Institution: Queen's University Belfast

Unit of Assessment: UoA3

Title of case study: Improving treatment and quality of life for patients with Prostate Cancer through clinical research.

Period when the underpinning research was undertaken: 2011-2016

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 Joe O'Sullivan	Clinical Professor	2004-2020
Prof Suneil Jain	Clinical Professor	2012-2020

Period when the claimed impact occurred: August 2013 – December 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Prostate cancer is now the most commonly diagnosed malignancy in the UK; 40,000 new cases and nearly 12,000 deaths estimated per year. Research at QUB has led and contributed to the following significant impacts:

- Contribution to the registration trial for the **first FDA-approved alpha particle** Radium-223 (Xofigo ®); resulting in **prolonged overall survival** and **improved quality of life** for men with metastatic castration resistant prostate cancer (mCRPC). Xofigo was licensed in 2013**;**
- Access for prostate cancer patients to advanced radiotherapies (within trials) and subsequent **introduction as standard care** to the Northern Ireland Health Service *i.e.,* SPORT and CHHiP
- **Influencing treatment guidelines** *i.e.,* European Society of Urology; European Society for Medical Oncology; Irish National Cancer Strategy and NICE

2. Underpinning research (indicative maximum 500 words)

In NI there are approximately 1,200 cases of prostate cancer diagnosed annually, of which 25% will die of metastatic disease. In response to this, Professor O'Sullivan (JOS), who has a joint appointment as Professor of Radiation Oncology at Queen's and was Director of Oncology at the Belfast Health and Social Care Trust (between 2014 and 2017), established the **Advanced Radiotherapy Group (ARG)** in 2004. This QUB-affiliated multidisciplinary group (including clinicians, nurses, laboratory scientists, radiophysicists and clinical trial specialists) aims to improve clinical outcomes for patients and is embedded in the Northern Ireland Cancer Centre. The ARG's research capabilities have been strengthened by additional clinical academic colleagues including Professor Suneil Jain (SJ) who is also a Senior Oncologist in the Cancer Centre. The ARG focusses on clinical trials of novel therapeutics in metastatic castration-resistant prostate cancer (mCRPC) and its precursor, metastatic hormone sensitive prostate cancer (mHSPC), as well as advanced radiotherapy in localised prostate cancer.

Clinical Trials of Radionuclide therapies

While treatment outcomes have improved significantly for localised prostate cancer, mCRPC remains a fatal condition responsible for the deaths of more than 11,000 men every year in the UK. Traditional chemotherapy treatments are not always effective in treating aggressive and advanced forms of prostate cancer, and mCRPC does not respond to castration therapy. The ARG's radionuclide therapy research, led by JOS, aims to treat mCRPC and has focused on two radiopharmaceuticals: Rhenium-186-HEDP and Radium-223 dichloride (Ra-223).

Rhenium-186 HEDP
The TAXIUM 1 trial (CI: JOS) was an international (UK and Netherlands) phase 1/2 trial which demonstrated tolerability and safety of a bone seeking beta radionuclide, Rhenium-186 hydroxyethyledine diphosphonate (Re-186 HEDP), combined with Docetaxel chemotherapy **[R1]**. A follow-on randomised trial, TAXIUM 2 (CI JOS), demonstrated no survival benefit for the combination and therefore did not progress further.

Radium-223 (Xofigo®)
Due to the ARG's experience in delivering TAXIUM 1 clinical trial, JOS was selected by the pharmaceutical company Algeta to be a local Principal Investigator in the phase 2 study (BC-104) of Ra-223 **[R2]**. Ra-223 (brand name **Xofigo®**) was proposed as novel alpha radionuclide treatment. Ra-223 is a "calcium mimetic" that, like calcium, accumulates preferentially in areas of bone that are undergoing increased turnover. The alpha particles have a narrow emission range (around 2-10 cell diameters) compared to beta particles, limiting damage to surrounding healthy tissues.
The phase 3 ALSYMPCA trial which demonstrated improved overall survival compared with placebo (14.0 months and 11.2 months, respectively) regardless of previous docetaxel-based chemotherapy use **[R3]**. This was the first radionuclide therapy to demonstrate survival benefit in a metastatic cancer of any type. JOS was CI on an International phase 4 trial (iEAP) of Ra-223 which suggested potential benefit of combination of Radium with Enzalutamide **[R4]**.

