Institution: Newcastle University

Unit of Assessment: UoA1

Title of case study: Rucaparib targeted therapy for a range of cancers characterised by homologous repair deficiency

Period when the underpinning research was undertaken: 2010-2018

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:
Prof Ruth Plummer	Clinical Prof of Experimental Cancer Medicine	1/4/01 to present
Prof Nicola Curtin	Prof of Experimental Therapeutics	25/10/85 to present
Dr Yvette Drew	Clinical Senior Lecturer & Hon. Consultant in Medical Oncology	1/12/06 to present
Emeritus Prof David Newell	Prof of Cancer Therapeutics	1/10/89 to 30/6/16
Mr Huw Thomas	Senior Research Associate	1/4/03 to present
Mrs Suzanne Kyle	Senior Technician	1/4/03 to present
Dr Christopher Jones	Clinical Research Associate	06/1/03 to 5/4/05
Prof Alan Boddy	Prof of Cancer Pharmacology	1/1/03 to 31/3/16
Prof Hilary Calvert	Prof of Medical Oncology	1/7/89 to 5/9/09
Dr Julie-Anne Sludden	Senior Research Associate	1/9/99 to 30/9/20
Dr David Jamieson	Senior Research Associate	1/7/06 to present
Dr Evan Mulligan	Research Associate	9/11/09 to 6/5/11
Dr Asima Mukhopadhyay	Hon. Clinical Senior Lecturer	15/7/13 to present
Prof Richard Edmondson	Hon. Clinical Prof	1/10/13 to 30/4/18
Dr Aiste Cerbinskaite	Clinical Research Associate	3/8/11 to 8/6/15
Miss Sarah Wilkinson	Research Assistant	1/11/09 to 29/1/17
Emeritus Prof Barbara Durkacz	Prof of Experimental Cancer Therapeutics	1/8/08 to 31/1/10
Dr Rachel O'Donnell	Honorary Clinical Senior Lecturer	1/4/16 to present
Mrs Lan-Zhen Wang	Technician	1/10/03 to present
Dr Tomasz Zaremba	PhD Student	1/2/07 to 30/9/09
Dr Samra Kahn	Clinician	2011 to 2013
Dr Ahmed Elattar	Clinician	2007 to 2010
Dr San Soohoo	Clinician	2011 to 2013
	Additionally, 1 clinician, 1 technician, 11 PhD students and 2 undergraduate students supported this research	

Period when the claimed impact occurred: 2015–present

Is this case study continued from a case study submitted in 2014? Yes

The REF2014 case presented Newcastle-led development of the first-in-class PARP inhibitor rucaparib, treatment of the first cancer patients in clinical trials (led by Newcastle) and worldwide investment in several PARP inhibitor programmes for germline breast and ovarian cancers.

Advances since 2014: FDA, EMA and NICE approval of rucaparib for germline and somatic ovarian cancers following clinical trials with key Newcastle involvement; clinical testing expanded to other homologous repair deficient cancers, informed by Newcastle research, leading to FDA approval for germline and somatic prostate cancer; increased number of clinical trials using rucaparib resulting in >9,000 patients outside of the original indication receiving cancer treatment; economic impacts to Clovis Oncology, global licence holders of rucaparib, from revenue generated by sales since 2016.

1. Summary of the impact

Newcastle research, reported in REF2014, led to the first-in-class PARP-inhibitor rucaparib. Further Newcastle research and industry clinical trials, involving Newcastle, has shown rucaparib to be successful in treating many cancers driven by somatic *BRCA* and similar mutations resulting in homologous repair deficiency. Thus rucaparib has achieved FDA and EMA approval and NICE recommendation for germline and somatic ovarian, peritoneal and fallopian tube cancers and FDA approval for germline and somatic prostate cancer. Approximately 43,000 units of rucaparib have been sold, driving increases in revenue for Clovis Oncology, the global licence holders of rucaparib, and an additional 9,000 patients receive rucaparib through international clinical trials.

