Institution: University of Southampton

Unit of Assessment: 01 Clinical Medicine

Title of case study: 01-27 Setting the standard in lymphoma therapy

1. Summary of the impact

Research conducted by a multidisciplinary team of oncologists and scientists at the University of Southampton has driven major advances in lymphoma care, leading to the development and standardisation of effective new antibody treatments and optimal drug regimens. Through their direction of international clinical trials, they have influenced care for Hodgkin and Burkitt lymphoma in the UK and internationally, affecting all stages of patient-experience from diagnosis to treatment. Their findings underpin significant improvements in survival and quality of life for the 14,000 people affected by lymphoma in the UK each year.

2. Underpinning research

Lymphoma is the fifth most common cancer in the UK with approximately 14,000 cases diagnosed each year. It is the most common cancer affecting under-30s and constitutes one in ten cancers diagnosed in children. Research led by academics at the University of Southampton's Cancer Sciences Unit, including Peter Johnson (Chair of Medical Oncology 1998-present), Ben Mead (Hon Senior Lecturer in Medical Oncology 1988-2011), Martin Glennie (Chair of Immunochemistry 1998-present) and Mark Cragg (Chair of Experimental Cancer Biology 2007-present), has resulted in the development of new monoclonal antibodies and immunoconjugates for the treatment of lymphoma, and the elucidation of key mechanisms of action.

Ofatumumab, a new anti-CD20 monoclonal antibody (mAb) developed by Glennie (2004), was administered to UK patients with low-grade lymphoma for the first time in a phase I/II trial led by Johnson **[3.1]**. Concurrently (2003-07) Johnson oversaw a study in which a novel conjugate of the anti-CD20 mAb rituximab to iodine-131 was tested in a phase I study of fractionated radioimmunotherapy **[3.2]**. These trials demonstrated for the first time the relationship between the bulk of lymphoma and antibody pharmacokinetics: while ofatumumab and rituximab bind the same antigen, ofatumumab was shown to dissociate from its target at a slower rate and bind a novel, membrane-proximal epitope. Further research using animal models and clinical material ex-vivo defined the mechanisms by which ligation of CD20 on the lymphoma cell surface can, through cooperation with inhibitory Fc receptors (CD32B), result in internalisation of the complex and loss of effective antibody. This has critical implications for the application of anti-CD20 mAb (e.g. rituximab) in lymphoma and chronic lymphocytic leukaemia, now being investigated in prospective combinational clinical studies testing different anti-CD20 and anti-CD32B mAb (WO Patent Application, PCT/GB2011/051572).

In the LY09 study led by Johnson (1998-2002), 807 patients with advanced Hodgkin lymphoma (HL) took part in a randomised trial comparing treatment with four-drug chemotherapy of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) with two multi-drug regimens. Findings indicated that initial dose intensity was not the principal determinant of outcome and, contrary to what had become the trend in practice, it also demonstrated the survival-benefits of including consolidation radiotherapy as a component of successful treatment **[3.3, 3.4]**. The Stanford V study (1998-2006, 520 HL patients) also led by Southampton confirmed ABVD was the optimum regimen, as it requires the use of less extensive irradiation than a weekly multi-drug regimen, while yielding strong survival rates, fewer complications and lower toxicity **[3.5]**.

Southampton's approach has since been incorporated into new efforts by international pharmaceutical and medical researchers to develop reagents. For example, the RATHL Study (2005-13, CI Johnson) conducted in the UK, Italy, the Nordic countries and Australasia, involved 1200 patients in evaluation of the use of positron emission tomography imaging to adjust chemotherapy. This work builds on the Stanford V trial and will provide a definitive answer to the

role of dose modulation in chemotherapy more widely, to the benefit of patients, clinicians and healthcare providers.

Two successive studies led by Mead, the LY06 (1995-1999, 72 patients) and LY10 (2002-2005, 128 patients; the largest prospective study yet performed), used state-of-the-art molecular diagnostics to differentiate between Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL), and to demonstrate the efficacy of cyclophosphamide, vincristine, doxorubicin, high dose methotrexate (CODOX-M)/ifostamide, estoposide and high-dose cytarabine (IVAC) intensive chemotherapy in this group **[3.6]**.

3. References to the research

3.1 A. Hagenbeek, O. Gadeberg, P. Johnson, L.M. Pedersen, J. Walewski, A. Hellmann, B.K. Link, T. Robak, M. Wojtukiewicz, M. Pfreundschuh, M. Kneba, A. Engert, P. Sonneveld, M. Flensburg, J. Petersen, N. Losic, J. Radford. First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase I/II trial. *Blood* 2008; 111:5486-95.

