Institution: University of Leeds

Unit of Assessment: UOA1 Clinical Medicine

Title of case study: Case Study 2

Clinical trials show that the novel cytotoxic drug eribulin prolongs survival in women with heavily pre-treated metastatic breast cancer

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

Clinical trials designed and led by Professor Chris Twelves (University of Leeds) showed eribulin to be the first single agent cytotoxic to prolong survival in women with heavily pre-treated metastatic breast cancer (MBC).

Eribulin has been approved by European, U.S. and other regulatory authorities since 2010. Cancer treatment guidelines in the U.S., Europe and elsewhere now recommend eribulin. Sales of eribulin generated many millions of pounds in the first full year following approval. Already tens of thousands of women have been treated with eribulin, who collectively have gained up to ten thousand added life years. The U.S. regulatory authorities have advocated the EMBRACE trial design for future trials.

2. Underpinning research (indicative maximum 500 words)

The survival of women with early breast cancer has improved at least in part as a result of trials such as NEAT/BR9601 (**Twelves, co-CI;** University of Leeds, Professor of Clinical Cancer Pharmacology and Oncology since 2003), to which Leeds contributed (**Perren**, University of Leeds, Senior Lecturer in Medical Oncology to 2002 and Professor of Women's Cancers and Oncology since 2013). (1). The treatment of women with MBC remains, however, palliative. Since 2000 only 8 new cytotoxic or targeted agents have been approved by the FDA in women with MBC; **Twelves** was closely involved with the development of two of them, capecitabine (2) and more recently eribulin, both of which prolong survival for women with MBC.

As Chair of the EORTC New Drug Development Group from 2002 to 2004, **Twelves** had previously worked with Dr Jantien Wanders in early drug development (2). Dr Wanders moved (as Executive Director, Oncology) to the Japanese pharmaceutical company Eisai that developed eribulin. This is a novel cytotoxic and synthetic analogue of a product derived from a marine sponge; eribulin inhibits mitosis through action on microtubules, but acts at a binding site different to that of other cytotoxics. Whilst in Leeds, **Twelves** worked with Dr Wanders and her colleagues at Eisai preparing their November 2005 submission to the European Committee for Medicinal Products for Human Use (CHMP) of initial phase II results with eribulin and participating in the meeting with the CHMP at which they requested three further studies.

Between 2006 and 2012, **Twelves** was played a key role, with Eisai and international co-investigators, in the design, planning, conduct and analysis of these three studies.

The first was a larger, confirmatory phase II study with eribulin (Dr Vahdat, Spain, Chief Investigator; **Twelves**, Co-Investigator and **Perren)** that substantiated the activity of eribulin in women with heavily pre-treated MBC (4).

EMBRACE was the second study and the definitive global phase III trial (**Twelves**, Co-Chief Investigator with Dr Cortes, Spain) that led to the adoption of eribulin in clinical practice. There being no currently approved standard treatment in heavily pre-treated patients, this was the first pivotal study to incorporate 'treatment of physician's choice' (TPC) as the 'control' arm. We also challenged the dogma that it was over-ambitious to seek improved overall survival in patients with such advanced disease, using survival as the "make or break" primary endpoint rather than a surrogate marker such as progression-free survival. EMBRACE recruited 756 women with heavily pre-treated MBC at over 100 centres worldwide (including Leeds, **Perren**) between 2006 and 2008. Survival was significantly longer, by 2.5 months, in women who received eribulin compared

to TPC; other efficacy outcomes also favoured eribulin. Toxicities were comparable between treatment arms (5).

Finally, the Study 301 phase III trial (**Twelves**, Co-Chief Investigator with Dr Kaufman, USA) recruited between 2006 and 2009 and compared eribulin with capecitabine in over a thousand women with less heavily pre-treated MBC. There was a trend for improved survival in the eribulin arm, but this did not reach statistical significance; sub-group analyses suggest that women with specific molecular sub-types of MBC (especially "triple negative" cancers) may gain particular benefit from eribulin. These data were presented at the 2012 San Antonio Breast Cancer Symposium.

