Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 – Clinical Medicine

Title of case study:
Changing Clinical practice from Imatinib to Nilotinib in Chronic Myeloid Leukaemia (CML)

1. Summary of the impact

Since 2000, the tyrosine kinase inhibitor (TKI) imatinib has transformed CML from a fatal disease for half of patients within 5 years, to a chronic disease whereby ~ 90% of patients lead normal lives for at least 9 years. This remarkable transformation has spawned a second phase of clinical and translational research aiming to cure CML. The University of Liverpool (UoL) CML research group headed by Prof Richard Clark has been integral in both phases, particularly in the development of the second generation TKI nilotinib. Important contributions have also shed light on CML biology and the possible mechanism of acute leukaemic transformation (blast crisis).

2. Underpinning research

CML is a malignant disease of the haemopoietic stem cell, characterised by expansion of myeloid cell production. It can progress to acute leukaemia (blast crisis) which is usually fatal within 6 months. CML is driven by the fusion oncoprotein BCR-ABL, formed by the t(9;22) Philadelphia translocation. The BCR-ABL gene product is a constitutively active version of ABL, a tyrosine kinase. In the late 1990s, the tyrosine kinase inhibitor (TKI) imatinib was introduced. This inhibits BCR-ABL to which CML cells are 'addicted'. Using sensitive PCR based molecular testing for BCR-ABL, imatinib has been shown to produce far deeper remissions than alpha interferon (IFN), and patients with such 'major molecular responses' (MMR) have an extremely low risk of blast crisis after at least 9 years of follow up. Imatinib has therefore become the standard of care in CML since endorsement by the National Institute of Clinical Excellence (NICE) in 2003. However, 40% of patients become resistant to or intolerant of imatinib. Resistance mechanisms include the evolution of subclones with BCR-ABL kinase domain mutations that interfere with imatinib binding, or the development of new genomic lesions that are unaffected by imatinib.

Prof Clark's group at the UoL showed that imatinib is actively transported into leukaemia cells by the transporter hOCT1 [1]. This was the first time that an INFLUX (as opposed to an efflux) transporter has ever been identified as of clinical relevance in any cancer. The group went on to show that this is a powerful clinical predictor of patients failing imatinib [2], subsequently confirmed by several other groups. Low hOCT1 expression/activity is therefore an additional and common mechanism of imatinib resistance, discovered by the Clark group.

In 2006, the second generation TKIs dasatinib and nilotinib were shown by others in phase II studies to achieve leukaemia clearance from the marrow and MMR in the majority of patients who fail imatinib. Research at the UoL showed that both drugs are transported into cells independently of hOCT1 [3,4]. This led to phase III trials of nilotinib vs. imatinib (ENESTnd, in which Clark was the UK Chief Investigator) and of dasatinib vs. imatinib (the ongoing NCRI SPIRIT2 trial, for which Clark chairs the management group). ENESTnd has demonstrated that nilotinib has higher MMR rates and lower acute leukaemia progression rates than imatinib [5] that are maintained at 5 years [data to be presented at ASH 2013].

Clark's CML group has also made important contributions to CML biology including the demonstration of HLA-associated expression of BCR-ABL fusion peptides [6], and the identification of cancerous inhibitor of PP2A (CIP2A) [7] and the loss of placental derived growth factor as biomarkers of disease progression [8].

3. References to the research

1. **Thomas J**, **Wang L, Clark RE**, **Pirmohamed M**. Active transport of imatinib into and out of cells: Implications for drug resistance. Blood 2004; 104: 3739-3745. Citations: 362 Impact Factor: 9.060

2. **Wang L**, **Giannoudis A**, **Lane S**, **Williamson P**, **Pirmohamed M**, **Clark RE**. Expression of the

uptake drug transporter hOCT1 is an important clinical determinant of the response to imatinib in chronic myeloid leukemia. Clinical Pharmacology & Therapeutics 2008; 83: 258-264. Citations: 135 Impact Factor: 6.846

3. **Giannoudis A**, **Davies A**, **Lucas CM**, **Harris RJ**, **Pirmohamed M**, **Clark RE**. Effective dasatinib uptake may occur without human Organic Cation Transporter 1 (hOCT1): implications for the treatment of imatinib resistant chronic myeloid leukaemia. Blood 2008, 112: 3348-3354. Citations: 65 Impact Factor: 9.060

4. **Davies A**, Jordanides NE, **Giannoudis A**, **Lucas CM**, Hatziieremia S, **Harris, RJ**, Jørgensen HG, Holyoake TL, **Clark RE**, Mountford JC. Nilotinib concentration and efficacy in CD34+ CML cells are not mediated by active uptake or efflux by major drug transporters. Leukemia 2009; 23: 1999-2006. Citations: 54 Impact Factor: 10.164

5. Saglio G, Kim D-W, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, **Clark RE**, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA, Kantarjian HM. ENESTnd: A randomized comparison of nilotinib and imatinib for newly diagnosed chronic myeloid leukemia. New England Journal of Medicine 2010; 362: 2251-2259. Citations: 444 Impact Factor: 51.658

