Institution: The Institute of Cancer Research

Unit of Assessment: Biological Sciences

Title of case study: PARP inhibition in *BRCA*-mutated cancer: improved survival for ovarian, breast, pancreatic and prostate 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
Professor Christopher Lord	ICR Team Leader	23/10/2000–Present
Dr Stephen Pettitt	ICR Independent Researcher	01/06/2011–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. This REF 2021 case study describes the impact of the approval of multiple PARP inhibitors, first licensed after the REF2014 submission.

1. Summary of the impact

Researchers at The Institute of Cancer Research (ICR) discovered a novel strategy for treating cancer patients with mutations in genes involved in the DNA homologous recombination repair (HRR) pathway—including *BRCA1* and *BRCA2*. ICR researchers demonstrated that HRR defective cancers were particularly sensitive to poly-ADP-ribose polymerase (PARP) inhibitors, leading to impact on:

- **Clinical policy.** PARP inhibitors are licensed in ovarian, breast, pancreatic, and prostate cancers.
- **Patients.** There are four PARP inhibitors approved—olaparib, rucaparib, niraparib, and talazoparib—improving quality of life and extending periods of remission for patients with HRR gene mutation-positive cancers. Olaparib, the first PARP inhibitor approved has been used to treat over 30,000 patients worldwide.
- **The pharmaceutical industry.** Between 2014 and 2020, there was over USD5,000,000,000 in sales of PARP inhibitors worldwide, generating economic benefit for pharmaceutical companies (AstraZeneca, Clovis, Tesaro/GSK, and Pfizer).

2. Underpinning research

Background. Germline *BRCA1* and *BRCA2* mutations confer increased risk of breast, ovarian, prostate, and pancreatic cancers. Approximately 10% of women with ovarian cancer and up to 5% of women with breast cancer carry a mutation in either *BRCA1* or *BRCA2*. These genes are involved in homologous recombination repair (HRR)—a mechanism in cells to repair double-strand DNA lesions—and are therefore important for suppressing the formation of cancer.

Understanding BRCA2 function and the sensitivity of BRCA-mutated cells to PARP inhibition. In the 1990s, an ICR team identified and isolated the *BRCA2* gene, and were first to publish this finding. Building on this work, Professor Alan Ashworth led a team (including Professors Andrew Tutt and Chris Lord), which investigated the function of the BRCA2 protein and demonstrated how BRCA2 modulates HRR and genome instability. The team also showed that BRCA2 deficiency increases errors during the repair of DNA damage (**Ref. 1**). From these studies, Professor Ashworth proposed that cells lacking functional BRCA1 or BRCA2 would be highly sensitive to drugs that inhibit PARP, an enzyme which plays a key role in an alternative DNA repair pathway. Experimentally, Professor Ashworth's team showed that BRCA1 or BRCA2

dysfunction profoundly sensitises cells to the inhibition of PARP, resulting in chromosomal instability, cell cycle arrest, and subsequent apoptosis. This work was patented in 2004 and published in 2005 (**Ref. 2**)—crucially, the model for sensitivity to PARP inhibition presented in this publication hinged on a deficiency in HRR, and not necessarily on inherited BRCA1 or BRCA2 deficiency. This model was supported by further work by the Ashworth team, which demonstrated that defects in other proteins involved in HRR (RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHK1, CHK2, FANCD2, FANCA, or FANCC) would cause profound PARP inhibitor sensitivity (**Ref. 3**). On this basis, Professor Ashworth's team pioneered the concept of 'BRCAness'—a term used to define a subset of tumours that lack *BRCA* mutations but share other similar characteristics, particularly defective HRR, and are therefore phenocopies of *BRCA*-mutant tumours. It was proposed that PARP inhibitors would likely be effective in the treatment of a range of sporadic cancers with BRCAness, or other impairments in HRR.

