Institution: King's College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: The development of "personalised treatments" for *BRCA1* and *BRCA2* associated breast and ovarian cancers using PARP inhibitors to prolong life

1. Summary of the impact

Work by Professor Andrew Tutt at King's College London (KCL), has had the following major impacts: (i) it has provided proof through first-in-man clinical trials (in collaboration with the Royal Marsden/ICR Phase I Clinical Trials Unit) and Phase II clinical trials designed and led by Professor Tutt that poly(ADP ribose) polymerase (PARP) inhibitors have an anti-cancer action in breast and ovarian cancers with *BRCA* mutations; (ii) it has demonstrated that the concept of 'synthetic lethality' can be applied to the selective targeting of cancer cells in humans; (iii) it has paved the way for a major programme of investment by the pharmaceutical industry (over $1 billion to date) in PARP inhibitors for the treatment of *BRCA*-related cancers (which are currently being tested in a range of cancers in Phase III trials); and (iv) it has been incorporated into UK, European, US and other international guidelines on genetic testing for breast and ovarian cancers that run in families.

2. Underpinning research

Background: About 10% of women with cancer of the ovaries and up to 5% of women with breast cancer carry a mutation in the genes *BRCA1* or *BRCA2*. These genes are key components of a pathway that repairs double-strand breaks in the DNA molecule. Cells carrying this mutation cannot repair double-strand DNA breaks. However, they still possess a single-strand repair mechanism, which uses the enzyme poly(ADP-ribose) polymerase (PARP).

KCL researchers contribute to the laboratory discovery that PARP inhibition is lethal to mutated cells: Working with Professor Alan Ashworth at the Institute of Cancer Research (ICR), Andrew Tutt (KCL / Guy's and St Thomas' NHS Foundation Trust [GSTFT]; 2001 - date) and co-workers showed in underpinning laboratory studies in cancer models with *BRCA1* or *BRCA2* mutation, that inhibiting PARP disables the single-strand repair mechanism and kills the mutated cancer cells (1, 2). Cell-killing results from the combination of the two non-lethal repair defects, a concept known as 'synthetic lethality'. Normal cells are better able to survive PARP inhibition. These findings indicated that PARP inhibitors that target and kill *BRCA*-deficient cells might be useful as a cancer treatment in patients with these mutations, while leaving normal tissues unaffected (3). This laboratory work was carried out at ICR while Andy Tutt was employed by GSTFT/KCL.

KCL researchers lead the development of PARP inhibitors for use in patients with BRCA-related cancer: Up until then, knowledge that a patient had a *BRCA* mutation had not affected their treatment, because no treatments specifically targeted to the mutation were available. PARP inhibition is an example of "personalised medicine", in which treatment is tailored to individual patients based on the genetic or other characteristics of their disease.

After proving the concept in the laboratory, Andrew Tutt moved back to GSTFT/KCL in 2003 and led the subsequent clinical trial development process of testing PARP inhibitors in patients. Andrew Tutt and colleagues developed the rationale, designed the trial protocols and conducted a series of clinical trials testing PARP inhibitors in patients with breast and ovarian cancers associated with *BRCA1* and *BRCA2*. This work ran from the first tests using human subjects (known as "first-in-man trials") to proof-of-concept Phase II trials. The first-in-man trials were designed by Professor Tutt at KCL and the Royal Marsden/ICR Phase I Clinical Trials Unit, and were conducted at the Royal Marsden/ICR from 2005 to 2007. The drug used was Kudos Pharmaceuticals' PARP inhibitor, which was then named olaparib and licensed to Astra Zeneca as a result of this first clinical data published in the New England Journal of Medicine (4).

KCL researchers demonstrate anti-cancer activity of PARP inhibitors in patients with BRCA-related tumours: Andrew Tutt then led, as global chief investigator, an international team that conducted two proof-of-concept Phase II trials from 2007 to 2009 to assess how effective and how safe olaparib is for treating advanced *BRCA1*/*BRCA2* ovarian or breast cancer (5, 6). These studies, funded by Astra Zeneca and Kudos Pharmaceuticals, were both published in the Lancet, and demonstrated a significant anti-cancer activity for olaparib in patients carrying *BRCA1* and *BRCA2* mutations with either breast cancer (5) or ovarian cancer (6). They were amongst the top ten most highly cited Lancet publications of 2010.

