Institution: The Institute of Cancer Research

Unit of Assessment: Clinical Medicine

Title of case study: Clinical development of olaparib, a PARP inhibitor, leading to improved outcomes for cancer patients

Period when the underpinning research was undertaken: 2001 to 2015

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 Alan Ashworth	ICR Team Leader	29/09/1986–31/12/2014
Dr Gerhardt Attard	ICR Team Leader	01/12/2007–30/11/2008; 01/07/2012–08/01/2018
Professor Johann de Bono	ICR Team Leader	01/07/2003–Present
Professor Ros Eeles	ICR Team Leader	01/12/1994–Present
Professor Emma Hall	ICR Team Leader	05/04/1999–Present
Professor Stan Kaye	ICR Team Leader	01/09/2000–30/11/2013
Professor Christopher Lord	ICR Team Leader	23/10/2000–Present
Dr Amanda Swain	ICR Team Leader	01/04/1998–Present
Professor Andrew Tutt	ICR Team Leader	01/04/1998–30/06/2002; 01/02/2007–30/11/2008; 31/10/2013–Present

Period when the claimed impact occurred: 2014 onwards

Is this case study continued from a case study submitted in 2014? No. The ICR submitted an impact case study about *BRCA* genes in cancer which is related to this case study. However, at the point of submission in REF 2014, no PARP inhibitors were approved in any cancers. This case study describes the impact of the approval of olaparib, a PARP inhibitor, which was first licensed in 2014 in ovarian cancer.

1. Summary of the impact

Researchers at The Institute of Cancer Research (ICR) carried out early phase trials of olaparib, a PARP inhibitor, as well as early and late phase trials in ovarian and prostate cancer, leading to impact on:

- **Patients.** Olaparib improves quality of life and extends periods of remission for patients with homologous recombination repair (HRR) gene-mutated cancer.
- **Clinical Policy.** Olaparib is approved for HRR gene-mutated ovarian, breast, pancreatic and prostate cancer therapy.
- **Pharmaceutical Industry.** In 2020, AstraZeneca reported olaparib (Lynparza) sales of over USD1,776,000,000 worldwide.

2. Underpinning research

Background. Homologous recombination repair (HRR) is a mechanism in cells to repair double-strand DNA damage. Germline mutations in HRR genes, such as *BRCA1* and *BRCA2*, confer increased risk of breast, ovarian, prostate, and pancreatic cancer.

First clinical trial of olaparib, a PARP inhibitor. ICR investigators in the Biological Sciences Unit of Assessment (UOA5) expanded the understanding of BRCA1/2 function and provided evidence for the sensitisation to PARP inhibition in *BRCA*-mutated cells. This work prompted the first phase 1 trial of olaparib led by Professor Johann de Bono (ICR Team Leader). This trial, published in 2009, demonstrated that olaparib, a novel, potent, orally active PARP inhibitor, had durable clinical effectiveness in breast, ovarian and prostate cancer patients carrying mutant forms of *BRCA1* or *BRCA2* **(Ref. 1)**. The treatment of *BRCA* mutant cancers with a PARP inhibitor was the first demonstration of the use of a synthetic lethality strategy in the clinic.

Synthetic lethality arises when a combination of deficiencies in two or more genes leads to cell death, whereas a deficiency in the genes individually does not.

In 2012, Professor Stan Kaye (ICR Team Leader) led an international and multi-centre phase 2 study of olaparib in *BRCA*-mutated ovarian cancer which confirmed the high level activity of this class of drug and established the likely importance of dose, recommending monotherapy with 400mg olaparib twice per day as a suitable dose to explore in further studies **(Ref. 2)**. Further trials of olaparib and other PARP inhibitors in ovarian and breast cancer have resulted in various regulatory approvals and patient impact as described in *Section 4*.