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

1. Earl HM, Hiller L, Dunn JA, Vallier AL, Bowden SJ, Jordan SD, Blows F, Munro A, Bathers S, Grieve R, Spooner DA, Agrawal R, Fernando I, Brunt AM, O'Reilly SM, Crawford SM, Rea DW, Simmonds P, Mansi JL, Stanley A, McAdam K, Foster L, Leonard RC, **Twelves** CJ, Cameron D, Bartlett JM, Pharoah P, Provenzano E, Caldas C, Poole CJ; NEAT Investigators and the SCTBG. Adjuvant epirubicin followed by cyclophosphamide, methotrexate and fluorouracil (CMF) vs CMF in early breast cancer: Results with over 7 years median follow-up from the randomised phase III NEAT/BR9601 trials. Br J Cancer. 2012 Oct 9;107(8):1257-67.
Updated analysis, carried out after Twelves had moved to Leeds, of the UK national trial (on which Twelves was co-CI) that definitively established the benefit of incorporating an anthracycline in adjuvant chemotherapy.

2. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L, **Twelves C**, Van Hazel G, Verma S, Leonard R. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002 Jun 15;20(12):2812-23.
This trial was one of the first to demonstrate superior survival with the addition of a new agent, in this case capecitabine, to standard therapy in the form of docetaxel as first line chemotherapy for MBC.

3. Ravaud A, Cerny T, Terret C, Wanders J, Bui BN, Hess D, Droz JP, Fumoleau P, **Twelves C** Phase I study and pharmacokinetic of CHS-828, a guanidino-containing compound, administered orally as a single dose every 3 weeks in solid tumours: an ECSG/EORTC study. Eur J Cancer. 2005 Mar; 41(5):702-7.
One of the Phase I trial by the EORTC through which important links were established between Drs Twelves and Wanders.

4. Cortes J, Vahdat L, Blum JL, **Twelves C**, Campone M, Roche H, Bachelot T, Awada A, Paridaens R, Goncalves A, Shuster DE, Wanders J, Fang F, Gurnani R, Richmond E, Cole PE, Ashworth S, Allison MA. Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2010; 28: 2922-28.
This large phase II study confirmed the activity of eribulin in women with heavily pre-treated MBC using the dose and schedule that was definitively tested in the EMBRACE trial and Study 301.

5. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat L, Petrakova K, Chollet P, Manikas A, Dieras V, Delozier T, Vladimorov V, Cardoso F, Koh H, Bougnoux P, Dutcas C, Seegobin S, Mir D, Meneses N, Wanders J, **Twelves C**. Erubulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label study. Lancet 2011; 377: 914-23.
Eribulin is the first single agent cytotoxic to improve survival in heavily pre-treated MBC; the benefits of eribulin compared to TPC were apparent across a wide range of patient sub-groups. This study has been central to the increasing use of eribulin in routine clinical practice.

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

Research led academically from Leeds University has demonstrated clinical benefit from a new drug, eribulin, for patients with metastatic breast cancer with eribulin now approved for use, being sold worldwide, incorporated into international treatment guidelines and bringing benefits to patients.

Dissemination

The key eribulin trials described here were reported in high profile, peer reviewed publications (4,5). The EMBRACE study (A) and Study 301 (B) both featured in the ASCO Post, the "house newspaper" for the American Society of Clinical Oncologists (which has more than 30,000 oncologists as members), as highlights from the annual meeting of the American Society of Clinical Oncology in 2010 and San Antonio Breast Cancer Symposium in 2012. The EMBRACE trial in particular attracted wide attention in the public media (C).

Recommendations for use: Professional bodies and guidelines

Primarily as a result of the EMBRACE results, showing a clinically and statistically significant increase in median overall survival of 2.49 months in women who had exhausted other approved therapies (5), eribulin has been included in the North American (NCCN) (D) guidelines amongst the "preferred drugs" for MBC and the European (ESMO) (E) guidelines as one of the "new cytotoxic agents" for the treatment of metastatic breast cancer. Eribulin was on the Cancer Drug Fund "approved" list in all 10 English regions; it is on the new National list and expected to continue under new arrangements with the Commissioning Board (F).

Changes in policy: Governmental/regulatory bodies

The EMBRACE results showed improved overall survival, an endpoint not achieved by any of the other four single agents approved since 1975 by the FDA for the treatment of MBC. Eribulin (marketed as Halaven) received regulatory approval from the United States FDA in 2010 (G); it was the first cytotoxic to be granted initial approval for refractory metastatic breast cancer on the basis of overall survival data. Subsequently, eribulin was approved in the E.U. by the EMEA (H), and is now approved in 81 countries world-wide.

The EMBRACE trial design was unique in using 'treatment of physician's choice' as the control arm for a registration trial, there being at the time no standard approved therapy for this group of patients. EMBRACE was also unusual being the first study in MBC to select improved overall survival as the primary endpoint and be successful. The US FDA has since commended the use of 'treatment of physician's choice' as the control arm in EMBRACE and the choice of overall survival as a primary endpoint in certain situations (I). Novel aspects of the EMBRACE trial design have been adopted by in registration trials of NKTR-102 (the BEACON trial by Nektar) (J) and T-DM1 (the TH3RESA trial by Roche/Genentech) (J).

