Institution: The Institute of Cancer Research

Unit of Assessment: Clinical Medicine

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

Period when the underpinning research was undertaken: 2004 to 2017

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:
Dr Gerhardt Attard	ICR Team Leader	01/12/2007–30/11/2008; 01/07/2012–08/01/2018
Dr Elaine Barrie	ICR postdoctoral researcher	03/10/1977–31/12/2013
Professor David Dearnaley	ICR Team Leader	01/12/1987–31/08/2020
Professor Johann de Bono	ICR Team Leader	01/07/2003–Present
Professor Mitch Dowsett	ICR Honorary Faculty	01/06/1993–Present
Professor Michael Jarman	ICR Team Leader	01/06/1976–31/05/2001; 01/11/2005–30/11/2008
Professor Ian Judson	ICR Team Leader	12/01/1987–31/03/2016
Professor Stan Kaye	ICR Team Leader	01/09/2000–30/11/2013
Professor Gerry Potter	ICR PhD student	05/10/1987–09/11/1990;
	ICR postdoctoral researcher	10/11/1990–29/04/1994; 01/12/2006–30/11/2008

Period when the claimed impact occurred: 2014 onwards

Is this case study continued from a case study submitted in 2014? Yes. In REF 2014, we submitted an impact case study outlining the discovery and clinical development of abiraterone by ICR researchers. At the point of submission in REF 2014, abiraterone was approved in various countries for men with metastatic castration-resistant prostate cancer before and after chemotherapy. Between 2014 and 2020, the REF 2021 impact assessment period, abiraterone continued to be an important therapeutic option for these patients. Moreover, this case study details the new impact of abiraterone, in combination with androgen deprivation therapy, as a first-line treatment for advanced prostate cancer.

1. Summary of the impact

Researchers at The Institute of Cancer Research (ICR) discovered and led the clinical development of the prostate cancer drug abiraterone, leading to impact on:

- **Clinical policy.** Between 2011 and 2018, abiraterone was approved in combination with prednisone/prednisolone in 105 countries.
- **Patients.** Abiraterone has transformed the care of prostate cancer. More than 500,000 men worldwide will have received treatment with abiraterone. It is estimated that this has given them >300,000 extra life years.
- **The pharmaceutical industry.** From 2014 to 2019, Johnson & Johnson reported total abiraterone sales of over USD15,500,000,000.

2. Underpinning research

The discovery of abiraterone. Since the 1940s, it has been known that prostate cancers rely on testosterone (an androgen) to grow. Up until the 1990s, therapies therefore focussed on trying to block the action of the hormone. Ultimately, however, most patients' cancers stopped responding to these treatments. Many at the time believed that this was a result of the cancer evolving to survive without testosterone—but the ICR's Professor Mike Jarman, Dr Elaine Barrie, and Professor Gerry Potter posed an alternative theory—that these cancers remained dependent on testosterone and were getting a supply of testosterone from elsewhere in the body, and therefore the disruption of testosterone synthesis could still be an effective treatment. In the early 1990s, this team discovered a compound which specifically and

irreversibly blocked CYP17, an enzyme required for androgen production. Working with the British Technology Group (BTG), the ICR team further developed this compound, called abiraterone.

The first clinical trials of abiraterone. The next stage was to assess abiraterone in a clinical trial. In the early 2000s, the first phase 1 trial of abiraterone was conducted by Professor Ian Judson at the ICR's partner hospital, The Royal Marsden NHS Foundation Trust (RM), in collaboration with Boehringer Ingelheim. This trial established that administration of abiraterone acetate (the prodrug of abiraterone) suppressed testosterone generation in patients with prostate cancer and most importantly showed the drug was safe in humans **(Ref. 1)**. However, Boehringer Ingelheim decided not to continue developing abiraterone at this point.
Several years later, the ICR's Professor Johann de Bono, working with Cougar Biotech, judged there was potential in abiraterone and led a series of trials demonstrating the effectiveness of the drug. Professor Johann de Bono then initiated a phase 1/2 trial of abiraterone with prednisone. Prednisone serves as glucocorticoid replacement therapy and reduces adverse effects. Evaluation of once-daily continuous abiraterone, established abiraterone's safety and revealed impressive tumour shrinkage and major falls in Prostate Specific Antigen (PSA) levels in the majority of the 21 patients (each with advanced prostate cancer who had previously received multiple lines of hormone therapy) **(Ref. 2)**. This trial confirmed that late-stage prostate cancer (known as metastatic castration-resistant prostate cancer, mCRPC) is still hormone driven, and therefore pharmacological intervention on hormone synthesis or hormone action could benefit patients. This trial also 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 8 months, with their PSA levels declining and scans showing that their tumours had decreased in size **(Ref. 3)**.

