Institution: University of Bradford

Unit of Assessment: A3

Title of case study: Apaziquone (EO9) as a new therapy for treating non-muscle invasive bladder cancer.

1. Summary of the impact

Bladder cancer is the fifth most common form of cancer, with over 70% of cases presenting as non-muscle invasive bladder carcinomas (NMIBC). Research in the Institute of Cancer Therapeutics at the University of Bradford led to the evaluation of Apaziquone (EO9) in phase II clinical trials against high risk NMIBC in The Netherlands, and two multi-centre phase III clinical trials involving 106 centres across the USA, Canada and Europe. A total of 1,746 patients with low or high risk NMIBC received EO9 and significant reductions in the rates of recurrence at two years have been reported. Our research has impacted upon the health and welfare of patients with NMIBC.

2. Underpinning research

The underpinning research was conducted at the Institute of Cancer Therapeutics (ICT) at the University of Bradford by a team of over 20 researchers. The research was led by Dr Roger Phillips (Lecturer 1996-2000, Senior Lecturer 2000-2003, Reader 2003-present) with notable contributions from John Double (Professor 1979-2003), Dr Paul Loadman (Lecturer 1996-2002, Senior Lecturer 2002-present), and a Consultant Urologist at Bradford Royal Infirmary.

In the mid 1990's Apaziquone (EO9) underwent clinical evaluation. The drug was administered intravenously but despite reports of three partial responses in the phase I study by Schellens *et al*. (*Journal of the National Cancer Institute*, 1994), neither partial nor complete responses were observed in phase II studies involving 130 patients with advanced breast, gastric, pancreatic, colorectal cancer and non-small cell lung cancer (Dirix *et al*., *European Journal of Cancer*, 1996; Pavlidis *et al*., *Annals of Oncology*, 1996). The lack of efficacy led investigators to conclude that EO9 was clinically inactive and it was abandoned.

Research conducted at the ICT identified the reason why intravenously administered Apaziquone failed and championed further research which resulted in substantial investment in clinical studies. Rapid pharmacokinetic elimination in conjunction with poor penetration through avascular tumour tissue suggested that delivery of Apaziquone to tumours was impaired (1). This result was fundamental as it demonstrated that the failure of Apaziquone was due to poor drug delivery (1,2). Direct intra-tumoural injection of Apaziquone into human tumour xenografts confirmed that significant tumour shrinkage occurred when Apaziquone was delivered directly to the tumour (3). The challenge therefore was to find a way to deliver Apaziquone.

The Bradford team reasoned that in bladder cancer, the 'negative properties' of Apaziquone could paradoxically be advantageous. Bladder cancer is a common disease and 70% of patients present with non-muscle invasive bladder carcinomas (NMIBC). Treatment is by surgery followed by a dose of chemotherapy administered directly into the bladder (intravesical administration). Intravesical administration of Apaziquone would circumvent the drug delivery problem and if any drug reached the blood supply, it would be rapidly eliminated (4). Apaziquone is enzymatically converted to cytotoxic metabolites and following the demonstration that human bladder cancers possess these enzymes (4), a phase I/II clinical pilot study was designed and conducted in Bradford, (2001 to 2006). Twelve patients with low grade NMIBC were treated with 6 doses of Apaziquone administered intravesically once per week. A total of 8 patients had complete histological responses to Apaziquone at doses that were well tolerated (5). A further phase II study using a multiple dose regimen was conducted independently in The Netherlands and 30 of the 46 patients treated had complete responses (van der Heijden *et al*., *Journal of Urology*, 2006).

Our research therefore provided the scientific rationale for conducting a further trial against NMIBC and demonstrated for the first time that Apaziquone was clinically active against NMIBC in humans at doses that were well tolerated. This underpinning research directly led to the impacts described in section 4.

3. References to the research

1. Phillips RM, Loadman PM, Cronin B. (1998) Evaluation of a novel in vitro assay for assessing drug penetration into avascular regions of tumours. *British Journal of Cancer* 77(12): 2112-2119.

2. Phillips RM. (1998) Prospects for Bioreductive Drug Development. *Expert Opinion on Investigational Drugs* 7(6): 905-928.

3. Choudry GA, Hamilton Stewart P, Brown JE, Double JA, Krul MRL, Naylor B, Phillips RM. (2001) A novel strategy for NQO1 (NAD(P)H:Quinone oxidoreductase, EC 1.6.99.2) mediated therapy of bladder cancer based on the pharmacological properties of EO9. *British Journal of Cancer* 85(8): 1137-1146.

