Institution: University of Strathclyde

Unit of Assessment: 3

Title of case study: Improved health and survival rates for patients with malignant brain and prostate cancer, and economic benefit from new chemotherapy treatments.

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

The Cancer Research UK Formulation Unit at the University of Strathclyde performed the pharmaceutical research and development of new chemotherapy treatments for malignant brain and prostate cancer (temozolomide and abiraterone acetate). These two drugs are now marketed globally, with FDA approval for the US market in 1999 and 2011 respectively, and have directly improved the quality of life and increased survival rates during treatment for over a quarter of a million cancer patients annually since 2008. Temozolomide achieved $1 billion sales per annum in 2008, and Abiraterone global sales reached $1.45 billion by 2013. Both drugs have produced economic benefit to the charity Cancer Research UK through royalty payments.

2. Underpinning research (indicative maximum 500 words)

Context

Development of a new anti-cancer agent is a long term, team-based process which takes many years from the isolation of a molecule through extensive clinical trials to eventual drug delivery to patients. Many scientists and clinicians were involved in the research for both drugs. For temozolomide and for abiraterone, the Cancer Research UK Formulation Unit at the University of Strathclyde performed the pharmaceutical research and development of new chemotherapy treatments which permitted both the manufacture of these treatments on a large scale and the optimal formulation for administration to patients.

Key Research Findings

Temozolomide is a pro-drug of MTIC (3-methyl-(triazen-1-yl) imidazole-4-carboxamide) a DNA methylating agent which triggers cell death. Professor M. Stevens was the synthetic chemist based at University of Aston at the time of the initial drug discovery research and Professor E. Newlands, Charing Cross Hospital was the lead clinician. During early clinical studies in the 1980's temozolomide was administered by intra venous injection in dimethylsulphoxide, which due to solubility and solvent toxicity issues limited the maximum administrable dose (and hence biological effect), required patient hospitalisation and was unpleasant. Temozolomide was initially produced in the relatively small quantities needed for the lab work at Aston University. Once Phase II clinical trials started, demand for the drug increased dramatically.

The Unit at Strathclyde conducted pharmaceutical formulation research to develop an oral capsule formulation (on which the current marketed formulation is based) determining an optimum blend of starch, lactose and aerosil, which maximised bioavailability and stability. Capsules at strengths of 25 mg, 50 mg and 100 mg were developed and manufactured allowing increasing doses to assess the maximum therapeutic and tolerated dose, and remove the requirement for parenteral therapy [1]. The ease of administration and treatment using the oral form assisted the conduct of Phase II trials, which were critical in determining efficacy and led to the eventual licensing of temozolomide by Schering-Plough (Woll, P.J., et. al., (1995) Phase II trial of temozolomide in low-grade non-Hodgkin's lymphoma. British J. Cancer, 72, 183-184). This pharmaceutical research was conducted in the Unit between 1993 and 1997.

Abiraterone acetate (CB7630) is a steroid inhibitor of the 17 α-hydroxylase/C17, 20 lyase (CYP17A1) enzyme which is expressed in testicular, adrenal and prostatic tumour tissue. Abiraterone's chemical structure is based on a steroid ring system and consequently has very poor aqueous solubility which limits oral bioavailability. Professors M. Jarman and I. Judson both from the Institute of Cancer Research were, respectively, the synthetic chemist and lead clinician in the drug discovery phase of the research. The Strathclyde Unit conducted the required pharmaceutical research to increase water solubility and dissolution to an extent suitable for oral administration, and subsequently carried out the research to develop formulations for animal and human trials. The main advance was achieved through particle size reduction by micronisation,

and close control of particle size during subsequent stages involving manufacture and storage. A suspension formulation for animal toxicology trials and a capsule formulation for human phase I dose escalation trials (10 mg, 50 mg, 100 mg and 200 mg) was researched, developed, tested and prepared. The trial results were published in 2004 [2] and subsequent clinical trials validated activity, leading to licensing and final marketing by Johnson and Johnson. This research was conducted in the Unit between 1995 and 2004 with the majority of research between 1995 and 2000.

Key researchers
Dr Gavin Halbert, a Senior Lecturer within Strathclyde University and Director of the CRUK Unit was the principal investigator on the Cancer Research Campaign/Cancer Research UK grant, which funded this research from 1992 to 2013. He was the key pharmaceutical scientist involved in the project teams for both drugs.

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

1. Beijnen, J.H., Flora, K.P., **Halbert, G.W**., Henrar, R.E.C., Slack, J.A. (1995) CRC/EORTC/NCI Joint Formulation Working Party: Experiences in the formulation of investigational cytotoxic drugs. British Journal of Cancer, 1995, 72, 210-218.
Notes on quality: General reference to the scope and extent of scientific research conducted within the Formulation Unit covering the range of challenges from analytical science to solubility, stability and formulation. Includes a section on research conducted on temozolomide and the introduction of the oral formulation. British Journal of Cancer is a Nature publication, has an impact factor of over 5 and is the key UK based publication for Cancer Research Campaign/Cancer Research UK funded scientists.

