Institution: Cardiff University

Unit of Assessment: Clinical Medicine (1)

Title of case study: Optimising treatment regimens for patients with acute myeloid leukaemia

Period when the underpinning research was undertaken: 2002-2015

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:
Hills, Robert	Professor	01/02/2006-31/8/2018
Knapper, Steve	Clinical Reader	01/10/2006-present
Thomas, Ian	Senior Trial Manager	01/07/2008-present
Burnett, Alan (Retired)	Head of Department	02/11/2006-16/6/2014

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? No

1. **Summary of the impact (indicative maximum 100 words)**

Acute myeloid leukaemia (AML) is an aggressive malignancy with a 20% five-year survival rate. From 2002, Cardiff University played a leading role in randomised clinical trials improving treatments for AML. The trials evidenced: (a) the targeted therapy agent Mylotarg® could improve survival rate in AML patients; (b) that treatment with Mylotarg® benefited patients with intermediate cytogenetic risk, as well as those with favourable risk; (c) chemotherapy-free regimens of all-trans retinoic acid plus arsenic trioxide were beneficial for AML patients with Acute Promyelocytic Leukemia (APL). The trial protocols also: (d) established new treatment algorithms and dosing schedules. The research supported new licensing assessments of Mylotarg® in the US and Europe and changed international clinical guidelines through NICE and the European Society for Medical Oncology.

2. Underpinning research (indicative maximum 500 words)

Approximately 3,000 UK patients are diagnosed with acute myeloid leukaemia (AML), an aggressive blood and bone marrow cancer, each year. AML has a 20% five-year survival rate, which diminishes to 5% in individuals over 65 years old.

The drug Mylotarg® (gemtuzumab ozogamicin), which was marketed by Pfizer in 2000, targets the CD33 antigen and provided one of the first significant advances in AML treatment since 1973. Since 2002, Cardiff played a leading role in four significant national UK AML clinical trials featuring Mylotarg®, which provided the majority of intensively treated UK AML patients aged between 18-75 years **[3.1, 3.2, 3.3]**. From 2010, Cardiff also sponsored and managed international AML clinical trials as part of the National Cancer Research Institute (NCRI) programme, involving patients from UK, Denmark and New Zealand. These extensive trials allowed the Cardiff team to identify best practice in the use of Mylotarg® as an effective treatment for AML.

2.1 AML15 and AML16: Mylotarg® improves survival rate in patients with AML

The AML15 and AML16 trials running from 2002 **[G3.1]**, were sponsored by Cardiff with Burnett as Chief Investigator, and Hills as Trial Statistician. Collaborators included University College Hospital and the University of Birmingham, with additional clinical coordination in Leeds, Leicester, Nottingham, and Manchester. AML15 was a randomised trial of 3,484 patients aged under 60 years, with 1,113 patients in the Mylotarg® treatment arm **[3.1]**. Older patients were included in the AML16 trial, involving 2,782 patients, with 1,115 patients randomised to the Mylotarg® treatment arm **[3.2]**.

Both trials compared standard induction chemotherapy with or without the addition of Mylotarg® across all cytogenetic risk groups. Cytogenetic risk refers to the genetic profile of AML patients and predicts response to treatment. Patients with AML are accordingly stratified into favourable, intermediate, or adverse cytogenetic risk groups. The two trials demonstrated

that a single dose of Mylotarg® could improve patient survival, compared to standard induction chemotherapy without Mylotarg®:

- AML15 demonstrated improved overall survival in patients with favourable cytogenetic risk (79% vs 51%) **[3.1]**.
- AML16 confirmed that Mylotarg® improved the three-year survival of older patients across all cytogenetic risk groups (25% vs 20%) and reduced their 30-month relapse rate (from 76% to 68%) **[3.2]**. The reduction in relapses suggested a better 'quality' of remission when Mylotarg® was included in treatment regimens **[3.2]**.

2.2 Meta-analysis of Mylotarg® trial data: Mylotarg® benefits an intermediate cytogenic risk group

In 2000, Mylotarg® was granted restricted approval in the USA for a subset of AML patients (specifically, relapsed patients over 60 years of age). In 2010, a US Mylotarg® randomised trial (SWOG-S0106) was terminated early due to excess mortality, leading to the withdrawal of Mylotarg® from the US market. In response, the Cardiff team undertook and published a comprehensive meta-analysis of outcomes from AML15, AML16, SWOG-S0106 and two smaller French trials (GOELAMS AML2006IR and ALFA 0701) **[3.4]**.