4. Loadman PM, Bibby MC, Phillips RM. (2002) Pharmacological approach towards the development of indolequinone bioreductive drugs based on the clinically inactive agent EO9. *British Journal of Pharmacology* 137(5): 701-709.

5. Puri R, Palit V, Loadman PM, Flannigan M, Shah T, Choudry GA, Basu S, Double JA, Lenaz G, Chawla S, Beer M, van Kalken C, de Boer R, Beijnen JH, Twelves CJ, Phillips RM. (2006) Phase I/II pilot study of intravesical Eoquin (EO9) against superficial bladder cancer. *Journal of Urology* 176(4): 1344-1348.

Evidence of quality:
The papers are published in either multidisciplinary journals (two publications in *British Journal of Cancer* Impact factor 5.082, ranked 35 out of 196 in the Oncology category, one in *British Journal of Pharmacology* Impact factor 5.067, ranked 21 out of 260 in the Pharmacology and Pharmacy category and one in *Expert Opinion on Investigative Drugs*, Impact factor 4.744, ranked 25 out of 260 in the Pharmacology and Pharmacy category) or a specialist Urology journal (*Journal of Urology* Impact factor 3.69, ranked 10 out of 75 in the Urology category). Indices of quality were obtained from the Journal Citation Reports database.

Sources of funding:
All the pre-clinical studies were funded by core support from the charity Bradford's War on Cancer and Cancer Research UK (Program grant C459/A2579) awarded to Double, 2000 to 2005, £1.9m.

The phase I/II clinical pilot study was funded by Spectrum Pharmaceuticals (Irvine, California, http://www.sppirx.com). The grant (£81,850) funded the phase I/II clinical trial work conducted between 2001 and 2006 and the lead investigators were Puri (Bradford Royal Infirmary) and Phillips (Bradford University).

4. Details of the impact

Bladder cancer is a common disease with an estimated 12 cases per 100,000 people in the UK. Despite surgery and chemotherapy, 80% of patients with NMIBC will have recurrent disease within 5 years. This high rate of recurrence illustrates the need to develop novel treatments for NMIBC. Our underpinning research led to investment in further phase II trials in high risk NMIBC, safety studies of Apaziquone administered directly after surgery and Phase III clinical trials in low risk NMIBC where recurrence rate was the primary endpoint.

Recurrence rates from follow-up of patients in the pilot phase I/II and phase II studies were

published in 2009 (a,b). Both studies reported that early recurrence was rare (a,b) and that recurrence rates after two years of follow up was 49.5% (b). In a systematic review of 23 studies of treatment of low grade NMIBC involving 6 different cytotoxics and 6 immune response modifiers, the highest complete response rate was obtained with Apaziquone (c). Furthermore, 49.5% of complete responders were recurrence free two years after the start of treatment (b,c). Only ThioTEPA gave a higher recurrence free period but this was achieved at the expense of significant systemic toxicity (leukopenia, (c)). In summary, phase I/II studies using a multiple dosing regimen demonstrated that Apaziquone is clinically active against low risk NMIBC, had a favourable toxicity profile and in those patients that experienced a complete response, the disease free interval increased (a,b,c). In July 2009, Apaziquone was awarded 'fast track' status by the Food and Drug Administration (FDA) in the USA, a process designed to facilitate the development and approval of drugs used to treat serious diseases and fill an unmet medical need (d).

Two additional phase II clinical studies were conducted in The Netherlands (e,f). In the first of these studies (NCT00141531, started in August 2005 and completed in December 2009 (e)), 53 patients with high risk NMIBC were treated with multiple doses of Apaziquone administered intravesically. The recurrence rate after 12 months was 34.7% and these results were considered encouraging compared to the 61% probability of recurrence calculated by the EORTC for high risk NMIBC (e). In the second study (NCT01475266, started November 2011 and completed in 2012), a single dose of Apaziquone was administered within 6 hours of surgery (f), a protocol that is widely used in the treatment of low risk NMIBC. Twenty patients were treated using this protocol and the results demonstrated that Apaziquone was again well tolerated with minimal local side effects and no systemic side effects, a result that is consistent with the absence of detectable levels of Apaziquone in the peripheral blood of patients (f).