This had immediate impact, and led rapidly to clinical trials. The first-in-man phase 1 trial, *BRCA1/2*-specific proof-of-concept phase 2 trial and a phase 3 trial demonstrating the broader efficacy of olaparib in HRR-mutated cancers were led by ICR investigators, including Professor Johann de Bono, are part of the ICR's Clinical Medicine (UOA1) submission. Three first-generation PARP inhibitors have received licensing approvals for marketing—olaparib, rucaparib, and niraparib (see *Section 4*). More recently, a more potent second-generation PARP inhibitor, talazoparib (previously BMN 673, Biomarin/Medivation/Pfizer), has been developed. Professor Ashworth's ICR team showed that, like other PARP inhibitors, talazoparib was selective for tumour cells with defects in HRR, but had between 20- and 200-fold greater potency than existing inhibitors. In pre-clinical mouse models, xenografted tumours that carried defects in DNA repair were shown to be profoundly sensitive to oral talazoparib treatment at well-tolerated doses (**Ref. 4**). Finally, Professors Ashworth and Lord's teams identified 'reversion' mutations in BRCAness genes, which cause PARP inhibitor resistance in experimental models (**Ref. 5**)—these were subsequently shown, by the ICR team, to be the cause of resistance in up to 40% of PARP inhibitor-treated patients (**Ref. 6**). This mechanism is recognised as the only clinically validated mechanism of PARP inhibitor resistance.

3. References to the research

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

(Ref. 1) **Tutt A**, **Bertwistle D**, **Valentine J**, **Gabriel A**, **Swift S**, **Ross G**, Griffin C, Thacker, J & **Ashworth A.** 2001, Mutation in Brca2 stimulates error-prone homology-directed repair of DNA double-strand breaks occurring between repeated sequences, EMBO J. 20, 4704-4716. (http://dx.doi.org/10.1093/emboj/20.17.4704). *Times cited: 326 (WOS).*

(Ref. 2) **Farmer H**, **McCabe N**, **Lord CJ**, **Tutt AN**, **Johnson DA**, **Richardson TB**, **Santarosa M**, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC *&* **Ashworth A.** 2005, Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy, Nature. 434, 917-921. (http://dx.doi.org/10.1038/nature03445). *Times cited: 3,637 (WOS).*

(Ref. 3) **McCabe N, Turner NC, Lord CJ**, Kluzek K, Bialkowska A, Swift S, Giavara S, O'Connor M, Tutt AN, Zdzienicka M, Smith G, **Ashworth A**. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res. 2006; 66:8109-15. (https://doi.org/10.1158/0008-5472.CAN-06-0140). *Times cited: 831 (WOS).*

(Ref. 4) Shen Y, **Rehman FL**, Feng Y, **Boshuizen J**, **Bajrami I**, **Elliott R**, Wang B, **Lord CJ**, Post LE, **Ashworth A**. BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency. Clin Cancer Res. 2013 Sep 15;19(18):5003-15. (https://doi.org/10.1158/1078-0432.CCR-13-1391). *Times Cited: 252 (WOS).*

(Ref. 5) **Edwards SL**, **Brough R**, **Lord CJ**, **Natrajan R**, **Vatcheva R**, Levine DA, Boyd J, **Reis-Filho JS**, **Ashworth A**. Resistance to therapy caused by intragenic deletion in BRCA2. Nature. 2008 Feb 28;451(7182):1111-5. (https://doi.org/10.1038/nature06548). *Times Cited: 651 (WOS).*

(Ref. 6) **Pettitt SJ**, **Frankum JR**, **Punta M**, **Lise S**, **Alexander J**, **Chen Y**, Yap TA, **Haider S**, **Tutt ANJ**, **Lord CJ**. Clinical *BRCA1/2* Reversion Analysis Identifies Hotspot Mutations and Predicted Neoantigens Associated with Therapy Resistance. Cancer Discov. 2020 Oct;10(10):1475-1488. (https://doi.org/10.1158/2159-8290.CD-19-1485). *Times Cited: 4 (WOS).*

Quality indicators.