Cardiff's meta-analysis found that the mortality rate in the SWOG-S0106 control arm was exceptionally low; specifically, 1%, where a 5% mortality rate is normally expected from standard induction chemotherapy. Consequently, 5% mortality in SWOG-S0106's Mylotarg® treatment arm was not higher than expected **[3.4]**. Further, the UK and France trials all showed improved outcomes for patients with favourable cytogenetic risk when treated with Mylotarg®. Importantly, the meta-analysis additionally confirmed that these benefits extended to the intermediate cytogenetic risk group, significantly increasing the AML patients who could benefit from Mylotarg® **[3.4]**.

2.3 AML17: Chemotherapy-free regimens for a subset of AML patients

Acute promyelocytic leukaemia (APL) makes up approximately 10% of all AML cases. As part of the AML17 clinical trial (**[G3.2]** involving King's College London) 235 APL patients were treated with a chemotherapy-free regimen of all-trans retinoic acid (ATRA) plus arsenic trioxide. In comparison with standard chemotherapy, the chemotherapy-free regimen reduced the incidence of relapse as well as reducing the requirement for supportive care and the incidence of side effects like neutropenic infections and alopecia **[3.3]**.

This body of research continues via two further significant UK trials, AML18 and AML19, led by Cardiff researchers; these opened for recruitment in 2014.

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

[3.1] Burnett AK, **Hills RK**, Milligan D, Kjeldsen L, Kell J, Russell NH, Yin JA, Hunter A, Goldstone AH, Wheatley K. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *J Clin Oncol.* 2011 Feb 1;29(4):369-77. DOI: 10.1200/JCO.2010.31.4310. Epub 2010 Dec 20.

[3.2] Burnett AK, Russell NH, **Hills RK**, Kell J, Freeman S, Kjeldsen L, Hunter AE, Yin J, Craddock CF, Dufva IH, Wheatley K, Milligan D. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. *J Clin Oncol.* 2012 Nov 10;30(32):3924-31. DOI: 10.1200/JCO.2012.42.2964. Epub 2012 Jul 30.

[3.3] Burnett AK, Russell NH, **Hills RK**, Bowen D, Kell J, **Knapper S**, Morgan YG, Lok J, Grech A, Jones G, Khwaja A, Friis L, McMullin MF, Hunter A, Clark RE, Grimwade D. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. *Lancet Oncol.* (2015) 16(13):1295-1305, October 01, 2015. DOI: 10.1016/S1470-2045(15)00193-X.

[3.4] Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, Estey EH, Dombret H, Chevret S, Ifrah N, Cahn JY, Récher C, Chilton L, Moorman AV, **Burnett AK**. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute

myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol.* (2014) Aug;15(9):986-96. DOI: 10.1016/S1470-2045(14)70281-5. Epub 2014 Jul 6.

Selected grants:

[G3.1] A Burnett and R Hills, 'A phase II/III trial for older patients with acute myeloid leukaemia and high risk myelodysplastc syndrome: Intensive Arm - AML 16', 01/08/2006-30/06/2013, Genzyme Therpeutics Ltd, £ 5,630,750

[G3.2] A Burnett and R Hills, 'AML17: A trial of development of the Myeloid Leukaemia and high risk Myelodysplastic Syndrome in younger patients', 01/08/2008-31/07/2014, Cancer Research UK, £968,641

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

Cardiff researchers' leadership of AML trials, and their robust meta-analysis of clinical trials involving Mylotarg®, provided the comprehensive evidence-base for the re-approval of Mylotarg® in the US, as well as its approval in Europe. The research also resulted in changes to international standards of care through NICE and the European Society for Medical Oncology. These impact outcomes delivered financial benefits for the NHS and Pfizer, and improved treatment options for AML patients globally.