2. O'Donnell, A., Judson, I., Dowsett, M., Raynaud, F., Dearnaley, D., Mason, M., Harland, S., Robbins, A., **Halbert, G.,** Nutley, B., Jarman, M., (2004) Hormonal impact of the 17 alpha-hydroxylase/C-17,C-20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. British Journal of Cancer, 2004, 90(12), 2317-2325.
Notes on quality: First clinical paper of the initial phase 1 clinical trial results of abiraterone acetate in prostate cancer patients conducted using pharmaceutical dosage forms based on the Unit's research and indicates that the research has led to a viable clinical formulation. British Journal of Cancer, see notes above.

Other evidence for quality of research (grants, patents etc.).
The Formulation Unit has been funded by Cancer Research UK (previously Cancer Research Campaign) from the date it was established in 1983 to the present day. The total peer reviewed grant funding awarded in the period 1993 to 2013 amounts to just over £14 million. The Formulation Unit has during the period 1993 to 2013 undergone three (1995, 2003 & 2009) Cancer Research UK Site Visits, external peer review assessments conducted every 5 years, by panels of leading international and national cancer and pharmaceutical drug development scientists. The Unit's research was highly praised during the 1995 review and in both 2003 and 2009 the reviewed research was rated as Forefront (*work which is at the forefront internationally and which, it is considered will have an important and substantial impact*) with the proposed activities for the next 5 years rated as Competitive Forefront (*proposal which is internationally competitive and will make a significant contribution*). Cancer Research UK's grant rating scale runs from a minimum of 2 to a maximum of 10, Forefront is 8 - 9.99 and Competitive Forefront 5 - 7.99.

4. Details of the impact (indicative maximum 750 words)
Process from research to impact
The Formulation Unit is funded directly by Cancer Research UK to conduct pure and applied research [Source 1] across a range of chemical drug and formulation types, which culminates in the manufacture of an investigational medicinal product for patient administration in clinical trial, compliant with EU regulatory requirements. Compounds are selected by the Cancer Research UK New Agents Committee, which does not operate with a traditional drug development pipeline. The Unit, therefore, has to be capable of covering pharmaceutical research ranging across analytical methods and

techniques, utilization of these techniques to understand and limit chemical degradation and assist stabilization, and the final development of formulations [Source 2]. The Unit collaborates with multiple clinical cancer centres in the UK, and nationally and internationally with multiple cancer drug discovery groups. As the only UK academic centre capable of conducting this formulation research, the Unit's research input has played a vital role in the formulation research, clinical testing and eventual marketing of these two anti-cancer drugs.

Before drugs can be marketed by pharmaceutical companies they must be tested on patients in clinical trials and approved by regulatory bodies. In the USA, the relevant body is the Food and Drug Administration (FDA). In the UK the Medicines and Healthcare Products Regulatory Agency (MHRA) approves the clinical trial, but this does not necessarily lead to use in the National Health Service until the National Institute for Health and Care Excellence (NICE) have assessed the cost benefit calculation and approved the use of the drug.

Temozolomide was licensed by Cancer Research UK to Schering Plough in 1995, received accelerated FDA approval in 1999 and was approved by NICE in June 2007 for the treatment of newly diagnosed glioblastoma multiforme (GBM) and anaplastic astrocytoma [Source 3]. Abiraterone acetate was licensed by the Institute of Cancer Research via BTG International to Cougar Pharmaceuticals, and on to Johnson and Johnson. It was FDA approved for use in castration resistant prostate cancer after chemotherapy in April 2011; European approval followed in July 2011, with NICE ratification in England, Wales and Northern Ireland in June 2012 [Source 4]. On December 10, 2012, the FDA approved an expanded indication for abiraterone acetate (Zytiga Tablets, Janssen Biotech, Inc.) in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer [Source 5].

Type of Impact
The research impacts directly on patients with brain and prostate cancers world-wide, through the provision of better therapies, which improve the quality of life and increase life expectancy. Sales of these drugs also produce economic benefits for the pharmaceutical industry at international level and to the UK economy through royalties.

