Institution: The Institute of Cancer Research

Unit of Assessment: UoA1

Title of case study: Development of abiraterone for the treatment of castration-resistant prostate cancer

1. Summary of the impact

Abiraterone (trade name Zytiga) was designed, synthesised and developed by a multidisciplinary team of academic chemists, biologists and clinicians at The Institute of Cancer Research (ICR). Following ICR-led phase I, II and III clinical trials, which demonstrated prolonged survival and improved quality of life for patients with castration-resistant prostate cancer (following cytotoxic therapy), abiraterone was granted approval by the FDA, EMA and NICE. In 2011-2012, abiraterone worldwide sales reached $2.755 billion. In 2012-13, FDA and EMA approval was extended to use in the treatment of metastatic castration-resistant prostate cancer in men who have not received standard chemotherapy.

2. Underpinning research

Prostate tumours are dependent on male sex hormones (androgens) such as testosterone. While the cessation of gonadal androgen production caused by castration is effective in early stages of the disease, tumours eventually progress, developing into castration-resistant prostate cancer, which is invariably fatal. Although they were previously known as hormone refractory prostate cancer. ICR scientists proposed that the malignant growth of these prostate cancers was driven be an alternative bodily source of androgens, rather than being truly hormone refractory. Their demonstration that this is the case has revolutionised the discovery and development of drugs for this disease by highlighting the androgen biosynthetic pathway as a target for pharmacological inhibition. In the early 1990s, Dr Gerry Potter (ICR postdoctoral researcher, 1990-1994) and Dr Elaine Barrie (ICR postdoctoral researcher) in Professor Mike Jarman's team (ICR Faculty, 1976-2001) were undertaking a drug discovery research programme to identify compounds that could inhibit the synthesis of testosterone, specifically targeting the pathway enzyme 17α -hydroxylase-17,20-lyase (CYP17). They designed and tested a series of chemical compounds, and after optimisation CB7598 – which exhibited selective and irreversible inhibition of the enzyme – was synthesised and patented. CB7598 was named abiraterone.

Together with Professor Mitch Dowsett (ICR Honorary Faculty), the team went on to carry out *in vivo* pharmacokinetic and biochemical research, which established that abiraterone blocked the synthesis of testosterone and reduced the size of androgen-dependent organs (Ref 1). It was these key results that provided the fundamental research basis to proceed into clinical trials. From 1996, a phase I trial, led by Professor Ian Judson (ICR Faculty) and conducted at the ICR and The Royal Marsden NHS Foundation Trust (RM), established that abiraterone acetate, the prodrug form of abiraterone, resulted in sustained suppression of testosterone generation in patients with prostate cancer (Ref 2).

In 2008, a phase I evaluation of once daily continuous abiraterone, led from the ICR by Professor Johann de Bono (ICR Faculty), confirmed its safety and revealed impressive tumour shrinkage and dramatic falls in Prostate Specific Antigen (PSA) levels in the majority of the 21 patients with advanced prostate cancer who had previously received multiple lines of hormone therapy (Ref 3). Another significant outcome of this research was the first demonstration that late stage prostate cancer is indeed still hormone driven and therefore amenable to pharmacological intervention targeted at hormone synthesis or hormone action. A further phase I/II trial led by de Bono confirmed the initial phase I results and showed that up to 70% of men with advanced prostate cancer responded to abiraterone. Two thirds of men experienced significant benefits for an average of eight months, with scans showing their tumours decreased in size and their PSA levels declined (Ref 4).

A randomised double-blind phase III trial (ClinicalTrials.gov identifier: NCT00638690), initiated in

2008 and involving 1195 patients, was conducted in 147 sites over 13 countries and was coordinated by de Bono. The patients enrolled in the trial all had late-stage prostate cancer resistant to standard hormone therapy and had previously been treated by cytotoxic chemotherapy. The overall results of this clinical research study (Ref 5) showed that treatment with abiraterone led to a 35% reduction in the risk of death in castration-resistant prostate cancer patients. Patients treated with abiraterone acetate also had consistently improved pain palliation as compared with those in the placebo group. These data were key to the drug's subsequent approval by the regulatory authorities for widespread usage.

