Institution: The University of Manchester

Unit of Assessment: 1 (Clinical Medicine)

Title of case study: Access to more effective therapies for Non-Hodgkin Lymphoma

Period when the underpinning research was undertaken: January 2011 – July 2020

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:
Tim Illidge	Professor of Targeted Therapy & Oncology	2004 – present
John Radford	Professor of Medical Oncology	2007 – present
Jamie Honeychurch	Senior Lecturer Senior Research Fellow Research Fellow	2019 – present 2016 – 2019 2005 – 2016

Period when the claimed impact occurred: 1 August 2013 – 31 December 2020

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

1. Summary of the impact

University of Manchester (UoM) investigators were pivotal to the development of two novel therapies in Non-Hodgkin Lymphoma (NHL), increasing patient access to more effective, targeted drugs.

Brentuximab Vedotin in T cell NHL improved long-term survival in relapsed disease, was practice-changing and established a new standard of clinical care. Approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), it was recommended in UK and US clinical guidelines.

Obinutuzumab, a treatment for B cell NHL and chronic lymphocytic leukaemia (CLL), was approved with chemotherapy in 2017 by the EMA and FDA for untreated advanced follicular lymphoma (FL). It brought the first change to standard of care for over 10 years, offering a more effective patient treatment.

2. Underpinning research

Background

Brentuximab and Obinutuzumab are monoclonal antibodies. Brentuximab binds to CD30 antigens, found on some cancer cells. The antibody is conjugated with anti-cancer drug Vedotin. Because Brentuximab Vedotin (BV) binds specifically to CD30 on the cancer cells, 10-100 times higher exposure to the conjugated cytotoxic drug is possible than with conventional delivery. Obinutuzumab binds to CD20 in B cells allowing the body's immune system to target and destroy the marked cells. It is primarily used in combination with chemotherapy. Stem cells do not contain CD20 antigens, so healthy B cells can regenerate after treatment.

In **T cell NHL**, Illidge was the first investigator to use BV in the European Union (EU) and contributed to the Phase I and II trials [1] that preceded the phase III trial ECHELON-2 [2] (Illidge was European lead). Illidge was one of four international investigators who designed ECHELON-2, the largest randomised trial ever performed in T cell lymphomas, including over 600 patients [2]. It compared the standard first-line chemotherapy regimen CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) to an experimental arm of BV and CHP chemotherapy (cyclophosphamide, doxorubicin, prednisone). This was the first

ever study to demonstrate an improvement in overall survival of patients with T cell lymphomas: 34% reduction in death after 3 years.

The five-year outcomes from the initial phase I trial [1] demonstrated real benefits for the patients involved: progression-free and overall survival rates 52% and 80%, respectively. The final results demonstrated durable remissions in 50% treated with frontline BV+CHP, suggesting potentially curative treatment for some patients.

In **B cell NHL**, the Illidge laboratory discovered the mechanisms of action of novel anti-CD20 antibody (GA101, subsequently renamed Obinutuzumab), demonstrating the proof of principle that it was much more effective at killing target CD20 expressing tumour cells than the "standard" anti-CD20 antibody Rituximab [3,4]. Subsequent translation into clinical studies established Obinutuzumab as the new clinical standard used in routine practice in some B-cell malignancies. UoM investigator Radford was one of the clinical investigators to translate these preclinical findings and led the first phase I combination study of Obinutuzumab, in FL, the second most common of the B cell NHLs, demonstrating efficacy and safety (GAUDI trial) [5].

The superiority of Obinutuzumab over rituximab in CLL and FL has been demonstrated in international phase III studies, which have followed as a result of UoM's initial preclinical work. The large phase III international GALLIUM study [6] on which UoM investigator Radford worked demonstrated that Obinutuzumab led to significantly prolonged progression-free survival relative to standard of care (chemotherapy and Rituximab). At a median follow-up of 34.5 months, there was a 34% lower risk of progression, relapse, or death when treated with an Obinutuzumab regimen rather than the rituximab regimen.