Practice-changing clinical trial. A randomised double-blind phase 3 trial of abiraterone acetate (Chief Investigator (CI): Professor de Bono) was initiated in 2008, involving 1,195 patients in 147 sites over 13 countries. The patients in this trial all had mCRPC, and had previously been treated with cytotoxic chemotherapy. The overall results of this study showed that treatment with abiraterone led to a 35% reduction in the risk of death **(Ref. 4)**. Patients treated with abiraterone also had consistently improved pain palliation as compared with those in the placebo group. These data led to approval by various regulatory authorities (see *Section 4*). This pivotal phase 3 trial showed increased overall survival in the abiraterone acetate–prednisone group than in the placebo–prednisone group (14.8 months vs. 10.9 months).

Additional clinical benefits of abiraterone. Further trials showed benefit of abiraterone therapy at earlier stages of prostate cancer. In the COU-AA-302 trial, in which Professor de Bono was a co-investigator, abiraterone improved progression-free survival in patients with mCRPC who had not had chemotherapy, showed a trend toward improved overall survival, and significantly delayed clinical decline and initiation of chemotherapy **(Ref. 5)**. The STAMPEDE trial involved 1,917 men with newly diagnosed (or relapsed) advanced prostate cancer, with 957 randomly assigned to standard of care alone (ADT, androgen-deprivation therapy) and 960 to ADT, abiraterone acetate, and prednisolone (combination therapy). The use of the combination therapy as compared with ADT alone was associated with a 71% relative improvement in the time to treatment failure, which translated into a 37% increase in overall survival **(Ref. 6)**. This provides the initial evidence that the use of abiraterone as a first-line therapy in men who are initiating long-term ADT could improve survival.

3. References to the research

Key: **ICR employed staff** at the time of publication, **ICR Team Leaders (including Honorary Faculty)** at the time of publication.

1. **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/C17,20-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). *Times cited: 282 (WOS).*

2. **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). *Times cited: 652 (WOS).*
3. **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). *Times cited: 456 (WOS).*
4. **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 Metastatic Prostate Cancer. N Engl J Med. 364 (21), 1995-2005. (http://dx.doi.org/10.1056/NEJMoa1014618). *Times cited: 2,717 (WOS).*
5. Ryan CJ, Smith MR, **de Bono JS**, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PF, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttmann H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE; COU-AA-302 Investigators. 2013, Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. Jan 10;368(2):138-48. (http://dx.doi.org/10.1056/NEJMoa1209096). *Times cited: 1,704 (WOS).*
6. James ND, **de Bono JS**, Spears MR, Clarke NW, Mason MD, **Dearnaley DP**, Ritchie AWS, Amos CL, Gilson C, Jones RJ, Matheson D, Millman R, **Attard G**, Chowdhury S, Cross WR, Gillessen S, Parker CC, Russell JM, Berthold DR, Brawley C, Adab F, Aung S, Birtle AJ, Bowen J, Brock S, Chakraborti P, Ferguson C, Gale J, Gray E, Hingorani M, Hoskin PJ, Lester JF, Malik ZI, McKinna F, McPhail N, Money-Kyrle J, O'Sullivan J, Parikh O, Protheroe A, Robinson A, Srihari NN, Thomas C, Wagstaff J, Wylie J, Zarkar A, Parmar MKB, Sydes MR; STAMPEDE Investigators. 2017, Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 207 Jul 27;377(4):338-35. (http://dx.doi.org/10.1056/NEJMoa1702900). *Times cited: 664 (WOS).*

Additional Quality indicators.

