Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

ACCURATE DIAGNOSIS: IMPROVING SURVIVAL RATES FOR CHILDREN WITH CANCER

Summary of the impact:

The production and use of monoclonal antibody, ALK1, by researchers in Oxford has been pivotal in enabling the accurate diagnosis and treatment of Anaplastic Large Cell Lymphoma (ALCL). This research also led to the formal classification of ALK-positive ALCL tumours by the World Health Organization in 2008. While ALCL accounts for 10-20% of paediatric/adolescent non-Hodgkin's lymphoma worldwide, its diagnosis had been problematical due to the absence of suitable reagents. This was remedied in 1997 when Oxford researchers created the first monoclonal antibody, ALK1, recognising anaplastic lymphoma kinase (ALK), a molecule that is associated with up to 90% of ALCL.

Underpinning research:

Before 1997 Anaplastic large cell lymphoma (ALCL) posed a major diagnostic problem to clinicians because of the lack of reagents able to distinguish ALCL from other tumours. Patients were frequently misdiagnosed with carcinoma, histiocytosis X or Hodgkin's disease, leading to unnecessary and often invasive therapy, including surgery. In 1997 the late Professor David Y. Mason (deceased Feb 2008), Dr Karen Pulford, and the Leukaemia Research Fund Immunodiagnostics Unit (now Leukaemia and Lymphoma Research Fund) produced the first monoclonal antibody, ALK1, against the anaplastic lymphoma kinase (ALK) protein, which is the principal cause of oncogenesis in ALCL[1]. Oncogenic translocations create fusion proteins of ALK and partners capable of high expression and dimerization, after which dimerisation leads to ALK autophosphorylation and constitutive activation.

The ALK1 antibody made a precise diagnosis of ALK-positive ALCL possible for the first time. The ALK1 antibody identified ALK-positive ALCL as a molecular pathological entity (distinct from ALK-negative ALCL), showing that this cancer accounts for 10-20% of childhood lymphomas and 3% of adult non-Hodgkins lymphomas[2]. Due to improved survival rates associated with ALK-positive ALCL, the ability to distinguish between ALK-positive and negative forms of the disease represented a vitally important step in achieving accurate diagnosis and appropriate treatment for patients.

Researchers at the University of Oxford have gone on to use the antibody ALK1 to identify additional ALK fusion proteins in ALCL and confirm the role of the ALK proteins play a primary role in tumour development [3]. They have shown that ALK fusion proteins may be immunogenic and candidates for immunotherapy[4].

The antibody ALK1 has been used to show ALK protein expression in neuroblastoma[5], and ALK has also been identified in a number of other solid tumours, such as lung cancer. Studies on the immune response to ALK, using ALK1 antibody as an essential reagent (initiated by Oxford and later performed as collaborative studies within international phase III clinical trials[6]), are included in the clinical trial 'ALCL 2012'. This phase III clinical study organised by the European Inter-group for Childhood non-Hodgkin's Lymphoma (EICNHL) will identify high-risk patients so that they can be directed to more effective therapies as soon as possible.

References to the research:

1. Pulford, K. *et al*. Detection of anaplastic lymphoma kinase (ALK) and nucleolar protein nucleophosmin (NPM)-ALK proteins in normal and neoplastic cells with the monoclonal antibody ALK1. *Blood* **89**, 1394-404 (1997). ***Describes the production and characterization of the monoclonal antibody ALK1.***

2. Stein, H. *et al*. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood* **96**, 3681-95 (2000). ***Collaborative review of the work leading up to description of ALK-positive ALCL.***

3. Bischoff, D., Pulford, K., Mason, D.Y., & Morris, S.W. Role of the nucleophosmin (NPM) portion of the non-Hodgkin's lymphoma-associated NPM-anaplastic lymphoma kinase fusion protein in oncogenesis. Mol Cell Biol. **17**, 2312-2325 (1997). ***Reference to the importance of the NPM-ALK fusion protein.***

4. Ait-Tahar, K., *et al*. Correlation of the autoantibody response to the ALK oncoantigen in pediatric anaplastic lymphoma kinase-positive anaplastic large cell lymphoma with tumor dissemination and relapse risk. *Blood* **115**, 3314-9 (2010). doi: 10.1182/blood-2009-11-251892. [a] From Oxford and *Joint last authors. ***Description of the immunogenicity of ALK protein and the first description of the immune response to ALK being of prognostic significance and also having a potential role in tumour spread.***

5. Lamant, L. *et al*. Expression of the ALK tyrosine kinase gene in neuroblastoma. *Am J Pathol* **156**, 1711-21 (2000). ***First description of ALK being expressed in neuroblastoma***.