3. References to the research

1. Fanale MA, Horwitz SM, Forero-Torres A, Bartlett NL, Advani RH, Pro B, Chen RW, Davies A, **Illidge T**, Huebner D, Kennedy DA, Shustov AR. Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. J Clin Oncol. 2014 Oct 1;32(28):3137-43. DOI:10.1200/JCO.2013.54.
2. Horwitz S, O'Connor OA, Pro B, **Illidge T**, Fanale M, Advani R, Bartlett NL, Christensen JH, Morschhauser F, Domingo-Domenech E, Rossi G, Kim WS, Feldman T, Lennard A, Belada D, Illés Á, Tobinai K, Tsukasaki K, Yeh SP, Shustov A, Hüttmann A, Savage KJ, Yuen S, Iyer S, Zinzani PL, Hua Z, Little M, Rao S, Woolery J, Manley T, Trümper L; ECHELON-2 Study Group. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019 Jan 19;393(10168):229-240.. Erratum in: Lancet. 2019 Jan 19;393(10168):228. DOI: 10.1016/S0140-6736(18)32984-2
3. Alduaij W, Ivanov A, **Honeychurch J**, Cheadle EJ, Potluri S, Lim SH, Shimada K, Chan CH, Tutt A, Beers SA, Glennie MJ, Cragg MS, **Illidge T**. Novel type II anti-CD20 monoclonal antibody (GA101) evokes homotypic adhesion and actin-dependent, lysosome-mediated cell death in B-cell malignancies. Blood. 2011 Apr 28;117(17):4519-29.. DOI: 10.1182/blood-2010-07-296913
4. **Honeychurch J**, Alduaij W, Azizyan M, Cheadle EJ, Pelicano H, Ivanov A, Huang P, Cragg MS, **Illidge T**. Antibody-induced nonapoptotic cell death in human lymphoma and leukemia cells is mediated through a novel reactive oxygen species-dependent pathway. Blood. 2012 Apr 12;119(15):3523-33. DOI: 10.1182/blood-2011-12-395541
5. **Radford J**, Davies A, Cartron G, Morschhauser F, Salles G, Marcus R, Wenger M, Lei G, Wassner-Fritsch E, Vitolo U. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood. 2013 Aug 15;122(7):1137-43. DOI: 10.1182/blood-2013-01-481341

6. Hiddemann W, Barbui AM, Canales MA, Cannell PK, Collins GP, Dürig J, Forstpointner R, Herold M, Hertzberg M, Klanova M, **Radford J**, Seymour JF, Tobinai K, Trotman J, Burciu A, Fingerle-Rowson G, Wolbers M, Nielsen T, Marcus RE. Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety. J Clin Oncol. 2018 Aug 10;36(23):2395-2404. DOI: 10.1200/JCO.2017.76.8960

4. Details of the impact

Context

NHL comprises over 60 subtypes of B and T malignancies. Over 500,000 people annually worldwide are diagnosed with NHL, over 14,000 in UK. Although most NHL patients respond well to initial treatment, the majority eventually relapse and ultimately die of their cancer. Novel therapies are needed to further improve outcomes.

Pathways to impact

Illidge was lead specialist clinician for EMA approval of BV.

BV was granted Breakthrough Therapy Designation by the US FDA in 2016.

Reach and significance of the impact

Availability of more effective cancer drugs: BV in NHL

In November 2018, the FDA approved BV with chemotherapy for untreated systemic anaplastic large cell lymphoma (sALCL) and Peripheral T Cell lymphomas (PTCL), rare types of fast growing NHL [Ai, 2]. It was the first treatment for previously untreated PTCL including sALCL to receive FDA approval.

Takeda and Seattle Genetics market BV as 'ADCETRIS'. Takeda Executive Medical Director confirmed UoM work *"provided early research results of brentuximab vedotin (ADCETRIS) in PTCL as well as key contributions to the pivotal ECHELON-2 phase III trial."* Illidge's "*contributions, including serving as a Steering Committee member of ECHELON-2, were instrumental in the approval by the U.S. Food and Drug Administration (FDA)…FDA approval was received 11 days after submission…..demonstrating both the strength of the trial data and the critical unmet medical need in this patient population*" [B].

