Institution: University of Plymouth		
Unit of Assessment: 1		
Title of case study: Improved outcomes for patients via new treatments for non-Hodgkin lymphoma.		
Period when the underpinning research was undertaken: **August 2013 - present**		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Simon Rule	**Role(s) (e.g. job title):** Clinical Professor	**Period(s) employed by submitting HEI:** 2013 - present
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)

Mantle cell lymphoma (MCL) is a rare and aggressive form of non-Hodgkin lymphoma. It is incurable with a poor outcome (2.4 yrs median overall survival in the UK in 2015). Prior to Professor Simon Rule's research, treatment consisted of chemotherapy where relapse was expected and drug resistance developed rapidly. Professor Rule's work led to adapted treatments with novel therapies that doubled the mean life expectancy of patients with MCL. His work was fundamental to the international licensing of Ibrutinib (90 countries worldwide) and the incorporation of the drug into all of the major guidelines for the treatment of the disease (American / European / British). To date, over 200,000 patients worldwide have been treated with Ibrutinib and generated sales in excess of $4.5 billion.

2. Underpinning research (indicative maximum 500 words)

Mantle cell lymphoma (MCL) is a rare and aggressive form of non-Hodgkin lymphoma that predominantly affects older men and has an average survival of 2.4 years. Treatment involves the use of chemotherapy, but relapse is inevitable and subsequent treatments, which usually involve alternative types of chemotherapy, have declining efficacy.

Professor Rule specialises in MCL and over the last 15 years has established the only MCL clinic in the UK, receiving referrals from all over the country. With this clinical insight he has designed and run a number of sequential trials exploring alternative approaches to the management of this disease, including:

- Exploring (in 2010) a range of non-chemotherapeutic approaches using single agent studies in MCL using Thalidomide, then Lenalidomide and the second generation anti-CD20 monoclonal antibody Ofatumumab. Rule's results demonstrated no real benefit for the use of ofatumumab, but activity was observed with thalidomide and the subsequent trial with lenalidomide demonstrated excellent long term responses when a dose-attenuated approach was applied as a maintenance strategy. This drug subsequently gained a license for the treatment of MCL in Europe and the USA.
- Two important follow-on multi-centre randomised trials, both showing survival benefits for the addition of an agent to standard chemotherapy. Trials with Rituximab [3.1] and Bortezomib [3.5] both showed that when added to conventional chemotherapy, there was a significant improvement in overall survival. Leading both studies, the trial with Rituximab was the definitive large randomised phase III trial (conducted in the UK and Australia) which demonstrated a survival advantage following the addition of rituximab to standard chemotherapy [3.1]. The trial was supported by Cancer Research UK (CRUK) and ran

from 2006 to 2012. The second randomised trial [3.5] demontrated that the addition of bortezomib to standard chemotherapy improved survival in the relapsed setting. A subsequent company-sponsored trial confirmed this effect when applied in the front line therapy and this combination is now licensed globally and NICE approved.

- Observing asymptomatic patients (Plymouth 2012 cohort) rather than treating immediately at diagnosis, a somewhat counter-intuitive approach in an aggressive form of cancer. This became adopted practice when population data from Scandinavia and British Columbia demonstrated that this new approach did not compromise survival.
- Establishing the largest biobank in the world of newly diagnosed patients managed from Plymouth. This contains data on over 600 patients together with their diagnostic specimens. The data has confirmed the clinical applicability of an observation strategy when applied across a population where just over 20% of patients have been observed for over two years without the need for any therapy. The samples from the two cohorts (immediate rather than delayed treatment) offer the possibility of finding a biomarker for indolent MCL. A programme of translational research is currently (Jan 2021) being evaluated within the NCRI translational science group.
- Early involvement with Pharmacyclics during their phase I trial with Ibrutinib. This demonstrated that Bruton's Tyrosine Kinase (BTK) inhibitors, which target cellular pathways (the B cell receptor pathway), appeared to be particularly effective for MCL. Professor Rule was involved in the design of a phase II trial for MCL patients only which demonstrated unprecedented activity and led to fast track license approval in 2013 in the USA of Ibrutinib in relapsed disease [3.2]. In Europe, where a randomised trial is required for registration, Professor Rule led the study which randomised Ibrutinib against Temsirolimus (the only licensed agent in MCL at that time). Rule's study showed a highly significant difference with respect to progression-free survival in favour of Ibrutinib [3.3].
- To date, there have been a total of three trials of Ibrutinib in MCL involving 370 patients. Professor Rule led an initiative between academic colleagues and the drug companies involved to pool all of the data to establish which patients derived the most benefit from this agent. This work clearly demonstrated that the earlier Ibrutinib was used in treatment, the more effective the drug was and the fewer associated side effects [3.4]. This led to the NICE approval of Ibrutinib at first relapse only, as that is where it is most cost effective.