Prizes:

- 2011 Royal Society of Chemistry's Teamwork and Innovation Award—Abiraterone Discovery and Development Team: https://www.rsc.org/prizes-funding/prizes/find-a-prize/industry-academia-collaboration-award/previous-winners/
- 2012 American Association of Cancer Research Team Science Award: https://www.aacr.org/professionals/research/scientific-achievement-awards-and-lecturships/scientific-award-recipients/aacr-team-science-award-recipients/
- 2018 AACR—Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research. Johann de Bono: https://www.aacr.org/professionals/research/scientific-achievement-awards-and-lecturships/scientific-award-recipients/aacr-burchenal-award-recipients/
- 2017 Queen's Anniversary Prize for ICR's drug discovery and development work: https://www.queensanniversaryprizes.org.uk/winners-archive/

4. Details of the impact

Regulatory approvals of abiraterone. In April 2011, based on the data from the ICR-led COU-AA-301 phase 3 trial **(Ref. 4)**, the US Food and Drug Administration (FDA) licensed abiraterone acetate for the treatment of men with mCRPC who have received prior docetaxel chemotherapy. After accelerated regulatory review by the European Medicines Agency (EMA), abiraterone was approved for use in Europe **[A]**, and approved by the National Institute for Health and Care Excellence (NICE) in June 2012. In the NICE approval it was estimated approximately 2,500 patients in England and Wales with mCRPC would benefit from the marketing authorisation of abiraterone **[B]**.

In 2012 and 2013 respectively, FDA and EMA approval was extended to the treatment of mCRPC in men who have not received standard chemotherapy. NICE approved this indication in 2016 and it was estimated that approximately 7,000 patients would be eligible for this therapy in England alone **[C]**. These approvals were based on the COU-AA-302 trial **(Ref. 5)**.

The phase 3 trial, LATITUDE (NCT01715285), involving 1,199 patients across 34 countries, showed there was a clear benefit to using abiraterone in combination with androgen-deprivation therapy as a first-line treatment for advanced prostate cancer, providing further support for the results seen in the STAMPEDE trial **(Ref. 6)**. Following publication of these results in 2017, abiraterone, in combination with androgen-deprivation therapy, was approved by the EMA as a first-line treatment for advanced prostate cancer **[D]**. In 2018, this indication was approved by the FDA **[E]**. This was the first approval in metastatic castration-sensitive prostate cancers, thus providing improved therapy options for a new group of patients.

Patient impact. Based on GLOBOCAN 2018 estimates, 1,276,106 new cases of prostate cancer were reported worldwide in 2018. Moreover, more than 358,000 men worldwide died from the disease in 2018—3.8% of all cancer-related deaths in men **[F]**. In addition the work of the ICR has changed the nomenclature in the field—patients that were called hormone refractory (because it was thought their tumours would no longer respond to testosterone) are now said to have castration-resistant prostate cancer.

The ICR-led COU-AA-301 phase 3 trial **(Ref. 4)** showed that, in patients where the standard therapies had failed, administration of abiraterone acetate with prednisone resulted in a 35% reduction in the risk of death compared to the placebo with prednisone. Therefore, abiraterone is prolonging the survival of patients worldwide receiving this treatment. The NICE approval in 2012 highlighted the patient benefit of abiraterone:

> "*The Committee concluded that abiraterone offers a step change in treatment because it is an oral drug taken by patients at home, and is associated with few adverse reactions."… "The Committee heard from the patient experts that the most important benefits of abiraterone were extension to life and improved quality of life, including less pain and improved mental and physical health."* **[B]**

The COU-AA-302 trial **(Ref. 5)** led to the regulatory approval above, and therefore resulting in mCRPC patients worldwide being treated with abiraterone, before treatment with chemotherapy. In the 2016 NICE approval, it was highlighted:

> "*…that chemotherapy can reduce a person's quality of life and that treatments delaying the need for chemotherapy are highly valued by patients."* **[C]**

Patient benefit, as seen in trials and described above, has been on a global scale. Between 2011 and 2018, treatment with abiraterone in combination with prednisone/prednisolone was approved in 105 countries. More than 500,000 men worldwide have received treatment with abiraterone **[G]**. It is estimated that this has given >300,000 extra life years to men suffering from prostate cancer. Data from the UK showed that prescription of abiraterone increased in 2012 after the NICE approval **[B]** to approximately 250,000 daily doses by 2014 (see *Figure 1*, adapted from the NICEimpact cancer report **[H]**). During the COVID-19 pandemic, NHS England made abiraterone available as a first-line treatment for men with advanced prostate cancer (who are intolerant to enzaluamide), in order to lower the risk of exposing these

vulnerable patients to the SARS-CoV-2 virus—patients can take their tablets at home and have their bloods checked by their General Practitioner, and, unlike chemotherapy, abiraterone has no significant effects on the patients' immune system.