In May 2020, BV (with chemotherapy) was approved in the EU for frontline treatment of adult untreated sALCL [Aii, 2]. Takeda noted this marked "*a significant milestone for people diagnosed with this devastating condition. ADCETRIS is the first and only targeted therapy approved in first-line sALCL in several decades*" [Aii].

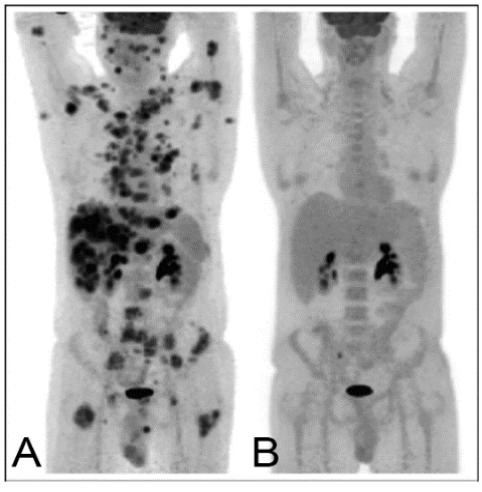

Figure A shows a baseline scan of the first BV clinical trial patient in the UK, a 42 year old male with ALCL.

Figure B demonstrates complete remission after four cycles of BV. Nine years later, this patient remains in remission.

Impact on Clinical Guidelines: BV

In August 2020, BV with CHP chemotherapy was recommended by the National Institute for Health and Care Guidance (NICE) as a treatment for adult untreated sALCL [C, 2]. NICE committee noted clinical advantages and concluded "*that brentuximab vedotin with CHP would replace CHOP* (the previous standard of care) *for sALCL in*

the NHS". Patient experts noted they "*experienced an improvement in their symptoms and had fewer side effects*" and it was noted that BV with CHP "*is given in an outpatient setting, reducing time in hospital*", a significant benefit in time and resources [C].

National Comprehensive Cancer Network® (NCCN®) is an alliance of 30 leading US cancer centres. There are >1,200,000 registered users of NCCN Guidelines® globally and they have been downloaded in >180 countries. NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for T-Cell Lymphomas recommend BV + CHP as the preferred first-line therapy regimen for ALCL and other CD-30 positive PTCL subtypes [D, 2].

Availability of more effective cancer drugs: Obinutuzumab in B cell NHL

In September 2017, Obinutuzumab (marketed by Roche as Gazyvaro in the EU) received EMA approval to treat (with chemotherapy) advanced FL based on GALLIUM [Ei, 6]. Roche announced "*Every year an estimated 19,000 people in Europe are diagnosed with follicular lymphoma, which is considered to be incurable.… these patients now have an improved initial treatment option available to them*" [Ei].

In November 2017, the FDA approved Obinutuzumab (marketed by Roche as Gazyva in the US) in the same indication for the first time, based on GALLIUM [Eii, 6]. Roche stated, "*We're pleased we can now offer patients…an initial treatment option shown to improve upon Rituxan, the standard of care in this setting for more than 10 years"* [Eii].

In July 2018, Obinutuzumab received approval from the Ministry of Health Labour and Welfare (MHLW), Japan, and was listed on Japan's National Health Insurance reimbursement price list the following month based on GALLIUM [Eiii, 6].

Impact on clinical guidelines: Obinutuzumab

In March 2018, a NICE technology appraisal recommended Obinutuzumab as an option for untreated advanced FL based on GALLIUM [F, 6].

The British Society of Haematology's FL management guidelines 2020 cited GALLIUM [6], noted NICE approval and recommended either "*rituximab or obinutuzumab with chemotherapy for people who require treatment*", allowing clinicians greater treatment choice to account for individual patient factors and resistance [G].

Impacts of later work based on preclinical science

Illidge's initial preclinical research discovering Obinutuzumab's mechanisms of action [3, 4] has directly led to further external clinical research, which in turn has generated new treatment options, that otherwise would not have occurred. For example, the international phase III CLL11 trial led to FDA and EMA approval of Obinutuzumab with chlorambucil for previously untreated CLL in November 2013 [Hi] and July 2014 [Hi], respectively. NICE recommended this use in June 2015 [Hi]. There are around 21,000 new cases of CLL in US each year, around 3,800 in UK. Based on the international multicentre GADOLIN trial, the FDA and EMA approved Obinutuzumab plus bendamustine chemotherapy for treatment of some relapsed/refractory FL in February 2016 and June 2016 [Hii].