2. Underpinning research

Unmet need: several cancers are linked to BRCA mutations

In the UK, the annual incidence of ovarian cancer is 11.7 per 100,000[1] and the risk is increased by *BRCA1* and *BRCA2* mutations by up to 63% and 27%, respectively[2]. In addition, these mutations have been observed to increase the risk of other cancers including fallopian tube and peritoneal cancer[3]. *BRCA* mutations also increase the risk of prostate cancer, the most common cause of cancer death in UK men (annual incidence = 79.1 per 100,000[1]). Though the relative risk for prostate cancer in *BRCA2* carriers is greater than that of *BRCA1* carriers (RR = 4.65 and RR = 1.82 respectively)[2]. The breadth of cancers caused by *BRCA* mutations means that a drug effective against these mutations would benefit a wider number of people.

Homologous repair, PARP1 inhibition and rucaparib

BRCA genes encode DNA repair proteins and are involved in homologous recombination repair (HRR), a DNA repair mechanism which repairs damage caused by the presence of single strand breaks during cell replication. Mutations in *BRCA* genes lead to errors in DNA repair resulting in the cells becoming homologous repair deficient (HRD) and enabling tumour development. Although HRD tumours lack DNA repair via homologous recombination they retain the PARP1 (poly ADP ribose polymerase) enzyme which repairs single strand breaks. Therefore, inhibiting the PARP enzyme removes the cell's ability to repair single strand breaks resulting in lesions in replicating cells and cell death. This process is termed synthetic lethality and makes PARP inhibition (PARPi) an effective and specific cancer treatment for all HRD tumours. Newcastle research, in collaboration with Cancer Research UK and Agouron Pharmaceuticals, led to the development of rucaparib, the first-in-class PARP inhibitor.

Development of rucaparib

Newcastle research identified and confirmed the effectiveness of PARP inhibitors through both laboratory investigation and clinical trials, culminating in rucaparib being used as the first PARP inhibitor to treat a cancer patient in a clinical trial setting. Since 2014, further Newcastle laboratory and clinical research has confirmed the safety of rucaparib in treating ovarian cancer (R1, R2, R3, R4) and identified that any HRD tumours can be the target of PARPi (R5, R6, R7) thereby increasing the number of patients who may benefit from PARPi therapy.

Newcastle research using functional assays showed that >50% of ovarian cancers are HRD (R6). Newcastle testing showed that 92.8% of the HRD primary ovarian cancer cultures treated with rucaparib had a 2-fold reduction in cell survival. In contrast, the HRR-competent cultures remained viable when treated with rucaparib (R6). Additionally, HRR status correlated with survival in platinum-treated patients, with either ovarian or non-ovarian cancer, suggesting a wider application of PARPi to other cancer types (R7). This research was followed by success in ovarian cancer clinical trials involving Newcastle (see section 4). In consequence, Clovis Oncology, the

[1] Cancer Research UK, cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence#heading-Zero and cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/incidence#heading-Zero, Accessed October 2020.

[2] Levy-Lahad E and Friedman E. (2007) Cancer risks among BRCA1 and BRCA2 mutation carriers. *British Journal of Cancer*. 96(1):11–15. DOI: 10.1038/sj.bjc.6603535.

[3] Finch MS, et al. (2006) Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. *JAMA*. 296(2):185-92. DOI: 10.1001/jama.296.2.185.

worldwide licence holders of rucaparib, expanded its scope to other HRD cancers, particularly prostate cancer.

3. References to the research

SciVal field-weighted citation impact (FWCI) as of December 2020. Newcastle researchers in **bold**.

R1. **Drew Y**, … **Sludden J**, **Murray J**, **Jamieson D**, … **Boddy A**, **Curtin N**, **Plummer R**. (2016) Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer. *British Journal of Cancer*. 114(7):723-30. DOI: 10.1038/bjc.2016.41. FWCI: 5.64.

R2. Wilson RH, … **Plummer R**. (2017) A phase I study of intravenous and oral rucaparib in combination with chemotherapy in patients with advanced solid tumours. *British Journal of Cancer.* 116(7):884–892. DOI: 10.1038/bjc.2017.36. FWCI: 2.66.