Clinical Trials of External Beam Radiotherapy
The ARG have made significant contributions to the development of radiotherapy technologies which have facilitated early adoption in the NHS in Northern Ireland, resulting in improved cure rates, reduced toxicity, and increased efficiency of radical radiotherapy.

CHHiP and CHHiP-IGRT Trials demonstrated equivalence of Hypofractionated radiotherapy (the delivery of fewer, larger doses of radiotherapy and for improving dose intensity) in localised prostate cancer using Intensity Modulated radiotherapy, IMRT (high-precision radiotherapy that uses computer-controlled linear accelerators to deliver precise radiation doses to specific areas within the tumour) and Image-Guided Radiotherapy, IGRT (use of imaging during radiation therapy to improve the precision and accuracy of treatment delivery) **[R5]**.

The 'SPORT trial' (A Study Evaluating Stereotactic Prostate Radiotherapy in High-Risk Localised Prostate Cancer), led by Professor Jain, was the first if its kind in the UK to use 'SABR' (Stereotactic Ablative Body Radiotherapy) to target tumours and deliver large doses per treatment, providing an opportunity for dose escalation beyond that achievable with conventional radiotherapy and allowing men to have their full course of radiotherapy in only five hospital visits instead of the typical 37. In addition, patients in the study were treated with SpaceOAR, a minimally invasive hydrogel technology, inserted prior to radiotherapy treatment which has been shown to significantly decrease unwanted radiotherapy side effects for patients **[R6].**

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

R1.van Dodewaard-de Jong, J. M., de Klerk, J. M. H., Bloemendal, H. J., van Bezooijen, B. P. J., de Haas, M. J., Wilson, R. H., and **O'Sullivan, J. M.** (2011) A phase I study of combined docetaxel and repeated high activity Re-186-HEDP in castration-resistant prostate cancer (CRPC) metastatic to bone (the TAXIUM trial), *European Journal of Nuclear Medicine and Molecular Imaging 38*, 1990-1998. https://doi.org/10.1007/s00259-011-1883-0

R2. Parker, C. C., Pascoe, S., Chodacki, A., **O'Sullivan, J. M**., Germa, J. R., O'Bryan-Tear, C. G., Haider, T., and Hoskin, P. (2013) A Randomized, Double-Blind, Dose-Finding, Multicenter, Phase 2 Study of Radium Chloride (Ra 223) in Patients with Bone Metastases and Castration-Resistant Prostate Cancer, *European Urology 63*, 189-197. https://doi.org/10.1016/j.eururo.2012.09.008

R3. Hoskin, P., Sartor, O., **O'Sullivan, J. M**., Johannessen, D. C., Helle, S. I., Logue, J., Bottomley, D., Nilsson, S., Vogelzang, N. J., Fang, F., Wahba, M., Aksnes, A. K., and Parker, C. (2014) Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate

cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial, *Lancet Oncology 15*, 1397-1406. https://doi.org/10.1016/S1470-2045(14)70474-7

R4. Saad F, Carles J, Gillessen S, Heidenreich A, Heinrich D, Gratt J, Lévy J, Miller K, Nilsson S, Petrenciuc O, Tucci M, Wirth M, Federhofer J, **O'Sullivan JM** (2016) Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial, *Lancet Oncology 17(9)*,1306-1316. https://doi.org/10.1016/s1470-2045(16)30173-5

R5. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, Graham J, Kirkbride P, Logue J, Malik Z, Money-Kyrle J, **O'Sullivan JM**, Panades M, Parker C, Patterson H, Scrase C, Staffurth J, Stockdale A, Tremlett J, Bidmead M, Mayles H, Naismith O, South C, Gao A, Cruickshank C, Hassan S, Pugh J, Griffin C, Hall E; CHHiP Investigators. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. 2016 Aug;17(8):1047-1060. https://doi.org/10.1016/S1470-2045(16)30102-4 Epub 2016 Jun 20. Erratum in: Lancet Oncol. 2016 Aug;17 (8):e321. PMID: 27339115; PMCID: PMC4961874.