Commercial impact of new drugs

BV is available in 72 countries. Seattle Genetics reported sales of USD477,000,000 in the US and Canada in 2018, 55% increase on 2017 and USD628,000,000 in 2019, 32% increase on 2018. The 2019 annual report stated global sales (including Takeda's) "*exceeded $1 billion in 2019, underscoring the importance of ADCETRIS to physicians and patients around the world"* [I]. Seattle Genetics confirm by end of 2019 ADCETRIS (BV) "*has been used in the treatment of more than 60,000 patients with lymphoma worldwide*" [I].

Roche reported Obinutuzumab sales of CHF390,000,000 in 2018 rising to CHF552,000,000 in 2019, a 43% increase on the previous year [J]. Obinutuzumab is available in >70 countries for untreated FL, in >80 countries with bendamustine for previously treated FL and in >90 countries with chlorambucil for untreated CLL [J].

5. Sources to corroborate the impact

A. Approval of BV for previously untreated sALCL - ***approval based on ECHELON-2 (UoM reference 2)***

   i. FDA press release 16 November 2018 – ***confirms US (FDA) approval***

   ii. Takeda press release 14 May 2020 – ***confirms EU (EMA) approval***

B. Testimonial from Executive Medical Director and Global Clinical Lead, ADCETRIS, Takeda Pharmaceuticals International, 24 August 2020 – ***confirming UoM contributions to ECHELON-2 and BV approval***

C. NICE guidance (Technology Appraisal TA641) BV in combination for untreated systemic anaplastic large cell lymphoma (12 August 2020) nice.org.uk/guidance/ta641- ***recommends BV +CHP (chemotherapy) based on ECHELON-2 (UoM reference 2)***

D. NCCN Guidelines® for T-Cell Lymphomas ***recommend BV +CHP as the preferred first line therapy for ALCL and other CD-30 positive PTCL subtypes.*** Referenced with permission from the NCCN Guidelines® for T-Cell Lymphomas V.1.2020 © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed [July 31, 2020]. To view the most recent and complete version of the guideline, go online to *www.NCCN.org*. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

E. Approval of Obinutuzumab for people with previously untreated advanced Follicular Lymphoma - ***approval based on GALLIUM (UoM reference 6)***

   i. Roche press release 22 September 2017 – ***confirms EU (EMA) approval***

   ii. Roche press release 17 November 2017 – ***confirms US (FDA) approval***

   iii. Roche Group press release 2 July 2018 – ***confirms Japanese (MHLW) approval***

F. NICE guidance (Technology appraisal TA513). Obinutuzumab for untreated advanced follicular lymphoma (21 March 2018) nice.org.uk/guidance/TA513 - ***recommends Obinutuzumab as a treatment option for untreated advanced follicular lymphoma – based on GALLIUM (UoM reference 6)***

G. British Society for Haematology – Guideline of the investigation and management of follicular lymphoma. June 2020. DOI: 10.1111/bjh.16872 - ***recommends Obinutuzumab as a treatment option for untreated advanced follicular lymphoma – based on GALLIUM (UoM reference 6)***

H. Regulatory approvals and NICE recommendation - ***leading on from Illidge's initial pre-clinical research***

   i. Untreated CLL(drugs.com article on FDA approval 1 Nov 2013, Roche Press release on EMA approval 29 July 2014, NICE Technology Appraisal Guidance TA343. 'Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia', 2 June 2015) – ***US, EU and UK (NICE) approvals***

   ii. previously treated Follicular Lymphoma (drugs.com article on FDA approval 26 Feb 2016, Roche Press release on EMA approval 16 June 2016)- ***US and EU approvals***

I. Seattle Genetics Annual Reports 2018-2019 - ***showing commercial impact/sales and wide availability of BV***

J. Roche Annual Report 2019 and product information.- ***showing commercial impact/sales and wide availability of Obinutuzumab***