Economic impact for the pharmaceutical industry. The clinical development of abiraterone (trade name Zytiga®) has led to significant economic impact in the pharmaceutical sector. 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. Cougar Biotechnology, Inc was acquired in 2009 by Johnson & Johnson. BTG, acquired by Boston Scientific in 2019, receives licensing royalties from abiraterone—these amounted to GBP155,400,000 in 2017/18, up from GBP123,200,000 the previous year **[I]**. Johnson & Johnson reported sales of almost USD2,800,000,000 of abiraterone in 2019. In annual report data from 2014 to 2019, Johnson & Johnson reported total abiraterone sales of over USD15,500,000,000 **[J]**.

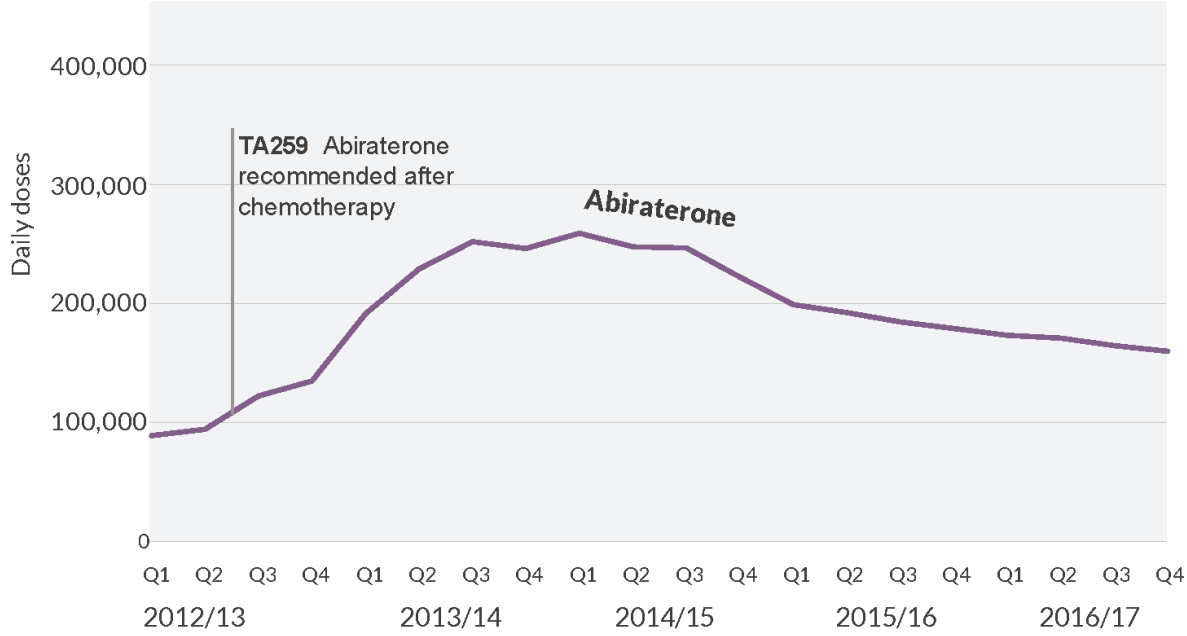

Figure 1: Prescribing of medicines for treating metastatic hormone-relapsed prostate cancer. Adapted from NICEimpact cancer. **[H]**

5. Sources to corroborate the impact

A. Johnson & Johnson Press Release: https://www.jnj.com/media-center/press-releases/zytiga-approved-in-the-european-union-for-metastatic-castration-resistant-prostate-cancer

B. NICE Technology appraisal guidance: https://www.nice.org.uk/guidance/ta259

C. NICE Technology appraisal guidance: http://nice.org.uk/guidance/ta387

D. European Society for Medical Oncology Press Release: https://www.esmo.org/Oncology-News/EMA-Recommends-Extension-of-Indications-for-Abiraterone-Acetate

E. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abiraterone-acetate-combination-prednisone-high-risk-metastatic-castration-sensitive

F. Prostate Cancer Statistics: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6497009/

G. Press release: https://www.jnj.com/janssen-to-highlight-depth-of-prostate-cancer-and-solid-tumor-portfolios-with-multiple-data-presentations-at-esmo-2019

H. National Institute for Health and Care Excellence impact cancer publication. https://www.nice.org.uk/Media/Default/About/what-we-do/Into-practice/measuring-uptake/nice-impact-cancer.pdf

I. BTG plc Annual Report and Account 2018: https://www.annualreports.co.uk/HostedData/AnnualReports/PDF/LSE_BCG_2018.pdf

J. Johnson & Johnson Annual Reports: https://www.jnj.com/about-jnj/annual-reports