The work is being extended in the ENRICH trial supported by CRUK and Janssen Pharmaceuticals with funding of ~£3M. This is the only trial in the world that is randomising Ibrutinib against chemotherapy (both groups with rituximab) as front line therapy and has the potential to fundamentally change the treatment paradigm for this disease. Whilst an academic study, this trial is currently with the FDA for consideration as the registration study for front line therapy.

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

3.1 The addition of Rituximab to Fludarabine and Cyclophosphamide chemotherapy results in a significant improvement in overall survival in patients with newly diagnosed mantle cell lymphoma: results of a randomized UK National Cancer Research Institute trial. **Rule S**, Smith P, Johnson PW, et al. Haematologica. 2016 Feb;101(2):235-40.

3.2 Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. Wang ML**,** **Rule S**, Martin P et al. N Engl J Med 2013 369:507-16.

3.3 Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Dreyling M, Jurczak W, Jerkeman M, …**Rule S.** Lancet. 2016;387:770–778.

3.4 Outcomes in 370 patients with mantle cell lymphoma treated with Ibrutinib: a pooled analysis from three open-label studies. **Rule S**, Dreyling M, Goy A, et al. Br J Haematol. 2017 179(3):430-438.

3.5 Addition of bortzomib to standard dose CHOP chemotherapy improves response and survival in relapsed mantle cell lymphoma. Furtado M, Johnson R, Kruger A, Turner D, **Rule S.** Br J Haematol. 2015 Jan;168(1):55-62.

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

Prior to the impacts described in this case, standard treatment for MCL was chemotherapy, the intensity of which depends on the age and fitness of the patient. However, the average age of presentation of MCL is over 70 years of age in the UK, which limits therapeutic options. Response rates are generally high with chemotherapy, but remissions are short and relapse is inevitable. Subsequent treatment, involving different forms of chemotherapy, is less active and resistance rapidly emerges.

The ultimate and most important benefit of Rule's work has been enhanced chances of survival and quality of life for over 200,000 MCL patients, including a doubling of the overall survival for patients diagnosed and managed in Plymouth compared to a matched population cohort from Yorkshire. In order to create this impact, Rule's work has underpinned improvements in global clinical guidelines including Europe, American and Britain and enabled commercial impact within drug manufacturing companies.

Creating improved clinical guidelines

Following the phase II trial in MCL (in 2013 [3.2]), which demonstrated unprecedented activity with Ibrutinib as a single agent, the FDA granted a license in the USA for relapsed MCL [5.1]. As a pre-eminent researcher in the field of BTK inhibitors, Rule was involved in the second-generation BTKi registration trials [5.2] of Acalabrutinib and Zanubrutinib [5.1]. The FDA have also recently licensed these treatments for MCL (in 2017 and 2019 respectively) [5.1].
In Europe, randomised trials are required by the EMA before a license can be granted. The randomised trial [3.3] that led to the EMA granting a license for the use of Ibrutinib in relapsed MCL was led by Rule. As a result of the Ibrutinib licence, over 200,000 patients have now been treated worldwide [5.3] and it is incorporated into all of the major guidelines, American (NCCN), European (ESMO) and British (BSH) [5.4]) and was NICE approved in 2018 [5.5].

The pooled analysis initiative clearly demonstrated that the earlier Ibrutinib was used in the treatment algorithm, the more effective the drug was and the fewer associated side effects [3.4]. This led to the NICE approval [5.5] in 2018 which was for the use Ibrutinib at first relapse only, as that is where it is most cost effective.

In summary, Rule's work has led to Ibrutinib being incorporated into all of the major global treatment guidelines [5.4] for this disease (European and American), and it has now been licensed in over 90 countries worldwide with over 200,000 patients treated [5.3].

Commercial benefits
Rule's work has played a major role in the change of MCL treatment algorithm to first use rituximab alongside chemotherapy treatments to increase their efficacy, in addition to the later use of Ibrutinib, Acalabrutinib or Zanubrutinib as single agents in relapsed MCL. Craig Tendler, M.D. Janssen Pharmaceuticals said, *"Professor Simon Rule, by way of his direct involvement as a clinical investigator in multiple global label enabling studies in mantle cell lymphoma and his thought leadership via study-related scientific publications, has contributed directly to the clinical development of ibrutinib."* [5.6]. The drug had over $4.5 billion sales worldwide in 2019 [5.3].

Improved patient survival and quality of life
Rule's 2016 work [3.1], leading the phase III trial of the addition of rituximab to traditional chemotherapy, demonstrated a doubling of progression-free survival (from 14.9 to 29.8 months) and an increase in average survival times by eight months. Although rituximab does not have a license in MCL, this data helped the NHS decision to allow rituximab as part of baseline commissioning for MCL and to incorporate this in subsequent NICE guidelines [5.7]

The 2012 work, to modify clinical approaches to MCL patients from “treat immediately” to “observe first”, was shown to have no detrimental impact on survivability [5.8] and has now been adopted as the standard approach in MCL and is NICE approved [5.7]. The avoidance of chemotherapy has obvious benefits with respect to greater quality of life and enhanced mental health. The large MCL biobank project run form Plymouth has confirmed at a population basis the benefits of an observation strategy, and with approximately 20% of patients requiring no treatment for over two years. This is a much higher percentage than has been observed before and attempts to establish a biomarker for this group are on-going.