Selected peer reviewed research grant support:

- Breakthrough Breast Cancer (now Breast Cancer Now) Centre funding 2003–2010, GBP30,872,915
- Lord | "Cancer Susceptibility Genes" Cancer Research UK Programme Grant, 2017–2022, GBP2,073,409.

Prizes:

- Professor Ashworth won the 2013 Basser Global Prize and 2017 Brinker Award for Scientific Distinction in Basic Science. He was also elected to Fellowship, Royal Society and Fellowship, Academy of Medical Sciences.
- Professor Tutt was elected to Fellowship, Academy of Medical Sciences.

4. Details of the impact

Clinical development of PARP inhibitors. ICR research led to significant impact in the clinical development of PARP inhibitors in the pharmaceutical industry, as well as inhibitors of other proteins involved in HRR (such as ATM and ATR). The ICR patented the discovery that PARP inhibition is selectively lethal in cells deficient in HRR (Patent No: US8143241) and licensed this patent to KuDOS who have then sub-licensed the biomarker patent to other companies who are developing PARP inhibitors. Four PARP inhibitors have licensing approvals: olaparib (AstraZeneca), rucaparib (Clovis), niraparib (Tesaro/GSK), and talazoparib (Pfizer). There has been huge interest in PARP inhibitors and as of 2017 there were more than 200 clinical trials for PARP inhibitors either completed or ongoing **[A]**.

First regulatory approvals of olaparib. A phase 1 trial in *BRCA1* and *BRCA2* mutation carriers, led by Professor de Bono (ICR Team Leader, UOA1), and including Professors Tutt and Ashworth—provided clinical proof of concept for the synthetic lethal approach, using the PARP inhibitor olaparib. A key phase 2 clinical trial, Study 19, demonstrated that women with ovarian cancer with germline or somatic *BRCA1* or *BRCA2* mutations showed the most profound benefit from olaparib maintenance therapy, which significantly extended their progression-free survival by, on average, 7 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 *BRCA*-mutant high-grade serous ovarian cancer patients, who have had either a complete or partial response to platinum-based chemotherapy **[B]**. The inclusion of both *BRCA1/2* germline and somatically mutated tumours in these approvals made olaparib the first targeted treatment for an inherited cancer disorder—it was also the first BRCAness-targeted therapy. 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."* **[C]**

The uptake of olaparib following the NICE recommendation in January 2016 is shown by the rapid, and continuing, increase in the national use of olaparib (*Figure 1*) **[D]**. In addition, there is a Cochrane systematic review on PARP inhibitors in ovarian cancer—considered an indicator of a change in clinical practice **[E]**.

Further regulatory approvals. Based on the results of the SOLO1 trial, olaparib is also approved in the EU, US, Canada, Japan, and Brazil for first-line maintenance of germline/somatic *BRCA1/2*-mutated high-grade epithelial ovarian cancer—providing significant benefits to patients across the world. The SOLO1 trial results showed that the mean time to progression in those treated with olaparib was greater than 40.7 months (the point of the follow-

up), compared to a median time of 13.8 months for the placebo group **[F]**. Based on the results from the PAOLA-1 phase 3 trial, in September 2020 olaparib was approved in EU as a first-line maintenance treatment with bevacizumab for HRR-mutated advanced ovarian cancer.

