 2001-2002)

[J] Testimonial from Professor and Head of Department in Breast Oncology in Beijing Cancer Hospital, China and editor-in-chief of the Chinese Advanced Breast Cancer Guidelines.

[K] Testimonial from Professor and Head of Department of Medical Oncology at the Shanghai Cancer Centre, China and member of Chinese Breast Cancer Society.

[L] Confirmation of 2020 update to CABC Guidelines https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2020&filename=AZJZ202019001&v=8DZ8He7MNK34Dn5s7PhBOkv0q3cF%25mmd2FXrhUF7DyXAzV7lKnYueGdGHEWzYh4nmjkmr

[M] Testimonial from Professor of Breast Oncology at Saitama Medical University, Japan and President of Japanese Association of Supportive Care in Cancer (JASCC) and past-President of the Japanese Breast Cancer Society (JBCS, 2018-2019).