6. **Clark RE**, Dodi IA, Hill SC, Lill JR, Aubert G, **MacIntyre AR**, **Rojas J**, Bourdon A, Bonner PLR, **Wang L, Christmas SE**, Travers P, Creaser CS, Rees RC, Madrigal JA. Direct evidence that leukaemic cells present HLA-associated immunogenic peptides derived from the BCR-ABL b3a2 fusion protein. Blood 2001, 98: 2887-2893. Plenary paper, with editorial in Blood 2001, 98: 2885. Citations: 179 Impact Factor: 9.060

7. **Lucas CM**, **Harris RJ**, **Giannoudis A**, **Clark RE**. Cancerous inhibitor of PP2A (CIP2A) at diagnosis of chronic myeloid leukaemia is a critical determinant of disease progression. Blood 2011; 117: 6660-6668. Citations: 18 Impact Factor: 9.060

8. Schmidt T, Loges S, Maes C, Jonckx B, Masouleh BK, Kleppe M, de Keersmaecker K, Tjwa1 M, Schenk T, Bee K, DeWolf-Peeters C, **Clark RE**, Vandenberghe P, Brümmendorf TH, Holyoake T, Hochhaus A, Cools J, Carmeliet G, Carmeliet P. Loss or Inhibition of Stromal-Derived PlGF Prolongs Survival of Mice with Imatinib-Resistant Bcr-Abl1+ Leukemia. Cancer Cell 2011; 19: 740-753. Citations: 26 Impact Factor: 24.755

Key research grants of over £150,000 since 2000. Liverpool grantholders are in bold:

2001 – 2006. **Kay Kendall Research Fund.** The Identification of Immunodominant Peptide Epitopes from bcr/abl and abl/bcr, and their use in monitoring immune responses in CML patients and in Clinical Translational Trials for Immunotherapy of CML'. £325k, Dodi AI, Travers PJ, Rees RC, Creaser CS, Bonner P, Falkenburg F, **Clark RE** and Madrigal JA.

2003 – 2009. **Leukaemia Research Fund**. 'A phase I/II feasibility study of peptide vaccination in chronic myeloid leukaemia', & 'extension to normal subjects, £551,688, **Clark RE**

2004 – 2007. **Leukaemia Research Fund**. Do transporter proteins contribute to clinical resistance to imatinib in chronic myeloid leukaemia? A combined study in Liverpool and Glasgow, correlating transporter expression and function with imatinib uptake and efflux, £300,056, **Clark RE**, Mountford J, **Pirmohamed M** and Holyoake TL

2005 – 2008. **Novartis** (invited application). Mechanisms of imatinib resistance in chronic myeloid leukaemia: A laboratory and clinical study of uptake and efflux transporters, $465,100 (£252,998), **Clark RE**

2008 – 2011. **Kay Kendall Leukaemia Fund** (2008): £276,959 over 3 years for 'The role of transporter proteins in the efficacy of imatinib and newer tyrosine kinase inhibitors in chronic

myeloid leukaemia, £276,959, PI **Clark RE** (PI) and **Pirmohamed M**

2008 – 2011. **Leukaemia Research Fund**. Development of a pharmacokinetic-pharmacodynamic model for imatinib to allow individualisation of therapy for chronic myeloid leukaemia, £167,510 , **Clark RE** (PI), **Pirmohamed M**, **Davies A** and **Lane S**

2009 – 2012. **Medical Research Council**. A randomised phase 2 trial of imatinib versus imatinib with hydroxychloroquine for patients with CML in major cytogenetic response with residual disease by quantitative PCR, £580,811, Holyoake TL, Marin D, **Clark RE.**

2010. **Genzyme Inc** (now Sanofi-Aventis) (2010). PHANTASTIC, a clinical trial of plerixafor for stem cell harvesting, £202,431 (plus ~£1m of free drug), **Clark RE**

2010 – 2013. **Leukaemia & Lymphoma Research**. The AML Pick a Winner Programme, £276,046, Burnett AK, Hills R, **Clark RE,** Russell N, Thomas I, Milligan D

2012. **Ariad Pharmaceuticals**. SPIRIT3: a randomised trial in newly diagnosed chronic myeloid leukaemia, £21.9m (of which £2,317,126 to UoL), O'Brien SG, Apperley JF and **Clark RE**

2013 – 2016. **Leukaemia & Lymphoma Research** (formerly Leukaemia Research Fund). DESTINY: a trial of de-escalation and stopping treatment in CML patients with excellent responses to tyrosine kinase inhibitor therapy, £160,530, **Clark RE** (lead), O'Brien SG, Copland M, Foroni L, **Cox T** and **Haycox A**.

4. Details of the impact

800 people develop CML each year in the UK and there are currently over 6,000 patients with the disease. The estimated cost to the NHS is £290m pa and rising.

