

Institution: University of Sheffield		
Unit of Assessment: A-01 Clinical Medicine		
Title of case study: PARP inhibitors as a therapeutic to treat BRCA-defective cancers		
Period when the underpinning research was undertaken: 2000–2005		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Thomas Helleday	Role(s) (e.g. job title): Chair of Translational Oncology	Period(s) employed by submitting HEI: 2000–2006; 2018–2020
Period when the claimed impact occurred: 2015–2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Sheffield University researchers developed a novel tailored therapy for some forms of cancer. This work showed, in 2005, the selective killing of a tumour using an inhibitor of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP) to induce synthetic lethality, heralding a new era in personalised cancer therapy. The discovery was patent-protected, and the development rights were sold to AstraZeneca. Following successful clinical trials, the resultant drug was licenced worldwide. Disclosure of the findings stimulated intense investment in research and development and has revolutionised approaches to cancer therapy. Currently four PARP inhibitors developed by several leading pharmaceutical companies are clinically approved for the treatment of various cancers, extending the progression-free survival for patients in 73 countries. The PARP inhibitor, <i>Lynparza</i>[®], developed by AstraZeneca has generated £1.2 billion in sales since 2017.</p>		
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>In 2001, Helleday showed that DNA double-strand breaks associated with DNA replication forks are predominantly repaired by homologous recombination (HR) involving a strand exchange mechanism in mammalian cells [R1]. In contrast to previous work showing PARP-1 causes increased sister chromosome exchange (SCE) (considered a sign of HR), Helleday demonstrated that HR following induction of a site-specific DSB reported by gene conversion is normal in PARP-1-inhibited cells [R2]. R2 also showed that inhibition or loss of PARP-1 increases spontaneous Rad51 foci formation (gene conversion and sister chromatid exchange are two alternative products of homologous recombination, both of which involve RAD51).</p> <p>Following this, Helleday hypothesised that loss of PARP-1 activity may increase the amount of endogenous or induced single strand breaks and that these may be converted into DSBs at replication forks, which may trigger SCE (homologous recombination). This was proven when the Helleday lab demonstrated that in the absence of exogenous DNA damage, a cell relies on HR to survive when replication forks collapse generating sister chromatid exchanges as a product [R3]. This publication also showed that lack of single strand break repair (SSBR) can cause HR to increase.</p> <p>It was these combined findings that led the team to test PARP inhibitors for treatment of BRCA deficient cells seen in [R4], as PARP is required for single strand break repair and BRCA for homologous recombination and are key to maintaining a cancer cell's viability. The team</p>		

proposed that cancer cells are dependent upon two DNA repair pathways in order to continue to replicate and grow leading to tumours. One pathway requires the PARP enzyme and the second depends upon BRCA2 with the pathways allowing redundancy in case one of the pathways fails. In cancer cells, if one of the pathways is lost, the other will still maintain the cancer's survival but if both pathways are lost, the cell will die. By treating BRCA-deficient cells with PARP inhibitors, the cells will apoptose through a process known as synthetic lethality.

A mouse model was used to demonstrate that BRCA2-deficient tumour cell growth was suppressed by PARP inhibition whilst cells that contained a working copy of the BRCA2 gene were unaffected [R4]. This evidenced the use of synthetic lethality as a therapeutic agent.

Based on these findings, the University of Sheffield filed a patent application in July 2003 for the use of PARP inhibitors as a targeted therapy for tumours in individuals with BRCA2 mutations [R5]. The patent has been granted in numerous countries, alongside the publication of the research [R4]. The patents were licensed to KUDOS therapeutics who, with researchers at Newcastle University and King's College London, developed Olaparib and were acquired by AstraZeneca in 2006.

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

University of Sheffield researchers are indicated in **bold**.