3. References to the research

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

1. **Barrie SE, Potter GA**, **Goddard PM**, **Haynes BP, Dowsett M, Jarman M.** 1994, Pharmacology of novel steroidal inhibitors of cytochrome *P*450$_{17\alpha}$ (17α-hydroxylase/C17-20 lyase), J Steroid Biochem Mol Biol. 50 (5-6), 267-273. (http://dx.doi.org/10.1016/0960-0760(94)90131-7)
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 17α-hydroxylase/$C_{17,20}$-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer, Br J Cancer. 90, 2317-2325. (http://dx.doi.org/10.1038/sj.bjc.6601879)
3. **Attard G, Reid AHM, Yap TA, Raynaud F, Dowsett M,** Settatree S**,** Barrett M**, Parker C, Martins V, Folkerd E, Clark J, Cooper CS, Kaye SB, Dearnaley D,** Lee G**, de Bono JS**. 2008, Phase I Clinical Trial of a Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms That Castration-Resistant Prostate Cancer Commonly Remains Hormone Driven, J Clin Oncol. 26 (28), 4563-4571. (http://dx.doi.org/10.1200/JCO.2007.15.9749)
4. **Attard G**, **Reid AHM**, **A'Hern R, Parker C**, Oommen NB, **Folkerd E, Messiou C**, **Molife LR, Maier G, Thompson E, Olmos D, Sinha R**, Lee G, **Dowsett M, Kaye SB, Dearnaley D**, Kheoh T, Molina A, **de Bono JS**. 2009, Selective inhibition of CYP17 with Abiraterone Acetate is Highly Active in the Treatment of Castration-Resistant Prostate Cancer, J Clin Oncol. 27 (23), 3742-3748. (http://dx.doi.org/10.1200/JCO.2008.20.0642)
5. **de Bono JS**, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, **Zivi A**, **Bianchini D**, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI, COU-AA-301 Investigators. 2011, Abiraterone and Increased Survival in Mmetastatic Prostate Cancer. N Engl J Med. 364 (21), 1995-2005. (http://dx.doi.org/10.1056/NEJMoa1014618)

Quality Indicators

Selected research grant support

1. De Bono – "Laboratory evaluation of Abiraterone", Prostate Cancer Research Foundation, 2009-2012, £143k
2. De Bono – "CYP17 Inhibition with Abiraterone", Prostate Cancer UK, 2009-2012, £248k

Prizes

1. 2011 Royal Society of Chemistry's Teamwork and Innovation Award – Abiraterone Discovery and Development Team. (http://www.rsc.org/ScienceAndTechnology/Awards/TeamworkinInnovation/2011winner.asp)
2. 2011 European Society for Medical Oncology (ESMO) Award – Professor Johann de Bono (http://www.esmo.org/Career-Development/Awards/ESMO-Award)
3. 2012 American Association of Cancer Research Team Science Award for the team's

tremendous impact in preclinical and clinical studies relating to cancer therapeutics which included the highly promising inhibitors of androgen biosynthesis (CYP17). http://www.aacr.org/home/scientists/scientific-achievement-awards/scientific-award-winners/team-science-award-.aspx

4. Details of the impact

The discovery and development of abiraterone at the ICR has had impacts on health and commerce, resulting in the improved treatment and patient survival for prostate cancer patients, changes to international clinical guidelines and the introduction of a new drug into the pharmaceutical market with major commercial benefit to the sector.

In the UK, more than 10,000 men die of prostate cancer every year, making it the second most common cause of cancer death in men. Worldwide, more than 258,000 men died from the disease in 2008 [1]. In 2010, only three agents were approved for treatment of castration-resistant prostate cancer by the US FDA, having demonstrated improvements in overall survival in clinical trials. Since that date, the introduction of abiraterone into clinical use is now significantly prolonging survival and improving quality of life for tens of thousands of patients worldwide for whom other forms of treatment have failed [2].

From 2008 onwards, patients have benefited from abiraterone, initially through clinical trials and now through prescribed use. 17 clinical trials involving 1648 patients have been completed and currently 62 trials are ongoing (estimated enrolment of over 14,000 patients). Abiraterone has now been approved for use in more than 80 countries [3]. Since its 2011 approval in the USA, abiraterone's share of the endocrine therapy market in prostate cancer reached 30%; this has increased further to 43% following the FDA ruling of December 2012, when abiraterone was also approved for use in metastatic castration-resistant prostate cancer patients who have not yet received chemotherapy. In the USA, abiraterone is the preferred second-line treatment of metastatic prostate cancer – with nearly 60% share of the market – and in the third-line setting it is used in approximately 30% of patients [3]. In 2012, 13,000 patients in Europe benefited from this drug [4].