DNA-repair defects in prostate cancer. Based on the promising therapeutic exploitation of the synthetic lethality between PARP inhibition and *BRCA* mutation combined with emerging data suggesting that HRR defects are common in prostate cancer, Professor de Bono's team hypothesised clinical benefit from olaparib for a subset of prostate cancer patients. Professor de Bono and Professor Emma Hall led the clinical trial, TOPARP-A, in which 50 metastatic castration-resistant prostate cancer (mCRPC) patients were enrolled and next-generation sequencing was used to identify mutations in DNA-repair genes—including *BRCA1/2*, *ATM*, Fanconi's anemia genes, and *CHEK2*. The results of the trial showed approximately 25% to 30% of all sporadic, castration-resistant prostate cancers have defects in HRR genes. This suggested that a common subset of metastatic prostate cancers can be molecularly stratified for treatment. Treatment with the PARP inhibitor, olaparib, in mCRPC patients who had defects in HRR genes led to a high response rate **(Ref. 3)**. In TOPARP-B, patients with mCRPC were preselected for HRR alterations and treated with olaparib in two dose cohorts. The data from TOPARP-B confirmed the antitumour activity of olaparib against metastatic prostate cancer with particular HRR gene aberrations, with the highest responses observed in patients with metastatic castration-resistant prostate cancer with germline (inherited) or somatic (tumour) *BRCA1/2* aberrations **(Ref. 4)**.

Results from the phase 3 PROfound trial, led by Professor de Bono, showed improved progression-free survival with olaparib in men with mCRPC who have HRR mutations and have progressed on prior treatment. Patients with HRR mutations who received olaparib had a significantly longer duration of overall survival than those who received a control therapy despite substantial crossover from control therapy to olaparib (19.1 months vs. 14.7 months) **(Ref. 5)**.

Alongside this work, Professor de Bono's team, working as part of the Stand Up to Cancer-Prostate Cancer Foundation Prostate Dream Team, created a comprehensive map of the genetic mutations within mCRPC. They established a multi-institutional clinical sequencing infrastructure to conduct prospective whole-exome and transcriptome sequencing of bone or soft tissue tumor biopsies from a cohort of 150 mCRPC affected individuals. Aberrations of *BRCA2*, *BRCA1*, and *ATM* were observed at substantially higher frequencies (19% overall) in metastatic disease compared to those in primary prostate cancers **(Ref. 6)**. Thus showing approximately one in five advanced prostate cancer patients could benefit from PARP inhibitor therapy.

3. References to the research

Key: **ICR employed staff** at the time of publication, **ICR Team Leaders** at the time of publication.

1. **Fong PC**, Boss DS, **Yap TA**, **Tutt AN**, **Wu P**, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O'Connor MJ, **Ashworth A**, Carmichael J, **Kaye SB**, Schellens JH, **de Bono JS**. 2009, Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers, N Engl J Med. 361 (2), 123-134. (http://dx.doi.org/10.1056/NEJMoa0900212). *Times cited: 2,441 (WOS).*
2. **Kaye SB**, Lubinski J, Matulonis U, **Ang JE**, Gourley C, Karlan BY, Amnon A, Bell-McGuinn KM, Chen LM, Friedlander M, Safra T, Vergote I, Wickens M, Lowe ES, Carmichael J, Kaufman B. 2012, Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and

recurrent ovarian cancer. J Clin Oncol. 2012 30(4): 372-9 (http://dx.doi.org/10.1200/JCO.2011.36.9215). *Times cited: 345 (WOS).*

3. **Mateo J, Carreira S, Sandhu S, Miranda S**, **Mossop H, Perez-Lopez R, Nava Rodrigues D**, Robinson D, **Omlin A**, **Tunariu N, Boysen G, Porta N, Flohr P, Gillman A, Figueiredo I, Paulding C, Seed G**, Jain S, Ralph C, Protheroe A, Hussain S, Jones R, Elliott T, McGovern U, **Bianchini D, Goodall J, Zafeiriou Z, Williamson CT, Ferraldeschi R, Riisnaes R, Ebbs B, Fowler G, Roda D, Yuan W, Wu YM**, Cao X, **Brough R, Pemberton H, A'Hern R, Swain A**, Kunju LP, **Eeles R**, **Attard G**, **Lord CJ**, Ashworth A, Rubin MA, Knudsen KE, Feng FY, Chinnaiyan AM, **Hall E**, **de Bono JS**. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med. 2015 Oct 29;373(18):1697-708. (http://dx.doi.org/10.1056/NEJMoa1506859). *Times cited: 1,088 (WOS).*