The involvement from an early phase in the development of all of the BTK inhibitors as well as the other agents with licenses in MCL (especially lenalidomide and bortezomib) allowed UK access to these exciting drugs. Including the ENRICH trial, hundreds of UK patients have benefitted as a result and have experienced enhanced survival rates/quality of life as a result. Rule also helped pioneer a number of ‘second generation’ BTK inhibitors. These are more specific with respect to BTK inhibition and have fewer off target effects. The phase I trials in all of the major drugs of this type to date (including acalabrutinib, tirabrutinib and zanubrutinib) have been performed in Plymouth, with the first in human subjects being treated in Plymouth for two of these (tirabrutinib and Merck 7583). On-going randomised trials will formally assess the clinical as well as quality of life benefits between the various BTKi drugs, and the Plymouth based trial (ENRICH) will do the same when BTKi treatment is compared with chemotherapy.

Having access to all of these novel approaches and with over 60% of MCL patients presenting in Plymouth being enrolled into clinical trials within a specialist clinic, patient management is optimised. The outcomes of patients presenting in Plymouth has recently been analysed using a case matched population cohort from Yorkshire. The baseline demographics are identical but being diagnosed and managed in Plymouth results in a doubling of the overall survival rate [5.9]. This data has been used to inform worldwide major guidelines for the treatment of the disease

5. Sources to corroborate the impact

5.1 FDA licence for Ibrutinib as a single agent used for relapsed MCL and links to licenses Acalabrutinib and Zanubrutinib for MCL.
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process (under ‘Imbruvica’, for Ibrutinib, ‘Calquence’ for acalabrutinib and Brukinsa for zanubrutinib)

5.2 Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial.
Wang M, **Rule S**, Zinzani PL, Goy A, Casasnovas O, Smith SD, Damaj G, Doorduijn J, Lamy T, Morschhauser F, Panizo C, Shah B, Davies A, Eek R, Dupuis J, Jacobsen E, Kater AP, Le Gouill S, Oberic L, Robak T, Covey T, Dua R, Hamdy A, Huang X, Izumi R, Patel P, Rothbaum W, Slatter JG, Jurczak W.
Lancet. 2018 Feb 17;391(10121):659-667.

A phase 1/2 single arm, multicenter study evaluating zanubrutinib in relapsed or refractory mantle cell lymphoma
Constantine S. Tam, Stephen Opat, David Simpson, Gavin Cull, Javier Munoz, Tycel J. Phillips, Won-Seog Kim, **Simon Rule**, Siminder Kaur Atwal, Rachel Wei, William Novotny, Jane Huang, Michael Wang, and Judith Trotman
Currently in review at target journal

5.3 AbbVie Reports Full-Year and Fourth Quarter 2019 Financial Results (https://news.abbvie.com/news/press-releases/abbvie-reports-full-year-and-fourth-quarter-2019-financial-results.htm)

5.4 Drug Guidelines

(1) NCCN guidelines: https://www.nccn.org/professionals/physician_gls/default_nojava.aspx

(2) ESMO guidelines:
Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.
Dreyling M, Campo E, Hermine O, Jerkeman M, Le Gouill S, **Rule S**, Shpilberg O, Walewski J, Ladetto M; ESMO Guidelines Committee.
Ann Oncol. 2017 Jul 1;28(suppl_4):

(3) BSH guidelines:
Guideline for the management of mantle cell lymphoma.
McKay P, Leach M, Jackson B, Robinson S, **Rule S**.
Br J Haematol. 2018 May 16. doi: 10.1111/bjh.15283.

5.5 NICE approval of Ibrutinib in MCL. https://www.nice.org.uk/guidance/ta502

5.6 Testimonial - Craig Tendler, M.D. Vice President, Late Development & Global Medical Affairs, Oncology, Janssen

5.7 NICE. NG52 Non-Hodgkin's lymphoma:diagnosis and management. Published July 2016. Available at http://www.nice.org.uk/guidance/ng52.

5.8 Abrisqueta P, Scott DW, Slack GW *et al.* Observation as the initial management strategy in patients with mantle cell lymphoma. Ann Oncology 2017:2489-95.

5.9 Receiving treatment at a specialist centre confers an overall survival benefit for patients with mantle cell lymphoma. McCulloch R, Smith A, Crosbie N, Patmore R, Rule S.Br J Haematol. 2019 Jun;185(5):1002-1004.