- R1.** Arnaudeau, C., Lundin, C., & **Helleday, T.** (2001). DNA double-strand breaks associated with replication forks are predominantly repaired by homologous recombination involving an exchange mechanism in mammalian cells. *Journal of Molecular Biology*, 307(5), 1235–1245. <https://doi.org/10.1006/jmbi.2001.4564>
- R2.** Schultz, N., **Lopez, E., Saleh-Gohari, N., Helleday, T.** (2003). Poly(ADP-ribose) polymerase (PARP-1) has a controlling role in homologous recombination. *Nucleic Acids Research*, 31(17), 4959–4964. <https://doi.org/10.1093/nar/gkg703>
- R3.** **Saleh-Gohari, N., Bryant, H. E., Schultz, N., Parker, K. M., Cassel, T. N., & Helleday, T.** (2005). Spontaneous Homologous Recombination Is Induced by Collapsed Replication Forks That Are Caused by Endogenous DNA Single-Strand Breaks. *Molecular and Cellular Biology*, 25(16), 7158–7169. <https://doi.org/10.1128/mcb.25.16.7158-7169.2005>
- R4.** **Bryant, H. E., Schultz, N., Thomas, H. D., Parker, K. M., Flower, D., Lopez, E., Kyle, S., Meuth, M., Curtin, N. J., & Helleday, T.** (2005). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*, 434(7035), 913–917. <https://doi.org/10.1038/nature03443>
- R5.** Patent: WO/2005/012524. Use of RNAi inhibiting PARP activity for the manufacture of a medicament for the treatment of cancer, **The University of Sheffield**. Publication date, 10/02/2005.

4. Details of the impact (indicative maximum 750 words)

Following successful phase II and III clinical trial completion using PARP inhibitor research from Sheffield, AstraZeneca was granted first in class drug status for Olaparib (*Lynparza*[®]). Since then, the status has been applied to eighteen versions of the PARP inhibitor, four of which are directly attributed to the Sheffield Patent: *Lynparza*[®], Niraparib, Rucaparib and Talazaparib [S1]. [Text removed for publication].

Building on those initial applications of PARP inhibitors, this work has led to a step-change in the development and accessibility of treatments for cancers with few options. In 2020 Nature Milestones cited R1 as a milestone in cancer research for personalised therapeutics [S3].

In 2014, *Lynparza*[®] became the world's first PARP inhibitor approved for use in America and Europe [S4]. This success led to further AstraZeneca investment, launching a collaboration with MSD UK to develop treatments for additional cancers with a BRCA mutation. *Lynparza*[®] has now had positive Phase III trial results in four different tumour types: pancreatic and prostate, as well as ovarian and breast [S5].

Initially indicated for the treatment of ovarian cancer, the successful trials led to *Lynparza*[®] expanding to further patient groups in 2017. It is now being prescribed by physicians in 73 countries for the treatment of multiple cancer types. This has increased progression-free survival time for an additional 15,000 patients [S6].

Increased survival of cancer patients worldwide

Germline BRCA1 and BRCA2 mutations account for 72% and 69% breast cancers in women by the age of 80. The BRCA1 mutation increases this risk of ovarian cancer from 1.3% to 44%, and for BRCA2 mutations, the risk increases to 17%. BRCA mutations also increase the risk of breast cancer in men as well as increasing the risk of prostate and pancreatic cancer. Clinical trials with PARP inhibitors have shown to delay progression by an average of 3 months compared to chemotherapy [S5].

Olaparib (*Lynparza*[®]) was approved for use in Europe (EMA) and the USA (FDA) in December 2014 and Japan in July 2018. In 2015, NICE approved the use of Olaparib and Niraparib for NHS ovarian cancer patients, who had had three or more courses of chemotherapy, through the National Cancer Drug Fund [S4].

In 2018, Olaparib became available through NHS prescription as a first-line maintenance therapy in BRCA-mutated, advanced ovarian, fallopian tube and peritoneal cancer. Olaparib also became the first FDA-approved treatment for patients with gBRCAm HER2-negative metastatic breast cancer [S4].

The phase III POLO trial explored the efficacy of *Lynparza*[®] as 1st-line maintenance monotherapy in patients with gBRCAm metastatic pancreatic cancer whose disease has not progressed on platinum-based chemotherapy. The trial determined that the median progression-free survival was significantly longer in the treatment group. POLO is the first positive phase III trial of any PARP inhibitor in a disease where there is a critical unmet medical need [S8] and has resulted in FDA approval for *Lynparza*[®] in the US for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated pancreatic cancer [S5].