4.1 Licensing of Mylotarg® in the United States and Europe

a. Re-approval for use in the USA

In 2017, Cardiff research was used in Pfizer's submission to the FDA for the re-evaluation of Mylotarg®, aligned to changing the previous FDA license which limited the drug to relapsed patients over 60 years. The submission cites outcomes from AML15 and AML16 **[3.1, 3.2]**, as well as a confidential Individual Patient Database (IPD) meta-analysis undertaken by Cardiff's Hills at the invitation of Pfizer, specifically to inform the company's FDA submission. This analysis, itemised in the FDA license, looked at overall survival and event-free survival from all randomised trials of Mylotarg® **[5.1**, p.37**]**. In the submission, it is acknowledged that "the Applicant [Pfizer] submitted an IPD Meta-Analysis to support the pivotal trial" and that the primary comparison came from "data [from the five trials, which] were provided to Dr. Robert K. Hills (Cardiff University) to perform the meta-analysis" **[5.1**, p.37**]**.

Based on Pfizer's submission, including Cardiff's AML15 and AML16 trials showing positive outcomes in newly diagnosed and untreated patients **[5.1]**, the FDA approved Mylotarg® "for the treatment of adults with newly diagnosed acute myeloid leukemia whose tumors express the CD33 antigen (CD33-positive AML)" **[5.1**, p.290**]**. The approval also covered treatment of patients aged 2 years and older with CD33-positive AML, where they experienced a relapse or were not responding to initial treatment **[5.1**, p.291**]**. The expansion of the patient criteria made Mylotarg® more widely available, effectively accessible to almost all the 21,380 new cases of AML diagnosed in the US in 2017.

b. Approval for use in Europe

Cardiff research further influenced licensing of Mylotarg® in the EU, as well as the European Society for Medical Oncology's clinical practice guidelines on treatment algorithms. The research also delivered financial benefits for Pfizer and the NHS.

In April 2018, Mylotarg® was licensed by the European Medicines Agency (EMA) for use in the EU, specifically "for combination therapy with DNR and AraC for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive AML, except APL" **[5.2]**. Cardiff's trial data and meta-analysis formed a key part of the evidence base for this decision **[5.2]**. Specifically, the EMA's analysis cited **[3.4]** as evidence that the benefits of Mylotarg® were not limited to the favourable cytogenetic risk group and could be extended to the intermediate risk group **[5.2]**.

The current European license now includes patients with both intermediate and favourable cytogenetic risk who are commencing intensive chemotherapy **[5.2]**. This significantly expanded the proportion of newly diagnosed AML patients able to receive Mylotarg®. For

example, in patients aged 66-75 years, while only 5% have favourable risk cytogenetics, 56% have intermediate risk cytogenetics.

Cardiff research on Mylotarg® efficacy also led to cost benefits for drug manufacturers and the NHS. For example, following the approval of Mylotarg® in the EU, Pfizer stated in their 2019 financial report that arrangements surrounding the licensing of the drug led to "a non-cash $17 million pre-tax gain…in the second quarter of 2018" **[5.3**, p.100**]**. Additionally, the AML18 and AML19 trials, which commenced in 2014, generated an overall cost-benefit to the NHS (e.g., estimated in an NHS 2014 Specialized Services Circular to be greater than £7.5M between 2014 and 2020 **[5.4]**). The cost-benefit arises from the Cardiff-led trials' eligibility for Blueteq Approval funding in England **[5.5** p.88**]**.

4.2 New standards of treatment in international clinical guidelines

a. European Society for Medical Oncology

Cardiff research influenced both the August 2013, and 2020, versions of the European Society for Medical Oncology's clinical practice guidelines for AML. In the 2020 guidelines, **[3.1]** is cited as evidence to support recommendations for treatment algorithms involving Mylotarg® as a first-line therapy for newly diagnosed adult AML patients **[5.6** p.700**]**. The 2020 guidelines stated: "Our recommendation is based primarily on the meta-analysis **[3.4]** of five studies with GO (Mylotarg®), in which patients with CBF-AML …benefit most from the addition of GO [GO improved 6-year overall survival (OS) by 20.7% to an OS of 75.5% in this meta-analysis]" **[5.6** p.702**]**. The 2020 clinical practice guidelines also cite AML17 **[3.3]** in recommendations for treating APL with all-trans retinoic acid (ATRA) and arsenic trioxide **[5.6** p.706**]**.