This KCL research has led to substantial investment by the pharmaceutical industry in PARP inhibitors for the treatment of a range of cancers in phase II and III trials. In addition, the need for genetic testing for breast and ovarian cancers that run in families has now been incorporated into UK, European, US and other international guidelines since the identification of *BRCA* mutations now affects clinical trial eligibility and the patient's treatment.

3. References to the research

PARP inhibition and DNA damage repair

1. 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. Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy. *Nature*. 2005;434:917–21.

2. 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) polymeraseinhibition. *Cancer Res*. 2006; 66:8109-15.

3. **Tutt AN**, Lord CJ, McCabe N, Farmer H, Turner N, Jackson SP, Smith GC, Ashworth A. Exploiting the DNA repair defect in *BRCA* mutant cells in the design of new therapeutic strategies for cancer. *Cold Spring Harbour Symposia Quantitative Biology*. 2005;70:139–48.

Phase I first-in-man trials

4. Fong PC, Boss DS, Yap TA, **Tutt AN**, **Wu P**, Mergui-Roelvink M, et al. Inhibition of poly(ADP-Ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009;361:123–34.

Phase II proof-of-concept trials

5. **Tutt A**, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, Friedlander M, Arun B, Loman N, Schmutzler RK, Wardley A, Mitchell G, Earl H, Wickens M and Carmichael J. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. *Lancet*. 2010;376:235-44.

6. Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, Scott C, Weitzel JN, Oaknin A, Loman N, Lu K, Schmutzler RK, Matulonis U, Wickens M, **Tutt A**. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial.. *Lancet*. 2010: 376:245-51.

4. Details of the impact

Translation of laboratory research to the clinic: Professor Tutt and colleagues demonstrated in preclinical and clinical trials that the *BRCA1* or *BRCA2* DNA repair defect that occurs in tumours can be exploited by targeting the DNA repair functions of PARP-1. This has been recognised as a first demonstration of the clinical usefulness of the long-described principle of **synthetic lethality**. This landmark in the development of "personalised treatment" for cancer has been recognised by many high profile articles and commentaries in leading journals such as the *New England Journal of Medicine, Cell*, and the *Lancet* (7), which cited both the preclinical and clinical studies described in Sections 2 and 3 above.

KCL research promotes substantial financial investment in large phase III clinical trials of PARP inhibitors: Following the proof-of-concept and Phase II clinical trials led by Professor Tutt's team at KCL/GSTFT, PARP inhibition has been recognised as a major avenue of research into new treatments for malignancies associated with *BRCA1/2*. Stimulated by the KCL-led trials, five pharmaceutical companies to date are initiating randomised Phase III clinical trials of different PARP inhibitors for the treatment of *BRCA*-related tumours (8-14). This amounts to a financial investment of well over $1 billion. Olaparib, the PARP inhibitor studied by Tutt and colleagues, is now being tested by Astra Zeneca in breast and ovarian cancer (8, 9). Other PARP inhibitors in planned clinical trials for *BRCA*-related cancers include rucaparib (Clovis Oncology [10]), niraparib (TESARO Inc. [11, 12]), BMN 673 (Biomarin [13]) and veliparib (Abbvie [14]). In addition, genetic testing for *BRCA* mutations is being incorporated as a companion diagnostic in many of these cancer trials [15].

KCL research alters national and international genetic testing guidelines: The KCL research by Professor Tutt and colleagues on *BRCA*-1 and *BRCA*-2 cancers has been incorporated into national and international clinical guidelines for the management of breast and ovarian cancer which mandate genetic testing for these mutations. These include national guidelines in the UK, France, Netherlands and Germany (16, 17); the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (18); and the US National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (19). The US NCCN guidelines are translated into multiple languages and adapted for use across the world, including China, Japan, the rest of Asia, Latin America, the Middle East, North Africa and Turkey. There has therefore been a far-reaching impact of this work.

Potential impact on treatment of *BRCA1/2* breast and ovarian cancers: Although only a small proportion of breast and ovarian cancers are associated with *BRCA1* and *BRCA2* mutation, the fact that breast and ovarian cancers are common means that a large number of patients may benefit from this new therapeutic approach – more patients than are diagnosed with Hodgkin's lymphoma or testicular cancer.