4. **Mateo J**, **Porta N**, **Bianchini D**, McGovern U, Elliott T, Jones R, Syndikus I, Ralph C, Jain S, Varughese M, Parikh O, Crabb S, Robinson A, McLaren D, Birtle A, Tanguay J, **Miranda S**, **Figueiredo I**, **Seed G, Bertan C**, **Flohr P**, **Ebbs B**, **Rescigno P**, **Fowler G**, **Ferreira A**, **Riisnaes R**, **Pereira R**, **Curcean A, Chandler R**, **Clarke M**, **Gurel B**, **Crespo M**, **Nava Rodrigues D**, Sandhu S, **Espinasse A**, **Chatfield P**, **Tunariu N**, **Yuan W**, **Hall E**, **Carreira S**, **de Bono JS**. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. 2020 Jan;21(1):162-174. (http://dx.doi.org/10.1016/S1470-2045(19)30684-9). *Times cited: 90 (WOS).*

5. Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, Chi KN, Sartor O, Agarwal N, Olmos D, Thiery-Vuillemin A, Twardowski P, Roubaud G, Özgüroğlu M, Kang J, Burgents J, Gresty C, Corcoran C, Adelman CA, **de Bono J**; PROfound Trial Investigators. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020 Sep 20. (http://dx.doi.org/10.1056/NEJMoa2022485). *(This is a recent publication so not yet accumulated citations).*

6. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM Montgomery B, Taplin ME, Pritchard CC, **Attard G**, Beltran H, Abida W, Bradley RK, Vinson J, Cao X, Vats P, Kunju LP, Hussain M, Feng FY, Tomlins SA, Cooney KA, Smith DC, Brennan C, Siddiqui J, Mehra R, Chen Y, Rathkopf DE, Morris MJ, Solomon SB, Durack JC, Reuter VE, Gopalan A, Gao J, Loda M, Lis RT, Bowden M, Balk SP, Gaviola G, Sougnez C, Gupta M, Yu EY, Mostaghel EA, Cheng HH, Mulcahy H, True LD, Plymate SR, Dvinge H, Ferraldeschi R, Flohr P, **Miranda S**, **Zafeiriou Z**, **Tunariu N**, **Mateo J**, **Perez-Lopez R**, Demichelis F, Robinson BD, Sboner A, Schiffman M, Nanus DM, Tagawa ST, Sigaras A, Eng KW, Elemento O, Sboner A, Heath EI, Scher HI, Pienta KJ, Kantoff P, **de Bono JS**, Rubin MA, Nelson PS, Garraway LA, Sawyers CL, Chinnaiyan AM.Cell. Integrative Clinical Genomics of Advanced Prostate Cancer. 2015 May 21;161(5):1215. (http://dx.doi.org/10.1016/j.cell.2015.05.001). *Times cited: 1,405 (WOS).*

Additional Quality Indicators

Selected peer reviewed research grant support:

- de Bono and Hall: "TO-PARP: Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer", Cancer Research UK, 2011–2014, GBP231,601.
- de Bono and Hall: "TO-PARP phase II trial Cancer Research UK, 2015–2021, GBP236,883.
- de Bono: “Precision Therapy of Advanced Prostate Cancer”, Stand Up To Cancer, 2012–2015 USD10,000,000.