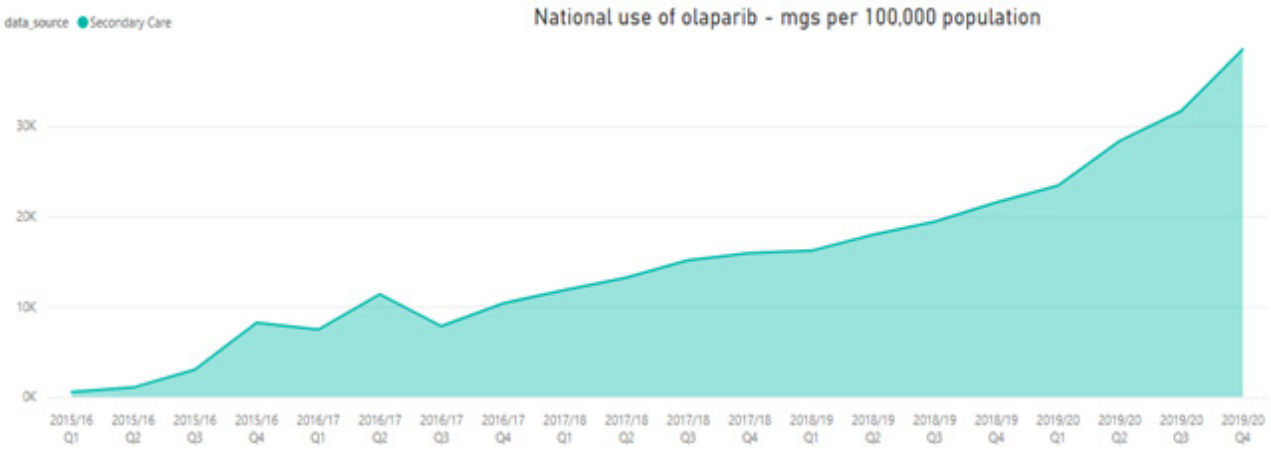

Figure 1: Prescribing rates of olaparib in the NHS in England adapted from **[D]**

Two other PARP inhibitors have also received regulatory approval for the treatment of ovarian cancer patients. Niraparib (Zejula) is now approved in over 35 countries (including the US and Europe). In April 2020, the FDA approved niraparib as a first-line monotherapy maintenance treatment for women with platinum-responsive advanced ovarian cancer, regardless of biomarker status. This new indication is supported by data from the phase 3 PRIMA study. Rucaparib (Rubraca) was approved by the FDA in 2016 and the EMA in 2018.

Impact in breast cancer. The first approvals of PARP inhibitors were in ovarian cancer, but there has been impact in other cancers. An international phase 3 clinical trial, OLYMPIAD, showed that olaparib delayed the progression of advanced breast cancer in women with inherited *BRCA* mutations for 42% longer than standard chemotherapies. Based on this, in January 2018 the FDA approved olaparib for advanced breast cancer in women who have inherited *BRCA1* or *BRCA2* mutations, and in April 2019 EMA approval followed. As of 2020, olaparib is approved in nearly 40 countries for germline *BRCA*-mutant HER2-negative metastatic breast cancer previously treated with chemotherapy **[F]**.

ICR pre-clinical work (**Ref. 3**) showed the efficacy of another PARP inhibitor, talazoparib, and in 2018 this was approved by the FDA and EMA in *BRCA* germline mutated advanced breast cancer **[G]**. The approval of talazoparib was based on data from the EMBRACA phase 3 study, which showed a 46% reduction in the risk of disease progression and a more-than-doubled overall response rate (63%) compared to chemotherapy (27%). This provides patients with limited treatment options an effective, once-daily, alternative treatment to chemotherapy.

Impact in other cancers. In 2019, the phase 3 POLO trial in pancreatic cancer showed that in metastatic pancreatic cancer patients with a germline *BRCA* mutation, progression-free survival was longer with maintenance olaparib (7.4 months) than with placebo (3.8 months). In December 2019, the FDA approved olaparib for the maintenance treatment of *BRCA*-mutated metastatic pancreatic adenocarcinoma, as detected by an FDA-approved test **[H]**. Pancreatic cancer is a deadly cancer with a high unmet medical need with approximately 460,000 new cases worldwide in 2018. There was previously no precision medicine treatment options for *BRCA*-mutated pancreatic cancer patients.