b. NICE Technical Appraisals

The Cardiff trial data was used by NICE as part of 'Technical Appraisal TA545 Gemtuzumab ozogamicin [Mylotarg®] untreated acute myeloid leukaemia' **[3.4, 5.7]**. Cardiff's Knapper advised the TA545 Appraisal Committee that approved Mylotarg® for treatment of AML. In their submission to the NICE committee, Pfizer used pooled survival data from the Cardiff trials including AML15 and AML16 **[3.1, 3.2]** as well as the Cardiff meta-analysis **[3.4]**. The cost-benefit analysis in the NICE Appraisal uses the Cardiff research survival rate of 5% after five years (i.e., at five years, one extra patient in 20 is alive) **[3.4, 5.7**, p.112**]**. The Appraisal further notes the importance of Cardiff's trial data, stating that the cost benefit was "derived using an analysis of pooled survival data from UK AML trials 10 to 16…performed by Professor Robert Hills (see Appendix M.4) which is ideally suited for calculating an excess mortality HR to better inform the economic evaluation of this submission compared to published literature" **[5.7,** p.112**]**.

The findings of AML17 **[3.3]**, with respect to beneficial treatment with ATRA plus arsenic trioxide, were also included as supporting evidence for NICE 'Technical Appraisal TA526 Arsenic trioxide for treating acute promyelocytic leukaemia' **[5.8** p.9**]**. Outcomes from AML17 were further used as evidence to support the EMA's 2020 decision to license arsenic trioxide for low-to-intermediate risk APL patients across Europe **[5.9]**.

These decisions had far-reaching benefits on clinical practice. For example, Spearing, Haematologist at Christchurch Hospital in New Zealand noted: *"As a result of the findings of Cardiff University-led research, we have implemented new standards in the treatment of AML in New Zealand patients"* **[5.10]**. Specific changes to treatment from AML17 **[3.3]** *"included … the use of arsenic trioxide and all-trans retinoic acid for low and standard risk acute promyelocytic leukaemia patients rather than the chemotherapy-centred Idarubucin and all-trans retinoic acid, which had been the previous standard"* **[5.10]**.

AML trials are now standard of care for patients in New Zealand **[5.10],** and Spearing noted that the new chemo-free regimen implemented in AML17 **[3.4]** "*resulted in a high cure rate with less relapse, and a lower requirement for ongoing supportive care of patients"* **[5.10]**. She also highlighted positive outcomes for patients from the ongoing AML19 trial: *"The minimal residual disease monitoring of AML19 has saved a significant number of patients undergoing allogeneic transplantation*" **[5.10]**, which is the most invasive and high-risk treatment for AML.

In summary, Cardiff's leadership of AML clinical trials on Mylotarg®, and meta-analysis of different clinical trial outcomes, provided robust data used to inform expansion of licensing for Mylotarg® in the US and EU, and changes to treatment standards in clinical guidelines (e.g., NICE and the European Society for Medical Oncology). Ongoing trials informed by this research continue to save lives, actively leading to better outcomes for AML patients.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[5.1] FDA drug approval of Mylotarg® documents: **a)** Clinical Review 1 (p.1-107 in the combined pdf), **b)** Clinical Review 2 (p.108-257 in the combined pdf), **c)** Statistical Review (p.258-288 in the combined pdf), **d)** Food and Drug Administration press release (p.289-290 in the combined pdf)

[5.2] EMA approval of Mylotarg

[5.3] Pfizer 2019 Financial Report

[5.4] NHS Commissioning Letter Specialised Services Circular AML18 and AML19

[5.5] National Cancer Drugs Fund List

[5.6] ESMO guidelines; **a.** ESMO 2013 Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, numbered 138-143 (p.1-6 in the combined pdf), and, **b.** ESMO 2020 Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, numbered 697-712 (p.7-22 in the combined pdf)

[5.7] NICE TA545 and associated committee papers and evidence appraisal documents

[5.8] NICE TA526 Arsenic trioxide for treating acute promyelocytic leukaemia

[5.9] EMA approval of arsenic trioxide, and recommendations from the European LeukaemiaNet expert panel

[5.10] Letter from Ruth Spearing, Christchurch Hospital, New Zealand