Prizes:

- 2018 AACR–Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research. Professor Johann de Bono: https://www.aacr.org/professionals/research/scientific-achievement-awards-and-lecturships/scientific-award-recipients/aacr-burchenal-award-recipients/

4. Details of the impact

First regulatory approvals of olaparib (trade name Lynparza). The ICR-led phase 1 and phase 2 trials **(Ref. 1** and **Ref. 2)** resulted in further phase 2 trials of olaparib in ovarian cancer. The pivotal trial, Study 19, was performed in high-grade serous ovarian cancer patients with platinum-sensitive relapse. This study showed increased progression-free survival which was even more pronounced in patients with germline/somatic *BRCA1/2* mutation, 11.2 months compared to 4.3 months. These results led to olaparib approval in December 2014 by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a monotherapy for the maintenance treatment of women with *BRCA1*- or *BRCA2*-mutant high-grade serous ovarian cancer, or fallopian tube or primary peritoneal cancer, who have had either a complete or partial response to platinum-based chemotherapy **[A]**. In the EMA assessment report of olaparib **[A]** both ICR trials described above are presented in the table of 8 supportive clinical studies. The phase 1 trial **(Ref. 1)** is one of two phase 1 trials listed, Study 00002, and the phase 2 **(Ref. 2)** is one of two "Key Supportive" trials listed as Study 00012.

The inclusion of both *BRCA1* or *BRCA2* germline and somatically mutated tumours in the approvals made olaparib the first targeted treatment for an inherited cancer disorder. The National Institute for Health and Care Excellence (NICE) approval of olaparib in this indication followed in January 2016. The Appraisal Committee *"concluded that a drug treatment that improves quality of life and extends periods of remission for patients with BRCA mutation-positive ovarian cancer would be highly valued by patients and their families."* **[B]**

Further regulatory approvals. The phase 3 SOLO-1 trial demonstrated that ovarian cancer patients treated with olaparib as first-line maintenance therapy experienced 3 more years of progression-free survival than those given placebo, a significant benefit not usually seen in oncology trials. *"Women with ovarian cancer are often diagnosed with advanced disease, which unfortunately is associated with poor long-term survival rates. The newly-diagnosed setting is our best opportunity to achieve a sustained remission, since once a patient's ovarian cancer recurs, it is typically incurable. The SOLO-1 results demonstrate the potential of Lynparza maintenance therapy earlier in the treatment pathway and reinforce the importance of identifying a patient's BRCA mutation status at the time of diagnosis – these results could change the way we treat women with advanced BRCA-mutated ovarian cancer*." **[C]**

Based on the results of the SOLO-1 trial, olaparib has been approved in the EU, US, Canada, Japan and Brazil for first-line maintenance of germline/somatic *BRCA1/2*-mutated high grade epithelial ovarian cancer **[D]**. Olaparib is available on the NHS via the Cancer Drugs Fund as a first-line maintenance treatment. Each year, approximately 700 women in England with advanced ovarian cancer are expected to benefit from this new treatment option **[E]**. Based on the results from the PAOLA-1 phase 3 trial, olaparib was recommended for approval in EU as first-line maintenance treatment with bevacizumab for HRR-deficient advanced ovarian cancer in September 2020.

As of 2020, olaparib is approved in 78 countries for the treatment of ovarian cancer **[F]**.

Impact in prostate cancer. Based on the results of TOPARP-A and B **(Ref. 3** and **Ref. 4)**, a phase 3 trial of the olaparib in mCRPC, the PROfound study, was initiated. Results from this trial showed a statistically significant and clinically meaningful improvement in the primary endpoint of radiographic progression-free survival with olaparib in men with mCRPC who have HRR gene mutation and have progressed on prior treatment (e.g. enzalutamide and abiraterone). Further results from the trial showed a statistically significant and clinically meaningful improvement in the key secondary endpoint of overall survival with olaparib versus enzalutamide or abiraterone in men with mCRPC selected for *BRCA1/2* or *ATM* gene mutation **[G]**.