R6. Lyons C, McGarry C, Hounsell A, Hynds S, Prise K, **O'Sullivan J**, **Jain S** (2016) SPORT high-risk trial: A randomised feasibility study evaluating stereotactic prostate radiotherapy in high-risk localised prostate cancer with or without elective nodal irradiation, *European Journal of Surgical Oncology* 42 (11), PS235 https://doi.org/10.1016/j.ejso.2016.07.076

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

Prostate cancer affects **1 in 9 men** in the UK, approximately 25% of whom will die from metastatic prostate cancer. Research from the ARG has meant that patients can benefit from participation in clinical trials. Those not involved in trials have benefitted from access to treatments that were not available as part of standard care. The research has also influenced clinical guidelines (locally and globally) and resulted in commercial impact through the development of Ra-223 treatment (Xofigo®).

Improving safety, efficacy, and efficiency of advanced radiotherapy in prostate cancer

The TAXIUM 1+2 trials (JOS -CI) demonstrated tolerability of Re-186 HEDP with Docetaxel, however there was no benefit on overall survival and this research strategy was discontinued, therefore averting further investment, and allowing full focus on Ra-223 a treatment for metastatic castration resistant prostate cancer.

The phase 2 (BC1-04) and phase 3 trials (ALSYMPCA) helped to determine the **safety profile** and **efficacy** of Ra-223 and were instrumental in the regulatory approval by **FDA** (May 2013) and **EMA** (September 2013). Ra-223 therapy was marketed as Xofigo®. The FDA reviewed Xofigo® under the agency's **priority review programme** and is the **first alpha radionuclide therapy** to be approved by the FDA **[S1]**. Following licensing of Xofigo, it was approved by NICE for treatment in the UK **[S2].**

Introduction of advanced radiotherapies into clinical practice in Northern Ireland

Radiotherapies that have been introduced as a result of clinical trials include Intensity Modulated Radiotherapy (IMRT) and Image-guided radiotherapy (IGRT). The table below demonstrates the increase in delivery of advanced radiotherapies in Belfast, the primary treatment centre for cancer patients from across Northern Ireland.

Ra-223 was introduced in 2006 as part of BC1-04 trial followed by ALSYMPCA in 2008. The drug was licensed in 2014 and NICE approved in 2016. Numbers decreased as a result of new toxicity

data from ERA-223 trial in 2018. At the peak, almost 300 treatments per year were administered in Belfast.

Year	IMRT	Stereotactic radiotherapy	Ra-223 treatment trials and non-trials)	Ra-223 treatment non-trials
2013	375	8	45	-
2014	622	22	5	4
2015	795	30	15	15
2016	908	54	230	185
2017	932	62	276	185
2018	1289	110	168	141
2019	1572	98	96	78
2020	2389	114	64	64

IMRT was introduced as part of the CHHiP trial in 2008. There has been steady increase in the use of this technology over the following 12 years increasing from 375 patients in 2013 to 2,389 in 2020. Now patients with multiple tumour types benefit from this therapy.**[S3]**

Skills gained in delivery of clinical trials have **built capacity of local healthcare staff** and encouraged the adoption of the cutting-edge techniques into routine practice. For example, Stereotactic Ablative Body Radiotherapy (SABR), an external beam radiotherapy which provides better tumour targeting, was introduced through the SPORT Trial as the **first if its kind in the UK** and led to **14 therapeutic radiographers** being trained in the technique **[S4].**

A patient involved in the SABR trial talks about how his life has improved **[S5]**

He said: *"If it wasn't for this research, I simply would not be here. My family and I are so thankful to the doctors who have helped us. This treatment has allowed me to live my life again."*
"I knew about the side effects of treatment, and they really frightened me, but this trial meant I had very little discomfort or complications and can return to normal life, for that I am very grateful."