R3. Shapiro GI, … **Drew Y**, … Xiao JJ. (2018) Pharmacokinetic Study of Rucaparib in Patients with Advanced Solid Tumors. *Clin Pharmacol Drug Dev*. 8(1):107-118. DOI: 10.1002/cpdd.575. FWCI: 2.39.

R4. Kristeleit R, … **Drew Y**, … Shapira-Frommer R. (2017) A Phase I-II Study of the Oral PARP Inhibitor Rucaparib in Patients with Germline BRCA1/2 Mutated Ovarian Carcinoma or Other Solid Tumors. *Clin Cancer Res*. 23(15):4095-4106. DOI: 10.1158/1078-0432.CCR-16-2796. FWCI: 8.21.

R5. **Drew Y**, **Mulligan EA**, **Vong WT**, **Thomas HD**, **Kahn S**, **Kyle S**, **Mukhopadhyay A**, … **Plummer ER**, **Edmondson RJ**, **Curtin NJ**. (2011) Therapeutic potential of poly(ADP-ribose) polymerase inhibitor AG014699 in human cancers with mutated or methylated BRCA1 or BRCA2. *J Natl Cancer Inst*. 103(4):334-46. DOI: 10.1093/jnci/djq509. FWCI: 6.43.

R6. **Mukhopadhyay A, Elattar A**, **Cerbinskaite A**, **Wilkinson SJ**, **Drew Y**, **Kyle S**, … **Edmondson RJ**, **Curtin NJ**. (2010) Development of a functional assay for homologous recombination status in primary cultures of epithelial ovarian tumor and correlation with sensitivity to poly(ADP-ribose) polymerase inhibitors. *Clin Cancer Res*. 16(8):2344-51. DOI: 10.1158/1078-0432.CCR-09-2758. FWCI: 4.69.

R7. **Mukhopadhyay A**, **Plummer ER**, **Elattar A**, **Soohoo S**, **Uzir B**, … **Aneke H**, **Curtin NJ**, **Edmondson RJ**. (2012) Clinicopathological features of homologous recombination-deficient epithelial ovarian cancers: sensitivity to PARP inhibitors, platinum, and survival. *Cancer Res*. 72(22):5675-82. DOI: 10.1158/0008-5472.CAN-12-0324. FWCI: 1.59.

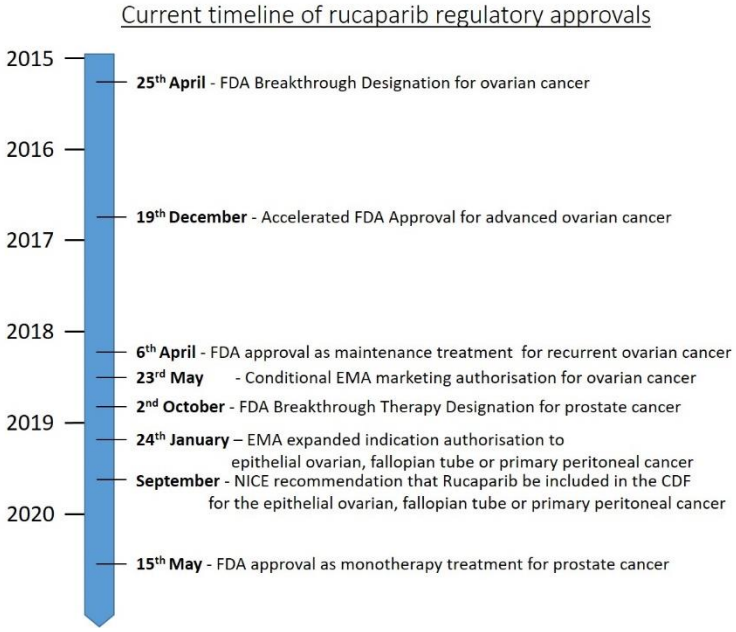
4. Details of the impact

Regulatory impacts for rucaparib

Between 2014 and July 31st 2020, rucaparib secured FDA, EMA and NICE regulatory approvals for ovarian, fallopian tube, peritoneal and prostate cancers, caused by both germline and somatic *BRCA* mutations (see diagram and EV1). In Europe, rucaparib was approved for use in 2019 by the EMA and within the Cancer Drugs Fund by NICE for the "*treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy*" (EV1). In the US, rucaparib was approved in 2019 by the FDA for the maintenance treatment of "*adult patients with deleterious BRCA mutation (germline and/or somatic) associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies*" (EV2).