Based on the concept of BRCAness, genomic sequencing has revealed that mutations in HRR proteins occur in a significant proportion of metastatic castration-resistant prostate cancers (mCRPC). Data from the PROFOUND phase 3 clinical trial has shown the efficacy of olaparib in mCRPC and this led to approval of olaparib in mCRPC with HRR defects in May 2020 **[I]**. Before this approval, 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 worldwide in 2018. FDA have also approved another PARP inhibitor, rucaparib, in mCRPC.

Clinical development of other inhibitors targeting HRR proteins. The success of using PARP inhibitors to exploit synthetic lethality was a result of the ICR's underpinning research, and has led to renewed research interest in using these approaches to target other HRR proteins for cancer therapy. Some of the most promising targets are ATR and ATM. ATR is involved in sensing DNA damage and activating the DNA damage checkpoint and ATM is recruited and activated by DNA double-strand breaks. ATM and ATR inhibitors are being investigated as single agents, as well as in combination with chemotherapy, radiation therapy, PARP inhibition, and/or immunotherapy. Potent inhibitors of ATR activity in clinical development as of December 2020 include VX-970 (16 trials on clinicaltrials.gov), AZD6738 (30 trials) and BAY1895344 (8 trials). A phase 1 trial involving the ATM inhibitor AZD0156 is ongoing (NCT02588105) and there are 3 registered trials of AZD1390 (NCT03423628, NCT03215381, and NCT04550104) **[J]**.

Pharmaceutical industry impact. Multiple companies have developed PARP inhibitors, generating value through sales of approved drugs. As of 2020, olaparib (Lynparza) is approved in 78 countries for the treatment of ovarian cancer; 76 countries for the treatment of metastatic breast cancer, and in 55 countries for the treatment of pancreatic cancer. It is also approved in the US, the EU, and Japan for mCRPC. In 2020, AstraZeneca reported olaparib sales of over USD1,776,000,000 worldwide, compared to USD1,198,000,000 in 2019 **[H]**. Worldwide rights to talazoparib, originally developed by BioMarin Pharmaceutica, were acquired by Medivation in August 2015 for USD410,000,000, with additional payments of up to USD160,000,000 in royalties and milestones. In 2016, Medivation was acquired by Pfizer for USD14,000,000,000. In January 2019, GSK completed the acquisition of Tesaro for USD5,100,000,000. Tesaro was a commercial-stage biopharmaceutical company with a major marketed product, Zejula (niraparib), a PARP inhibitor approved in ovarian cancer **[K]**. Further, as PARP inhibitor therapies are given to patients with HRR mutations, a need for companion gene tests has emerged—to date the FDA has approved two BRCA tests as companion diagnostic devices (BRACAnalysis CDx and FoundationFocus CDxBRCA), providing further commercial impact.

5. Sources to corroborate the impact

A. Clinical trials of PARP inhibitors: https://academic.oup.com/nsr/article/4/4/576/3101040

B. AstraZeneca press release: https://www.astrazeneca.com/media-centre/press-releases/2014/lynparza-approved-us-fda-brca-mutated-ovarian-cancer-treatment-19122014.html

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

D. The Innovation Scorecard data on olaparib use: https://digital.nhs.uk/data-and-information/publications/statistical/nice-technology-appraisals-in-the-nhs-in-england-innovation-scorecard/to-march-2020

E. Cochrane systematic review: https://doi.org/10.1002/14651858.CD007929.pub3

F. 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

G. Pfizer press release: https://www.pfizer.com/news/press-release/press-release-detail/european_commission_approves_talzenna_talazoparib_for_patients_with_inherited_germline_brca_mutated_locally_advanced_or_metastatic_breast_cancer

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

I. Astrazeneca 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

J. Clinical trials involving ATM and ATR trials: https://clinicaltrials.gov/. Search for the following drugs under "other terms": AZD6738, BAY1895344, AZD0156 and AZD1390.

K. GSK press release: https://www.gsk.com/en-gb/media/press-releases/gsk-completes-acquisition-of-tesaro-an-oncology-focused-biopharmaceutical-company/