6. National Cancer Institute (NCI). COG-ANHL0131 - Phase III Randomized Study of Consolidation Chemotherapy Comprising Doxorubicin and Prednisone in Combination With Vincristine Versus Vinblastine in Patients With Advanced Anaplastic Large Cell Lymphoma. In ClinicalTrials.gov [Internet]. Bathesda (MD): National Library of Medicine (US). 2000- [cited 2013 Apr 04]. Available from: http://clinicaltrials.gov/show/NCT00059839 NLM Identifier: NCT00059839. ***Clinical trial on ALCL in which the biological studies on the immune response to ALK involving the ALK1 antibody was studied.***

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Details of the impact:

The production and use of the antibody ALK1 by the University of Oxford has had a major impact on lymphoma diagnosis and provided invaluable information on tumour development. ALK-positive ALCL is now also included in the World Health Organization's (WHO) current classification of haematological malignancies.

Accurate Diagnosis

The production and use of the antibody ALK1 by the University of Oxford has had a major impact on lymphoma diagnosis, enabling the definitive diagnosis of the tumour entity ALK-positive ALCL. ALCL was previously regarded as an aggressive incurable disease and frequently misdiagnosed as a carcinoma or other haematological malignancy, resulting in inappropriate treatment. Not only has the antibody ALK1 revolutionised the accurate diagnosis and understanding of ALK-positive ALCL, this tumour now represents the best characterised T-cell lymphoma, with the exception of cutaneous T-cell lymphoma, which has a far worse prognosis[7,8,9]. Importantly, the sensitivity of the antibody has permitted the detection of minimal residual disease. The latter is an important factor in cancers since it can lead to a failure to detect disease and result in the patient relapsing. A vital element of the value of an antibody for diagnostic use is its inclusion in the NEQAS scheme. The

United Kingdom National External Quality Assessment Service (UK NEQAS) ensures the accuracy and reliability of laboratory tests and is used by all diagnostic labs. ALK1 fulfills this category. The following statement was received via email on the 19th of September 2012, from Doctor Merdol Ibrahim, Manager of UK NEQAS-ICC. This email, and the antibody usage table, has been kept on file: *"NEQAS requested ALK for its lymphoma module about 1.5 years ago for the first time. We distributed a composite control of a tonsil and anaplastic large cell lymphoma for participants to stain. Participants also submitted their methodologies and I have attached the antibody usage table (second table on the right), which shows that 104/179 (58%) participants used the Dako CD246 clone. It is one of the most popular antibodies and had a very good pass rate with respect to the expected staining levels."*[10]

Policy and Guidelines

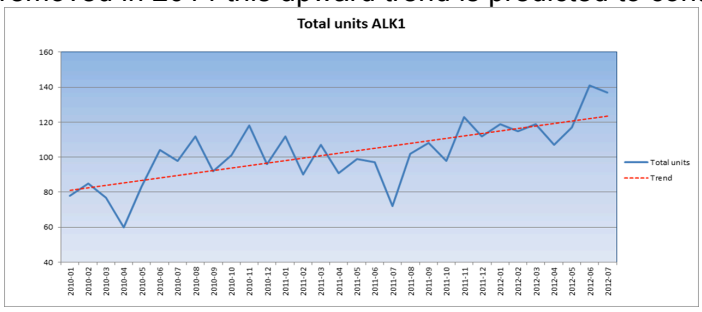
The identification of ALK-positive ALCL (as opposed to ALK-negative ALCL) has gained worldwide acceptance and is now included in the current classification of haematological malignancies, first published by the World Health Organization in 2008. ALK1 is considered to be the gold standard antibody for the diagnosis of ALK-positive ALCL[9].