Benefits for brain cancer patients
Malignant brain cancer accounts for 2% of all new UK cancer cases. There are around 4,800 new malignant brain tumour cases per annum in the UK with 3,700 deaths and around 240,000 new cases per annum, world-wide [Source 6]. Temozolomide is currently available as a treatment in 39 countries worldwide. Before the availability of temozolomide, approximately 29% of adult patients with malignant brain tumours survived one year after diagnosis and 13% at five years. Treatment was only offered to robust patients using surgical excision followed by radiotherapy, providing a 4 to 5 month increase in median survival but with a high percentage (70%) recurring locally, leading to a rapid deterioration in quality of life. Further chemotherapy options were limited and would only provide a further median increase in survival of around 2 months. By making temozolomide available orally, it is easier to administer than standard chemotherapy regimes and, in relapsed cases, increased progression-free survival at 6 months from 8% on previous therapy to 21%, and survival from 44% to 60%. Other studies have indicated that in malignant glioma about 10% of patients on temozolomide therapy show a complete response, 25% a partial response and 30% exhibit periods of stable disease. In addition, temozolomide significantly improves quality of life prior to disease progression. The Strathclyde research made these benefits possible.
The CRUK website states that "the standard of care for glioblastoma multiforme - also known as glioma - includes chemotherapy during and after radiotherapy. The use of temozolomide both during radiotherapy and for six months post radiotherapy is now the gold standard treatment for most cases of the disease." [Source 4].

Benefits for patients with prostate cancer:
Prostate cancer accounts for 12% of all new UK cancer cases, and 25% of new cancers in men. In the UK around 37,000 men are diagnosed with prostate cancer per annum with around 10,200 dying from the disease - a figure that expands to 258,000 worldwide deaths annually with around 50,000 castrate resistant [Source 6]. Around 20 to 30% of men with primary prostate cancer present with metastatic disease (for which surgery and/or radiotherapy treatments are inappropriate). Hormone treatment will increase median survival by around two and a half years and provide symptomatic relief. However, metastatic prostate cancer will nearly always become refractory to hormone therapy (castrate resistant) with the only remaining treatment option being chemotherapy, with docetaxel and steroids only

recommended for robust patient groups. In metastatic castrate resistant patients who have progressed after chemotherapy, abiraterone significantly increased median survival from 10 to 15 months and median prostate specific antigen progression from 6 to 10 months.

Wider benefits of these anti-cancer drugs: The use of temozolomide in other malignancies, for example melanoma, is currently under active research. The clinical use of abiraterone is also expanding with potential extension into third or even second line metastatic prostate cancer therapy. In addition the method of action of abiraterone is applicable in certain breast cancers, and clinical studies in this indication are on-going [Source 7].

Economic benefits: Annual sales of temozolomide reached $1 billion in 2008, providing profits to Schering Plough and economic impact in the UK through royalty payments to Cancer Research UK. The Chief Executive of CRUK notes on their website "The royalties we receive from the sales of temozolomide go straight back into the pot to fund further research to aid the development of even more drugs to help in our fight against the disease." [Source 8]. Merck and Schering Plough merged in 2009, and in the US temozolomide is sold as Temodar until the licence expires in August 2013. Temodar's estimated global sales for 2012 amount to $882 million [Source 9].

BTG plc received an undisclosed milestone payment following the licensing of abiraterone acetate (Zytiga) in the EU, together with a royalty on worldwide sales [Source 10]. Annual sales of abiraterone in the USA for the years 2011, 2012 and 2013 were 221.1, 462.2 and 730.4 million US dollars, respectively. In Europe, sales for these years were 96.0, 465.5 and 721.4 million US dollars, respectively, giving an overall total of $1.45 billion dollars worldwide for this drug [Source 11].

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

1. http://www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2003-04-25-scotland-to-be-uk-leader-in-anticancer-drugs Role of the CRUK Formulation Unit in drug delivery
2. Document: Newell, D.R., Searle, K.M., Westwood, N.B., Burtles, S.S., on behalf of the Cancer Research UK Phase I/II Clinical Trials Committee (2003) Professor Tom Connors and the development of novel cancer therapies by the Phase I/II Clinical Trials Committee of Cancer Research UK. British J. Cancer 89, 437-454.
3. The story of temozolomide, Cancer Research UK, shows role of Strathclyde Formulation Unit. http://info.cancerresearchuk.org/cancerandresearch/progress/cancer_drugs/drug_discovery/temozolomide/
4. Prostate cancer drug abiraterone launched in UK, http://info.cancerresearchuk.org/news/archive/cancernews/2011-09-20-Prostate-cancer-drug-abiraterone-launched-in-UK.
5. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails Abiraterone gains FDA approval
6. http://www.cancerresearchuk.org/cancer-info/cancerstats/incidence/commoncancers/#Top New diagnosis of cancer rates in the UK (2010 figures)
7. http://www.cancerresearchuk.org/cancer-help/trials/a-trial-of-abiraterone-acetate-for-breast-cancer-that-has-spread Abiraterone being trialled for breast cancer treatment
8. http://www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2009-02-06-temozolomide-sales-reach-$1-billion - 2008 figures on sales of temozolomide
9. http://www.fiercepharma.com/special-reports/temodar 2012 sales of temozolomide
10. http://www.btgplc.com/page/15431/btg-plc-zytiga8482-abiraterone-acetate-approved-in-the-eu Economic benefits of abiraterone acetate (Zytiga)
11. Document with data requested from http://www.decisionresourcesgateway.com will confirm abiraterone sales figures.