The AstraZeneca sublicensing of the Sheffield patent has led to the development of PARP inhibitors from other pharmaceutical companies for use as treatment of BRCA-mutated ovarian,

fallopian tube, primary peritoneal and BRCA mutated breast cancers. Niraparib (GSK) and Talazoparib (Pfizer) have been approved for use in America since 2018 and Rucaparib (Clovis Oncology) was approved for use in America and Europe in 2019 [S1].

In Europe, the use of PARP inhibitors has been extended to ovarian, fallopian tube or peritoneal cancers to delay the next cycle of platinum chemotherapy, as well as increase survival.

Economic impact

Sales of *Lynparza*[®] in the census period have continued to increase each year and have exceeded \$1.2 billion in 2020 [S6]. AstraZeneca developed a strategic oncology collaboration with Merck (MSD UK) to expand the uses of *Lynparza*[®] to other forms of cancer [S7]. This collaboration, which involved MERCK buying 50% of *Lynparza*[®] for \$8.5 billion, has achieved phase III clinical trial success in BRCA-mutated pancreatic cancer, which has the worst survival rate of all common cancers [S7]. The collaboration went on to work with Myriad Genetics Inc on their BRACAnalysis CDx test to identify BRCA mutations in patients. This test is now used in the USA and Japan to better target PARP inhibitor treatment [S7].

The sublicensed patent enabled other companies to produce PARP inhibitors for additional cancer types. Tesaro's agreement with AstraZeneca contributed to the development of Niraparib launched in 2016 for the treatment of ovarian, fallopian tube and primary peritoneal cancers [S8]. In January 2019, GSK bought Tesaro, for \$5.1 billion, to strengthen their commercial oncology capability [S8].

The Sheffield group was recognised by Universities UK as one of the 2019 Nation's Lifesavers – the top 100 individuals or groups based in universities whose work is saving lives and making a life-changing difference to health and wellbeing [S9].

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

- S1. Current drug approvals report: table documenting current drug approvals.
- S2. [Text removed for publication].
- S3. Nature Milestones 2005 cited R1 as a milestone in cancer research for personalised therapeutics (<https://www.nature.com/immersive/d42859-020-00083-8/index.html>).
- S4. Regulatory approvals: UK NICE Guidance (TA598), Aug 2019 (<https://www.nice.org.uk/guidance/ta598>); USA FDA approvals for *Lynparza*[®] from Dec 2014 to May 2020 (<https://bit.ly/38yxklu>) and Europe EMA list of approval from Dec 2014 to May 2020 (<http://bit.ly/30EoVPp>).
- S5. List of *Lynparza*[®] trials and results showing increased progressions free survival (<http://bit.ly/38AYhLI>); SOLO Trial Results (Moore, K., et. al. (2018). Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine*, 379(26), 2495–2505. <https://doi.org/10.1056/nejmoa1810858>) and POLO Trial Results (Golan, T. et. al. (2019). Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. *New England Journal of Medicine*, 381(4), 317–327. <https://doi.org/10.1056/nejmoa1903387>).
- S6. Annual report of sales for AstraZeneca which contains *Lynparza*[®] sales to Q3 2020 (<https://www.astrazeneca.com/content/dam/az/PDF/2020/q3/Year-to-date-and-Q3-2020-results-announcement.pdf>).

Impact case study (REF3)

- S7.** AstraZeneca and Merck (MSD UK) with Myriad sponsored the POLO trial and BRACAnalysis CDx testing to be used in selecting patients for treatment (<http://bit.ly/30EpwAD> and <http://bit.ly/2OsjwLL>).
- S8.** GSK Press release on buying Tesaro 22 January 2019. PDF of webpage accessed 28/09/2020.
- S9.** Universities UK, 'The 'Nation's Lifesavers' – The exceptional 100 keeping us healthy' (<https://www.universitiesuk.ac.uk/news/Pages/the-nations-lifesavers.aspx>).