The initial Breakthrough FDA approval for rucaparib (EV3) was underpinned by two clinical trials, Study 10 (clinicaltrial.org ID: NCT01482715) and ARIEL2 (NCT01891344), both of which had Newcastle input: the President and CEO of Clovis Oncology stated "*Newcastle expertise was… essential to the successful completion of Study 10 and ARIEL2 clinical trials demonstrating rucaparib's safety and efficacy and which ultimately informed regulatory approval decisions."*

(EV3). Study 10 was the first phase I–II study to evaluate single agent oral rucaparib at multiple doses (R3, R4). Results showed that *"Rucaparib was tolerable and had activity in patients with platinum-sensitive germline BRCA1/2–mutated [High-grade Ovarian Carcinoma]*" (R4). EMA and NICE approval of rucaparib were informed by the subsequent ARIEL3 clinical trial (NCT01009190).



Showing that rucaparib was effective against all HRR deficient tumours expanded the potential targets for therapy. This gave confidence to Clovis to trial rucaparib in prostate cancer and other solid tumours with HRR mutations (as confirmed by the CEO, EV3). The subsequent TRITON2 clinical trial (NCT02952534) led to 2020 FDA approval of rucaparib for the treatment of adult metastatic castration-resistant prostate cancer patients with deleterious germline and/or somatic *BRCA* mutations (EV2, EV4). Regulatory approval for rucaparib in prostate cancer expands its application to a greater population of patients with *BRCA* mutations.

Impact on patients

Clinical trials are often the only way cancer patients can receive novel non-chemotherapeutic treatment. As of July 2020, approximately 9,000 patients have received rucaparib through various clinical trials, including 136 as part of Study 10, 493 as part of ARIEL2, and 375 patients (breast, ovarian/peritoneal, and other primary cancers) as part of ARIEL3 (EV5). In addition, ovarian cancer patients are receiving rucaparib through the ongoing international phase III ARIEL4 (NCT02855944) and ATHENA (NCT03522246) trials, testing rucaparib versus chemotherapy and rucaparib in combination with nivolumab. ARIEL4 aims to recruit 345 patients (EV6) while the ATHENA trial completed recruitment of 1,000 patients in June 2020 (EV7).

Following the success of trials in ovarian, fallopian tube and peritoneal cancer, the Clovis-run TRITON2 trial investigated rucaparib in 360 prostate cancer patients (EV6). Patients showed an objective response rate of 53.6%, i.e. a reduction in tumour size and/or number (EV8), ultimately informing the FDA approval of rucaparib for castration-resistant prostate cancer (EV4).

The efficacy of rucaparib is also being investigated in at least 49 other international clinical trials covering 13 cancers (including lung, pancreatic, and colorectal cancer), with a total recruitment target of 6,380 patients, including those with *BRCA1* and *2* mutations and other homologous recombination defects (EV6).