3.2 T.M. Illidge, M. Bayne, N.S. Brown, S. Chilton, M.S. Cragg, M.J. Glennie, Y. Du, V. Lewington, J. Smart, J. Thom, M. Zivanovic, P.W. Johnson. Phase I/II study of fractionated 131I-rituximab in low grade B-cell lymphoma: The effect of prior rituximab dosing and tumor burden on subsequent radioimmunotherapy. *Blood* 2009; 113:1412-21

3.3 P.W.M. Johnson, J.A. Radford , M.H. Cullen, M.R. Sydes, J. Walewski, A.S. Jack, K.A. MacLennan, S.P. Stenning, S. Clawson, P. Smith, D. Ryder, B.W. Hancock. Comparison of ABVD and Alternating or Hybrid multi-drug regimens for the treatment of advanced Hodgkin's Lymphoma: Results of the UK Lymphoma Group LY09 Trial. *Journal of Clinical Oncology* 2005; 23:9208-18.

3.4 P.W.M. Johnson, M.R. Sydes, B.W. Hancock, M.Cullen, J.A. Radford, S.P. Stenning. Consolidation radiotherapy in patients with advanced Hodgkin lymphoma: survival data from the UKLG LY09 randomised controlled trial. *Journal of Clinical Oncology* 2010; 28:3352-9.

3.5 P. Hoskin, L. Lowry, A. Horwich, A. Jack, G. Mead, B. Hancock, P. Smith, W. Qian, P. Patrick, B. Popova, A. Pettitt, D.Cunningham, R. Pettengell, J. Sweetenham, D. Linch, P.W.M. Johnson. Randomized Comparison of the Stanford V Regimen and ABVD in the Treatment of Advanced Hodgkin lymphoma: Results from a UK NCRI Lymphoma Group Study, ISRCTN 64141244. *Journal of Clinical Oncology* 2009; 27(32):5390-6

3.6 G.M. Mead, et al., A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). *Blood* 2008; 112(6): 2248-60.

Grants

- C328/A 9619 CRUK/07/033: RATHL: A randomised trial to assess Response Adapted Therapy using FDG-PET imaging in patients with advanced Hodgkin lymphoma. Cancer Research UK 2007-2014 £797,000 Johnson Chief Investigator.
- C328/A 12128 CRUKE/10/024: REMoDL-B: A Randomised Evaluation of Molecular guided therapy for Diffuse Large B-cell Lymphoma with Bortezomib. Janssen-Cilag 2010-2015. £1.14M Johnson Chief Investigator
- C328/A 7933 CRUK/07/038: SCHRIFT: Phase II study of abbreviated immuno-chemotherapy followed by 90Y Ibritumomab tiuxetan in relapsed follicular lymphoma Cancer Research UK 2007-2010. £44,294 Johnson Chief Investigator
- A randomised phase III study of the Stanford V regimen compared with ABVD for the treatment of advanced Hodgkin's disease. (PI Dr Peter Hoskin). Cancer Research UK 2000-2006 £280,000. Johnson, Sweetenham, Co-Investigators.

4. Details of the impact

Southampton research has driven major advances and changes in international standards for lymphoma care, greatly improving survival rates and quality of life for the 14,000 people affected by the disease in the UK each year, establishing standards of care in the UK **[5.1-5.4]** and internationally **[5.5, 5.6]**, and reducing healthcare costs across the NHS.

The use of anti-CD20 reagents represents the single biggest improvement in lymphoma survival rates over the last two decades. The Southampton team has played a key role in defining their mechanisms of action, and developing new reagents. Southampton's integration of lymphoma care provision with pre-clinical research and experimental medicine has enabled rapid, robust development of reagents effective against chemotherapy-resistant or relapsed lymphomas (e.g. ofatumumab / Arzerra; licenced by the FDA in 2009), giving patients early access through trials. GlaxoSmithKline is currently conducting clinical trials of ofatumumab for relapsed follicular non-Hogkin's lymphoma and DLBCL and, in May 2013, announced it was filing for approval of Arzerra as a first-line chronic lymphocytic leukaemia therapy on the back of phase III trials **[5.7]**. Moreover, Southampton's trial of a novel ritiximab radioconjugate defined a regimen yielding improved survival rates, good quality of life and low complication rates for patients, whilst also defining the critical relationship between bulk of lymphoma and antibody pharmacokinetics. Combined with Southampton's elucidation of the key biological mechanism limiting efficacy of these reagents, these studies underpin current prospective studies aimed at further improvements in survival rates and efficacy against a wider range of lymphoma types.