Based on data from the PROfound study olaparib was approved by the FDA in May 2020 and by the EMA in November 2020 in *BRCA* mutant prostate cancer. Rucaparib, another PARP inhibitor was also approved by the FDA at the same time based on the results from TRITON-2. The rucaparib approval is an accelerated one, which will require the results to be replicated in a

confirmatory trial. Olaparib remains the only PARP inhibitor to have demonstrated it can improve overall survival, versus enzalutamide or abiraterone for men with *BRCA* or *ATM* mutations.

Before the prostate cancer approvals, olaparib had already been used to treat more than 30,000 patients worldwide and this will only increase as there were approximately 1,300,000 new cases of prostate cancer diagnosed worldwide in 2018. Approximately 10-20% of men with advanced prostate cancer will develop mCRPC within five years and HRR gene mutations occur in approximately 20-30% of patients with mCRPC **[H]**. This therefore represents a large amount of patients that could benefit from olaparib treatment.

ICR research contributed to the understanding that approximately 20-30% of mCRPCs have mutations in HRR genes that may make them sensitive to PARP inhibitors **(Ref. 5** and **Ref. 6)**. As a consequence of this increased understanding and the importance of these findings, the National Comprehensive Cancer Network (NCCN) 2018 guidelines were updated to recommend consideration of testing mCRPC patients for germline and somatic mutations in DNA-repair genes (*BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*), and referring patients who have these mutations for genetic counselling. This information can be used to refer mCRPC patients with DNA-repair gene mutations *"for early use of platinum chemotherapy, or eligibility for clinical trials (e.g. PARP-inhibitors)"* **[I]**.

Impact in other cancers. The first approvals of PARP inhibitors were in ovarian cancer but there has been impact in breast and pancreatic cancers. As of 2020, olaparib is approved in 76 countries for the treatment of metastatic breast cancer, and in 55 countries, including the US, for the treatment of pancreatic cancer **[F]**.

Pharmaceutical industry impact. Olaparib was initially developed by the British company KuDOS, which was acquired by AstraZeneca in 2006. In 2020, AstraZeneca reported olaparib (Lynparza) sales of over USD1,776,000,000 worldwide compared to USD1,198,000,000 in 2019. The growth is in part as a result of regulatory approval for expanded uses in various cancers **[F]**.

5. Sources to corroborate the impact

A. EMA Assessment report of Lynparza (olaparib) see Table on pages 50 to 51: https://www.ema.europa.eu/en/documents/assessment-report/lynparza-epar-public-assessment-report_en.pdf

B. NICE guidance for olaparib: https://www.nice.org.uk/guidance/ta381

C. SOLO-1 trial results press release: https://www.astrazeneca.com/media-centre/press-releases/2018/solo-1-phase-III-trial-demonstrates-lynparza-maintenance-therapy-cut-risk-of-disease-progression-or-death-by-70-percent-in-patients-with-newly-diagnosed-advanced-brca-mutated-ovarian-cancer.html

D. AstraZeneca press release: https://www.astrazeneca.com/media-centre/press-releases/2019/lynparza-approved-in-japan-for-1st-line-maintenance-therapy-in-brca-mutated-advanced-ovarian-cancer-19062019.html

E. NICE press release: https://www.nice.org.uk/news/article/innovative-treatment-for-gynaecological-cancers-approved-for-cancer-drugs-fund

F. AstraZeneca 2020 annual report: https://www.astrazeneca.com/content/dam/az/Investor_Relations/annual-report-2020/pdf/AstraZeneca_AR_2020.pdf

G. AstraZeneca press release: https://www.astrazeneca.com/media-centre/press-releases/2020/lynparza-shows-overall-survival-in-prostate-cancer.html

H. Olaparib regulatory approval press release: https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/lynparza-approved-in-the-us-for-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.html

I. National Comprehensive Cancer Network NCCN 2018 guidelines: https://jnccn.org/view/journals/jnccn/16/5S/article-p620.xml