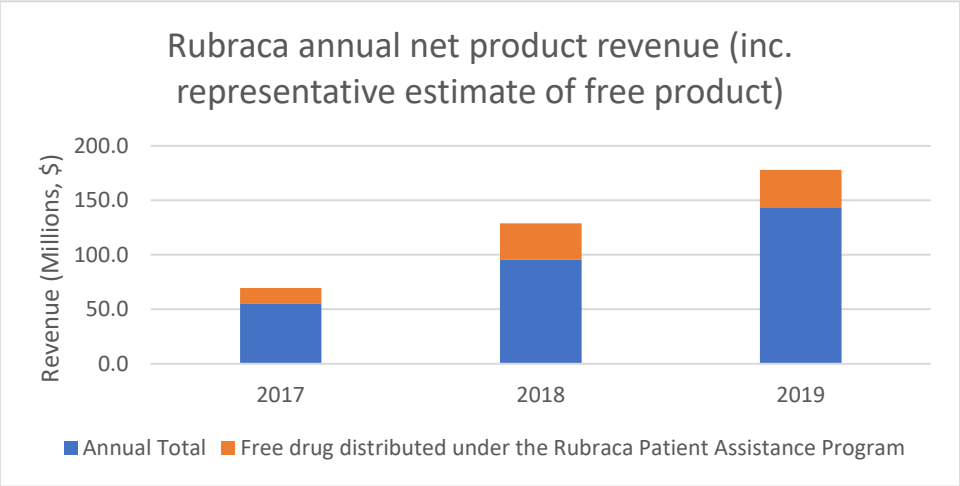
Economic impact on Clovis from sales of Rucaparib

In 2011, Pfizer sublicensed the worldwide rights of rucaparib to Clovis Oncology. Between 2016 and June 2020, Clovis Oncology reported $376.5M net product revenue for rucaparib (EV9). This equates to over 43,000 units of rucaparib with sales growing year on year (see graph below). As the first territory to gain approval (FDA approval, 2015), the US has seen sales of $288.2M (approx. 33,000 units), and sales are also growing in other countries with $5.8M (approx. 660 units) reported between January 2019 and June 2020 (EV9). Additionally, since 2017 Clovis has provided rucaparib free of charge to eligible patients in the US under its Patient Assistance Programme (EV4). An average of 20% of the US commercial supply of rucaparib (the equivalent of a further $82.3M or approx. 9,400 units), has been provided to patients free of charge who

otherwise would not be able to access the drug (EV4, EV9). The economic impact of rucaparib allows Clovis to employ 450 people in the US and Europe (EV4).

In summary

Rucaparib has been recognised as a leading PARP inhibitor for the treatment of ovarian, fallopian tube, peritoneal and prostate cancer. It is being provided as a treatment option for thousands of patients and its further development and application are being actively pursued by Clovis and other clinical institutions.



5. Sources to corroborate the impact

EV1. Combined FDA, EMA and NICE regulatory approval information, available on request.
EV2. Clovis Second quarter 2020 press release. PDF
EV3. Rubraca prescribing information. PDF. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s004lbl.pdf
EV4. Clovis Press Release - FDA prostate cancer Breakthrough Therapy Designation. PDF. https://s22.q4cdn.com/778348918/files/doc_news/Clovis-Oncology-Receives-Breakthrough-Therapy-Designation-for-Rubraca-rucaparib-for-Treatment-of-BRCA12-Mutated-Metastatic-Castration-Resistant-Prostate-Cancer-mCRPC.pdf
EV5. Statement Letter from Clovis Oncology. PDF available on request
EV6. Clinicaltrials.org search (January 2021) of other clinical trials using rucaparib. PDF
EV7. Clovis Press Release – Clovis announce completion of target enrolment in the ATHENA phase 3 trial. PDF. https://ir.clovisoncology.com/investors-and-news/news-releases/press-release-details/2020/Clovis-Oncology-Announces-Completion-of-Target-Enrollment-in-the-ATHENA-Trial-a-Phase-3-Maintenance-Treatment-Study-in-Front-line-Newly-Diagnosed-Advanced-Ovarian-Cancer/default.aspx
EV8. Abida W, et al. (2019) – Preliminary results from the TRITON2 study of rucaparib in patients with DNA damage repair-deficient metastatic castration-resistant prostate cancer. *Annals of Oncology*. 30(5):327-328. DOI: 10.1093/annonc/mdz248.
EV9. Financial data collected from combined Clovis Oncology operating reports (annual reports for 2016, 2017, 2018 and 2019 and 2020 2nd Quarter operating results), available on request.