For Hodgkin lymphoma (HL) between 2005-2009, dissemination of the LY09 and Stanford V studies' findings resulted in UK practice moving away from more toxic multi-drug regimens to a standard ABVD regimen **[5.2, 5.4, 5.8, 5.9]**, improving survival rates from 70-75% in the 1990s to 85% in 2009 at five years, according to Cancer Research UK. International practice has similarly been influenced, with current guidelines in the USA **[5.5]** and Italy **[5.6]** advocating the same approach since 2009.

For Burkitt lymphoma (BL), the LY06 and LY10 studies establishing the CODOX-M/IVAC regimen as optimal, led to greatly improved survival rates from under 50% to over 70% between the 1970s and 2013 (Cancer Research UK). Further, Southampton's establishment of diagnostic standards to differentiate BL from DLBCL has had ongoing impacts for those patients with non-Hodgkin lymphomas diagnosed every year who previously would have been wrongly diagnosed and treated with higher intensity chemotherapy than necessary **[5.9]**. Following its publication in 2008, this standard has been adopted in the best practice guidance by the British Society of Haematology since 2010 **[5.3]** and in overseas lymphoma care guidelines, e.g. in the USA **[5.5]**.

As Chief Clinician at Cancer Research UK (2008-) and chair of the National Cancer Research Institute's Lymphoma Clinical Studies Group (2005-2011), Johnson has represented Southampton research at the highest levels of professional policy-making. Since 2008 he has been actively involved in writing and updating guidelines and patient information for the Lymphoma Association **[5.8]** and Macmillan Cancer Support **[5.9]**. He has influenced professional practice through his role on the organising committee of International Conference on Malignant Lymphoma (2008, 2011, 2013) and at the International Symposium on HL (2010, 2013). Since 2009 he has been contributing editor to *The Hematologist*, distributed to more than 14,000 international members of the American Society of Hematology. This is the world's largest professional society concerned with the causes and treatments of blood disorders.

Awareness of Southampton research and improved lymphoma treatments has been communicated to the general public through contributions to BBC Radio 4's *Today Programme* (28/9/11, 22/11/11, 21/5/13), BBC2's *Newsnight* (7/4/09, 17/7/12, 13/6/13), and *The Daily Telegraph* (6/12/10, 13/2/12, 15/5/12) among many others **[5.10]**. These profile-raising efforts have underscored Southampton's leadership in the field, in part contributing to, in July 2012, a

philanthropic donation of £10m to further translational cancer immunology, and linking it to basic immunology research of the Francis Crick Institute; the recipient of a matched £10m gift from the same donor.

5. Sources to corroborate the impact

5.1 Current UKCN Burkitt's care guidelines example:
http://www.mccn.nhs.uk/userfiles/documents/Guidelines%20for%20treatment%20of%20Burkitts%20Lymphoma%20DEC%202010.pdf

5.2 Current UKCN Hodgkin's care guidelines example:
http://www.greatermidlandscancernetwork.nhs.uk/uploads/gmcn_hd_updated_rc_sf240210a2e635c0.pdf

5.3 Current BCSH Burkitt diagnosis best practice document:
http://www.bcshguidelines.com/documents/Lymphoma_disease_app_bcsh_042010.pdf

5.4 NICE guidelines; 2003, remain in force:
http://www.nice.org.uk/nicemedia/live/10891/28786/28786.pdf

5.5 US National Comperehensive Cancer Network clinical practice guidelines for Non-Hodgkin's care: http://www.jnccn.org/content/8/3/288.full

5.6 Current Italian Hodgkin's care guidelines:

http://www.haematologica.org/content/94/4/550.full

5.7 Ofatumumab/Arzerra clinical trials:
http://www.pmlive.com/pharma_news/gsk_eyes_first-line_use_for_leukaemia_drug_arzerra_480459

http://www.gsk.com/media/press-releases/2013/fda-grants-gsk-and-genmabs-arzerra---ofatumumab--breakthrough-th.html

5.8 Current Lymphoma Association Hodgkin Lymphoma patient information:
http://www.lymphomas.org.uk/sites/default/files/pdfs/Hodgkin%20Lymphoma%20booklet.pdf

5.9 Current Macmillan Hodgkin Lymphoma patient information:
http://be.macmillan.org.uk/be/p-248-understanding-hodgkin-lymphoma.aspx

5.10 Peter Johnson in press/media/public engagement:

http://www.news-medical.net/news/2008/09/09/41296.aspx

http://www.bbc.co.uk/news/health-18060777

http://scienceblog.cancerresearchuk.org/2011/09/28/radio-interview-the-challenge-of-sustaining-top-quality-cancer-care/

http://news.bbc.co.uk/today/hi/today/newsid_9645000/9645073.stm

http://www.bbc.co.uk/programmes/b01sj1sm/live

http://www.telegraph.co.uk/health/healthnews/8179902/Drug-increases-healthy-years-for-cancer-patients.html