Potential impact in triple negative breast cancer (TNBC): TNBCs account for 12–15% of new breast cancers. They do not carry the oestrogen, progesterone or HER2 receptors that are the basis of targeted treatments for the majority of breast cancers. Chemotherapy is currently the only option for attempting to eradicate TNBC cells from the body. There is thus an unmet need for an effective targeted therapy against TNBC. Many TNBCs have key similarities to *BRCA1* mutation-related cancers, and appear to share an impaired response to DNA damage. PARP is also up-regulated in TNBC, suggesting that PARP inhibition could be used as part of the treatment of TNBC (20).

In 2008, the Breakthrough Breast Cancer Research Unit was opened at KCL with a £5 million award, dedicated to understanding TNBC subtypes and developing novel therapeutics for this disease. The KCL team are collaborating with the Breast International Group (BIG) and with pharmaceutical partners to develop clinical trials for TNBC.

5. Sources to corroborate the impact

Recognition of landmark in the development of personalized cancer treatment.

7. Iglehart JD, Silver DP. Synthetic lethality – a new direction in cancer-drug development. *N Engl J Med.* 2009;361:189–91
Carey LA, Sharpless NE. PARP and cancer – if it's broke, don't fix it. *N Engl J Med.* 2011;364:277–9;
Ashworth A, Lord CJ, Reis-Filho JS. Genetic interactions in cancer progression and treatment. *Cell*. 2011;145:30–8
Chan SL, Mok T. PARP inhibition in BRCA-mutated breast and ovarian cancers. *Lancet*. 2010;376:211-3.

Financial investment in PARP inhibitors

8. Olaparib in BRCA mutated Ovarian Cancer - Olaparib Monotherapy in Patients With BRCA

Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy. http://www.clinicaltrials.gov/ct2/show/NCT01844986

9. Olaparib in Patients With BRCA Mutated Platinum-Sensitive Relapsed Serous Ovarian Cancer: New Data Presented at ASCO http://online.wsj.com/article/PR-CO-20130601-902744.html

10. Pivotal Phase III study or Rucaparib in platinum-sensitive ovarian cancer patients starting in late 2013, as well as a biomarker study in platinum-sensitive ovarian cancer patients http://www.businesswire.com/news/home/20130603005476/en/Clovis-Oncology%E2%80%99s-Rucaparib-Demonstrates-Encouraging-Results-Ongoing

11. A Phase III Trial of Niraparib Versus Physician's Choice in Her2 Negative, Germline BRCA Mutation-positive Breast Cancer Patients (BRAVO) http://clinicaltrials.gov/ct2/show/NCT01905592

12. Phase III Trial of Niraparib in ovarian cancer http://www.allfordrugs.com/2013/07/29/tesaro-begins-phase-iii-trial-of-niraparib-for-treatment-of-ovarian-cancer/

13. BioMarin Provides BMN 673 Program Update http://www.reuters.com/article/2013/06/03/us-cancer-breast-biomarin-idUSBRE9520MA20130603 http://investors.bmrn.com/releasedetail.cfm?ReleaseID=780454 http://clinicaltrials.gov/ct2/show/NCT01945775

14. Abbvie plans Randomised Phase III trial of Veliparib in gBRCA Breast cancer in combination with temozolamide http://clinicaltrials.gov/show/NCT01506609

15. Myriad readying to take BRCA analysis into pivotal trial for AstraZeneca's Olaparib as companion diagnostic http://www.genomeweb.com/clinical-genomics/myriad-readying-take-bracanalysis-pivotal-trial-astrazenecas-olaparib-companion

Guidelines for the assessment of breast and ovarian cancer

16. National Institute for Health and Care Excellence. CG164 Familial Breast Cancer, 2013. http://guidance.nice.org.uk/CG164/

17. Gadzicki et al. Genetic testing for familial/hereditary breast cancer—comparison of guidelines and recommendations from the UK, France, the Netherlands and Germany. *J Community Genet*. 2011;2:53–69. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3186026/

18. BRCA in breast cancer: European Society for Medical Oncology (ESMO) Clinical Practice Guidelines. *Ann Oncol.* 2011;22 (suppl 6): vi31-34. http://annonc.oxfordjournals.org/content/22/suppl_6/vi31.full

19. US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast and ovarian. (V3.2013) http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf

20. Gelmon, KA et al. (2010) Can we define tumors that will respond to PARP inhibitors? A phase II correlative study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer. Journal of Clinical Oncology, 2010 ASCO Annual Meeting Proceedings Vol 28, No 15 (May 20 Supplement), 2010:3002.