Due to his work on imatinib resistance and on nilotinib and dasatinib, Prof Clark became one of two experts co-opted by the National Institute of Clinical Excellence (NICE) to appraise these drugs, on behalf of the Royal College of Pathologists and the British Society for Haematology. Based on the data of nilotinib superiority over imatinib in ENESTnd, on which Clark was the UK Chief Investigator, and also the parallel study of dasatinib, NICE considered the use of second line nilotinib and dasatinib in a multitechnology appraisal from 2009-2011, resulting in approval for nilotinib but not dasatinib in January 2012 [9]. NICE similarly involved Prof Clark in a second Technology Appraisal in 2012 that recommended that nilotinib should also be approved for **first** line treatment of chronic phase CML [10]. Clark and the UoL's studies over the past few years have been key to this shift of the standard of care for newly diagnosed CML patients from imatinib to nilotinib. A similar change from imatinib to nilotinib is also happening in most other Western countries, where their current clinical trials offer only nilotinib (with or without other treatments) to newly diagnosed CML patients. Nilotinib (trade name *Tasigna*) is licensed as first line therapy for newly diagnosed CML patients throughout the EU, Switzerland, Japan and the US, and as a second line treatment in over 100 countries for patients resistant or intolerant to existing treatments [11].

The change to nilotinib as the treatment of choice [12] is underlined by the £21.9m industry funded SPIRIT 3 trial that will soon be underway in the UK (as of November 2013, applications for ethical and MHRA approval are currently under consideration but see next paragraph). This randomised phase III trial intends to recruit 1,000 newly diagnosed chronic phase CML patients. It will examine whether nilotinib remains a superior treatment to imatinib if patients who have inadequate early molecular responses are offered an early switch of treatment. The trial will also examine whether treatment de-escalation and then cessation can be achieved in patients with excellent and sustained treatment responses for some years, in case these patients are functionally cured [13]. This de-escalation and stopping strategy is being piloted in a phase II trial called DESTINY, led from Liverpool and for which Clark is the Chief Investigator (supported by Leukaemia & Lymphoma Research) which is opening in November 2013.

However, during 2013 several reports have emerged on a small apparent excess of cardiovascular

events on nilotinib than imatinib. It is not possible to be certain on this as ENESTnd and smaller studies were not designed to test this. In addition, on October 8th 2013, the US Food & Drugs Administration unexpectedly announced an investigation into cardiovascular events in patients receiving ponatinib, a 3rd generation TKI that is part of the 'early switch' strategy in the UK SPIRIT3 trial. Interest in nilotinib (and ponatinib) has therefore evolved to determining whether cardiovascular events are a genuine and clinically relevant unwanted effect, and also on the underlying mechanism.

Finally, the UoL group's scientific observations have also had clinical impact, partly in relation to the switch from imatinib to nilotinib. The UoL's demonstration of HLA-associated expression of BCR-ABL fusion peptides [6] led directly to several studies of peptide vaccination in CML and other leukaemias [14]. There is also much interest in biomarkers in CML, to predict a poor clinical outcome (transformation to acute leukaemia), and the UoL's identification of CIP2A [7] has evolved into a more thorough study of this protein in many other cancers (exemplified by 30 further reports on CIP2A in the 2 years since publication). The most recent data in Liverpool indicate that while CML patients with high CIP2A expression have a high probability of disease progression to blast crisis if treated with imatinib, this is not true if receiving nilotinib, and that this may be due to differential effects of the two drugs on various ancillary proteins involved in CIP2A regulation (data presented at the European School of Haematology 2013 and manuscript submitted to a high impact journal in November 2013 [15]). These laboratory observations support the case that high CIP2A expressing patients should preferentially receive nilotinib from original diagnosis.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

9. National Institute for Health and Clinical Excellence. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. January 2012. http://publications.nice.org.uk/dasatinib-high-dose-imatinib-and-nilotinib-for-the-treatment-of-imatinib-resistant-chronic-myeloid-ta241)

10. National Institute for Health and Clinical Excellence. Leukaemia (chronic myeloid, first line) - dasatinib, nilotinib and standard-dose imatinib (TA251). April 2012. http://guidance.nice.org.uk/TA251

11. Novartis Annual Report 2012. p155-6. http://www.novartis.co.uk/cs/groups/public/@nph_uk_corp/documents/document/n_prod_477856.pdf

12. ARIAD and the U.K. National Cancer Research Institute to Collaborate on SPIRIT 3 Clinical Study. Business Wire 2013. http://www.businesswire.com/news/home/20130107005605/en/ARIAD-U.K.-National-Cancer-Research-Institute-Collaborate

13. The trial specific SPIRIT 3 website is not fully functional as of November 2013. The following public website has some details: http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=15142

14. **Rojas JM, Knight K, Wang L, Clark RE**. Clinical Evaluation of BCR-ABL Peptide Immunisation in Chronic Myeloid Leukaemia: results of the EPIC study. Leukemia 2007; 21: 2287-2295. *This paper was selected by Biomed Central for inclusion in their Faculty of 1000.*

15. **Lucas CM, McDonald E, Holcroft AK, Giannoudis A, Harris RJ, Clark RE**. Second generation tyrosine kinase inhibitors prevent high CIP2A patients progressing to BC by targeting the CIP2A/C-MYC/E2F1 pathway. Submitted to Lancet Oncology November 2013.