Clinical outcomes

Approximately 870 children are diagnosed with non-Hodgkin's lymphoma every year in the USA [11], equating to about 175 new cases of ALK+ALCL annually. For adults, this figure rises to approximately 1,500[12]. Before 1997 it was difficult to compare the survival rates of patients with ALCL due to problems with the actual diagnosis of the disease. This was compounded by a lack of common staging systems, relatively small numbers of patients, and a variety of different treatment regimens being used in the clinics. This meant that patients may have undergone unnecessary surgery or invasive therapies as a result of misdiagnosis. The availability of the ALK1 antibody in 1997 enabled the correct diagnosis of ALK-positive ALCL, resulting in improvements in targeted therapy and greater survival rates for patients with this lymphoma. For example, the five year overall survival rates increased from 71% in 1999[13] to 89% in 2008[14]. It is expected that additional improvements in patient survival will continue from future clinical trials. The widespread introduction of ALK-specific kinase inhibitors is a distinct possibility.

Commercialisation

The ALK1 antibody is licensed commercially throughout the world by DakoCytomation[15] and is considered to be the international gold standard for identifying this ALK-positive ALCL. The below graph shows the upward trend in total units of ALK1 sold by Dako from 2010 to 2012[15]. When patent restrictions are removed in 2014 this upward trend is predicted to continue.



Total royalties received for ALK reached approximately £50,000 for the period 1998-2005. Sales of the antibody have since increased due to worldwide interest in ALK. The total amount of royalties received by the University of Oxford for ALK from 2008 to 2009 reached £22,875, with royalties now consistently exceeding £10,000 per annum[16].

Sources to corroborate the impact:

7. Benharroch, D. *et al*. ALK-positive lymphoma: a single disease with a broad spectrum of morphology. *Blood* **91**, 2076-84 (1998). ***First paper in which the antibody ALK1 was used to identify ALK-positive lymphomas as a distinct entity.***

8. Delsol, G. *et al*. Anaplastic large cell lymphoma (ALCL), ALK-positive. In: Swerdlow, S.H. *et*

al, editors. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon. IARC Press; 2008. ***Reference refers to the description of ALK-positive ALCL in the current World Health Classification scheme for Haematological malignancies.***

9. Kinney, M.C. *et al*. Anaplastic large cell lymphoma: twenty-five years of discovery. *Arch Pathol Lab Med* **135**,19-43 (2011). doi: 10.1043/2010-0507-RAR.1. ***This reference refers an important update on ALK-positive ALCL.***

10. NEQAS-ICC. UK Manager. Email statement explaining inclusion of ALK in the NEQAS lymphoma module labs, received 19th September 2012 (available on request). ***Statement confirming use of ALK by NEQAS-ICC.***

11. Childhood Cancer Statistics. *American Childhood Cancer Organization* at http://www.acco.org/Information/AboutChildhoodCancer/ChildhoodCancerStatistics.aspx (Accessed 2013) ***Website for statistics on childhood cancer in the USA.***

12. Lymphoma Statistics at http://www.lymphomation.org/statistics.htm#keyfacts (Accessed 2013) ***Website for statistics on adult cancer in the USA.***

13. Falini, B. *et al*. ALK+lymphoma: clinico-pathological findings and outcome. *Blood* **93**, 2697-2706 (1999). ***Paper showing increase in 5 year overall survival rates for ALK***.

14. Lamant, L. *et al*. Prognostic impact of morphologic and phenotypic features of childhood ALK-positive anaplastic large-cell lymphoma: results of the ALCL99 study. *J Clin Oncol*. **29**, 4669-4676 (2011). doi: 10.1200/JCO.2011.36.5411. ***Reference describing prognosis in ALK+ALCL where antibody ALK1 was used.***

15. Monoclonal Mouse Anti-Human CD246, ALK Protein, Clone ALK1. *Dako* at http://www.dako.com/uk/ar38/p118620/prod_products.htm (Accessed 2013) ***The antibody ALK1 has been commercialised by DakoCytomation.***

16. University of Oxford Finance Division. Royalties Officer. Email stating royalties for licensed antibodies against ALK, received 30th July 2012 (available on request). ***Details of the commercialisation and upward sales trend of the ALK1 antibody from DAKO and information on royalties received by the University of Oxford.***