The successful phase I and II studies paved the way for two large, multi-centre phase III trials (g). The first, NCT00598806 (started in September 2007 and completed in December 2009) was conducted across 77 clinical centres in the USA, Canada and Poland with 813 patients and the second, NCT00461591 (started in April 2007 and completed in December 2009) across 74 medical centres across the USA with 802 patients enrolled. Both trials were sponsored by Spectrum Pharmaceuticals in partnership with Allergan Inc (Irvine California), an investment of more than $41.5m (h), and involved a single dose of Apaziquone administered intravesically within 6 hours of surgery. The results were recently reported on public domain websites (i) and the combined results of both studies reached significance at both the primary (recurrence rate at 2 years) and secondary (time to first recurrence) outcome measures (i). Following a meeting with the FDA (January 2013), Spectrum Pharmaceuticals announced that they expect to file for a New Drug Application and have also committed to conduct a further phase III trial (NCT01410565, (j)) using the multiple dosing schedule that was efficacious in phase II clinical trials.

To summarise, the original research from Bradford led to investment in clinical trials of Apaziquone that demonstrated clinical benefit in patients with low risk NMIBC, a disease for which no new therapies have been approved for the past twenty years. 1,746 patients have been treated with Apaziquone in medical centres across the UK, USA, Canada and Europe and patients who responded well typically experienced longer periods of remission compared to standard therapies for NMIBC. Furthermore, Apaziquone was well tolerated with low levels of drug-induced toxicity to the bladder and no systemic side effects reported. Further clinical trials are underway and a New Drug Application to the FDA is expected.

5. Sources to corroborate the impact

a. Jain A, Phillips RM, Scally AJ, Lenaz G, Beer M and Puri R. (2009) Response of multiple recurrent TaT1 bladder cancer to intravesical Apaziquone (EO9): Comparative analysis of tumour recurrence rates, *Urology* 73: 1083-1086.

b. Hendricksen K, van der Heijden AG, Cornel EB, Vergunst H, de Reijke TM, van Boven E, Smits GAHJ, Puri R, Gruijs S and Witjes JA. (2009) Two year follow up of the phase II marker lesion study of intravesical apaziquone for patients with non-muscle invasive bladder cancer.

World Journal of Urology, 27: 337-342.

c. Gofrit ON, Zorn KC, Shikanov S and Steinberg GD. (2010) Marker lesion experiments in bladder cancer – what have we learned? *Journal of Urology* 183: 1678-1685.

d. Details of the meeting between Spectrum and the FDA together with information about the new phase III clinical trial can be found at these public domain websites http://investor.spectrumpharm.com/releasedetail.cfm?ReleaseID=737020 and http://clinicaltrials.gov/show/NCT01410565

e. Hendricksen K, Cornel EB, de Reike TM, Arentsen HC, Chawla C and Witjes JA. (2012) Phase 2 study of adjuvant intravesical instillations of Apaziquone for high risk non-muscle invasive bladder cancer. *Journal of Urology* 187: 1195-1199. The following website provides details of the clinical trial that are linked to this publication: http://clinicaltrials.gov/ct2/show/NCT00141531?term=NCT00141531&rank=1

f. Hendricksen K, Gleason D, Young JM, Saltzstein D, Gershman A, Lerner S and Witjes JA. (2008) Safety and side effects of immediate instillation of Apaziquone following transurethral resection in patients with non-muscle invasive bladder cancer. *Journal of Urology*, 180: 116-120 The following website provides details of the clinical trial that are linked to this publication: http://clinicaltrials.gov/ct2/show/NCT01475266?term=NCT01475266&rank=1

g. Phase III clinical trial documentation provided by ClinicalTrials.gov, a service of the US National Institute of Health. Details of both clinical trials can be found at: http://clinicaltrials.gov/show/NCT00461591 and http://clinicaltrials.gov/ct2/show/NCT00598806?term=apaziquone&rank=4

h. This public domain website provides some details of the agreement between Spectrum and Allergan in relation to their plans to progress the clinical development of Apaziquone: http://investor.spectrumpharm.com/releasedetail.cfm?ReleaseID=395363

i. No formal publications of the single dose phase III clinical trials have been published in peer reviewed journals but the following public domain websites provide details:

http://www.businesswire.com/news/home/20120405005360/en/Spectrum-Pharmaceuticals-Announces-Results-Apaziquone-Phase-3

http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=4825

http://www.streetinsider.com/Corporate+News/Spectrum+(SPPI)+Pops+Higher+Following+Reacquisition+of+Apaziquone+Rights/8047788.html