Overall, 605 men have participated in prostate cancer clinical trials in NI since 1 August 2013 allowing access to novel treatments and improving their quality of life. **[S4]**

Metastatic prostate cancer moves to the bones in most patients and so the development of Ra-223, which specifically **targets the bone,** is a **breakthrough treatment**. The ALSYMPCA phase 3 trial, in which O'Sullivan was Northern Ireland lead, showed that patients treated with Ra-223 had a **median survival of 3.6 months** more than men treated with placebo **[S6]** with **an excellent safety profile** and a **6-month delay in skeletal events** (fractures or spinal compression) commonly associated with mCRPC **[S6].** Belfast was the biggest recruitment centre for the trial with **44 patients** recruited directly by JOS and colleagues. The NICE Radium-223 impact resource report 2016 estimated that around 360 people in England would receive Ra-223 each year **[S7]**.

Patients have also benefitted from early access to advance radiotherapy treatments introduced as a result of trials. For example, as a result of the CHHiP trial which tested hypofractionated radiotherapy there are now new recommendations for a new standard of care for men with prostate cancer. **Men now receive fewer treatments with the same results, leading to less disruption to their lives, including a reduction in hospital visits, with an average saving of 17 visits per patient.** It is estimated that this will save the **NHS in England at least GBP8,000,000 per year [S8]**. The use of IMRT, IGRT, and hypofractionated radiotherapy are now included in NICE guidance **[S9]**

Policy impact
ARG research underpinned the guidance for Ra-223 therapy at the national (NICE guideline TA412) **[S2,S9]** and international levels including the Irish Cancer Strategy, and guidance produced by the European Association of Urology and the European Society for Medical Oncology. **[S10].**

Commercial Impact

Ra-223 was co-developed by Algeta ASA and Bayer Schering Pharma AG in a collaboration that started in 2009. The success of the ALSYMPCA phase 2 and phase 3 trials brought economic benefit to Algeta ASA with the positive trial results leading to **acquisition** of Algeta by Bayer for a sum of **USD2,900,000,000** in December 2013 with Bayer claiming it was one of its top 5 most important cancer drugs at the time. **[S11].**

Xofigo is approved for use in more than **50 countries**, including the U.S., the European Union, China and Japan **[S12].** Bayer recorded sales of Xofigo of EUR270,000,000 in the 3rd quarter of 2018. **[S13]**

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

S1) Bayer's Xofigo® wins FDA approval for treatment of metastatic prostate cancer https://www.drugtopics.com/view/bayers-xofigo-wins-fda-approval-treatment-metastatic-prostate-cancer

S2) NICE Guidance Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases

S3) Radiotherapy statistics from Nuclear Medicine Team Belfast Health and Social Care Trust

S4) Prostate cancer trial statistics from Operations Director Northern Ireland Clinical Trials Network

S5) Patient quote about the benefit of SABR 2018 | Men with prostate cancer could benefit from new radiotherapy techniques | News | Queen's University Belfast (qub.ac.uk)

S6) Hoskin, P., Sartor, O., **O'Sullivan, J. M**., Johannessen, D. C., Helle, S. I., Logue, J., Bottomley, D., Nilsson, S., Vogelzang, N. J., Fang, F., Wahba, M., Aksnes, A. K., and Parker, C. (2014) Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial, *Lancet Oncology 15*, 1397-1406.

S7) NICE Radium-223 impact resource report https://www.nice.org.uk/guidance/ta412/resources/resource-impact-report-pdf-2670730669

S8) Article on the CHHiP Trial CHHiP trial | Reducing prostate cancer treatment burden (ncri.org.uk)

S9) NICE Guideline Prostate Cancer: Diagnosis and Management Overview | Prostate cancer: diagnosis and management | Guidance | NICE

S10) Multiple guidelines citing the research in one document

S11) Press release on Bayer acquisition of Algeta

S12) Web link Bayer: Prostate cancer drug approved in China - MarketWatch

S13) Bayer financial report 2018 (see page 11)