Changes in practice: treatment, services and commerce

Eribulin, and subsequent use of eribulin, have generated commercial impacts. Total sales of eribulin across all regions of the world were £330m, including £72m in the EU, from 2011 to September 2013 (K). Eisai, which is based in the US but with its European office in the UK, has increased its EU workforce from none in 2009 to over 100 in 2013 for the production, distribution and marketing of eribulin both within the UK and internationally (K). Sales of eribulin underpinned R & D investment by Eisai which has a budget of many millions in 2012 (K).

Changes in health outcomes: patients

Sales figures from Eisai show that thousands of women with metastatic breast cancer have been treated with eribulin (K). It is too early to measure directly the impact of eribulin on the survival of women with MBC, and this would be complicated by other changes in care. Given the 2.49 month survival benefit shown by level 1 data from the EMBRACE study, with over 40,000 women with MBC having received eribulin to date (K), approaching 10,000 additional life years have been gained from treatment with eribulin.

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

[A] Helwick C. Novel agent improves survival in women with heavily pre-treated locally recurrent or metastatic breast cancer. The ASCO Post, July 2010, vol 1, issue 2, p 14.

http://issuu.com/ascopost/docs/tap-vol-1-issue-2

Article for oncologists describing the EMBRACE trial after its presentation at the American Society of Clinical Oncology in May 2010.

[B] Helwick C. Primary endpoint not met for eribulin vs capecitabine in breast cancer. The ASCO Post, February 2013, vol 4, issue 2.

http://www.ascopost.com/issues/february-1,-2013/primary-endpoint-not-met-for-eribulin-vs-capecitabine-in-breast-cancer

Article for oncologists describing the Study 301 results after its presentation at the San Antonio Breast Cancer Symposium in May 2012.

[C] Marine sponge drug extends breast cancer survival: study. The Independent Online 7th June 2010. An example of extensive international coverage of the EMBRACE trial in the general media.

[D] NCCN guidelines version 1.2013.
http://www.nccn.org/professionals/physicians_gls/pdf/breast.pdf.

North American guidelines for the treatment of breast cancer that recommend the use of eribulin in women with metastatic disease.

[E] Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E, on behalf of the ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23 (suppl 7): vii11-vii19.

http://annonc.oxfordjournals.org/content/23/suppl_7/vii11.full. *European guidelines for the treatment of breast cancer that recommend the use of eribulin in women with metastatic disease.*

[F] http://www.commissioningboard.nhs.uk/about/

[G] US Food and Drug Administration eribulin mesylate approval for granted November 15th 2010. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm234527.htm .

Documents regulatory approval of eribulin from the United States FDA in 2010 (G) and specifically refers to the Phase II trial and to EMBRACE.

[H] European Medicines Agency approval for eribulin mesylate granted March 23rd 2011.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002084/human_med_001427.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125.
As above (see G) *documents approval of eribulin in this case by the European regulators.*

[I] Cortazar P, Justice R, Johnson J, Sridhara R, Keegan P, Pazdur R. US Food and Drug Administration approval overview in metastatic breast cancer. J Clin Oncol. 2012; 30(14):1705-11.

Review describing FDA approvals of drugs in metastatic breast cancer, including eribulin and the EMBRACE trial, that also discusses the use of "treatment of physician's choice" and the importance of improved overall survival as an outcome measure.

[J] The BEACON Study (Breast Cancer Outcomes With NKTR-102): A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 Versus Treatment of Physician's Choice (TPC) in Patients With Locally Recurrent or Metastatic Breast Cancer Previously Treated With an Anthracycline, a Taxane and Capecitabine.
http://clinicaltrials.gov/ct2/show/NCT01492101?term=NKTR-102&rank=6.

A Study of Trastuzumab Emtansine in Comparison With Treatment of Physician's Choice in Patients With HER2-Positive Breast Cancer Who Have Received at Least Two Prior Regimens of HER2-Directed Therapy (TH3RESA).

http://clinicaltrials.gov/ct2/show/NCT01419197?term=TH3RESA&rank=1

Important clinical trials that incorporate major novel aspects of the EMBRACE trial design, reflecting impact on breast cancer research worldwide.

[K] Letter from Global Medical Affairs Director (Oncology), Eisai Europe Limited.