ICR researchers played a key role in the discovery and development of this new drug from target identification and compound synthesis through pre-clinical evaluation to clinical trials research. Briefly, the development of abiraterone was stalled by the concern of pharmaceutical companies regarding the potential side effects of targeting CYP17, such as adrenal insufficiency, and the licence for development was returned. Professor de Bono and Dr Gerhardt Attard (ICR Clinical Research Fellow) proposed that CYP17 blockade would not result in adrenal insufficiency based on previous reports describing congenital autosomal recessive CYP17 deficiency in children [5]. This proved to be the case in the initial clinical trials, giving the biotechnology company Cougar Biotechnology, Inc. confidence to take up the license to commercially develop abiraterone.

The phase I/II trials at the ICR and the RM provided the confirmation that abiraterone elicited anti-tumour effects in prostate cancer patients, and the impetus to escalate the studies to large multi-centre phase III trials. The randomised placebo controlled phase III trial led by de Bono provided the evidence that abiraterone could increase survival in castration-resistant prostate cancer patients. Interim overall survival analysis demonstrated a statistically significant improvement in survival in patients receiving abiraterone acetate compared to those on the placebo, to such an extent that the trial's Independent Data Monitoring Committee recommended that the study be unblinded to allow any patient on placebo to receive the drug.

Following an expedited review, the US Food and Drug Administration (FDA) approved abiraterone acetate in April 2011 [6] for the treatment of men with late-stage (metastatic) castration-resistant prostate cancer who have received prior docetaxel chemotherapy. Also, after accelerated regulatory review by the European Medicines Agency (EMA), abiraterone was approved by the European Commission for use in Europe [7] (EMEA/H/C/002321), followed by approval by NICE in June 2012 (NICE guideline TA259) [8].

Most recently, an international, randomised, double-blind, placebo controlled study (NCT00887198), involving 135 locations and 1,088 asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer, was unblinded based on the interim analysis. This led to the expansion of the FDA (December 2012) and EMA (January 2013) approval for the use of abiraterone, in combination with prednisone, in the treatment of patients with metastatic castration-resistant prostate cancer who have not yet received chemotherapy [9].

During the development of the drug, ICR researchers have worked with BTG, Cougar Biotechnology, Inc and Johnson & Johnson, all of which have greatly benefited commercially. BTG have reported receiving a better than expected revenue from abiraterone royalties, becoming their largest royalty stream in 2012 [10]. Cougar Biotechnolgy, Inc was acquired, in 2009, by Johnson & Johnson for just under $1billion [11]. Worldwide drug sales of abiraterone between 2011 and 2013 have reached $2.755 billion [12], which is expected to increase dramatically this year due to the recent approval for abiraterone to be used in a wider patient population. The ICR has also received £15.5 million in royalties during the REF period.

A further commercial impact stems from the important concept, revealed by the ICR research, that late stage prostate cancer remains hormone driven. This has focussed pharmaceutical company resource investment into inhibition agents targeted at androgen hormone action, such as enzalutamide – developed by Medivation – which the FDA approved for the treatment of castration-resistant prostate cancer in 2012 [13].

5. Sources to corroborate the impact

[1] http://www.cancerresearchuk.org/cancer-info/cancerstats/keyfacts/prostate-cancer/

[2] Janssen Global Services (Identifier 1)

[3] http://www.kantarhealth.com/news-events/news-article/2013/04/23/kantar-health-data-show-zytiga-is-most-used-first-line-treatment-in-prostate-cancer#sthash.i9rDM1b3.dpuf

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

[5] Attard et al. 2005, Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as therapeutic strategy for treating metastatic prostate cancer, Br J Urol. 96, 1241-1246. (http://dx.doi.org/10.1111/j.1464-410X.2005.05821.x)

[6] http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=202379&DrugName=ZYTIGA&ActiveIngred=ABIRATERONE%20ACETATE&SponsorApplicant=JANSSEN%20BIOTECH&ProductMktStatus=1&goto=Search.DrugDetails

[7] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002321/human_med_001499.jsp&mid=WC0b01ac058001d124

[8] http://guidance.nice.org.uk/TA259

[9] http://www.investor.jnj.com/releasedetail.cfm?ReleaseID=740080

[10] http://www.btgplc.com/page/22556/btg-annual-report-and-accounts-2013

[11] http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aOieUhNZNRlo

[12] http://www.investor.jnj.com/annual-reports.cfm

[13] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317838.htm