HELPING INTRODUCE NEW BREAST CANCER THERAPY TO THE GLOBAL MARKET

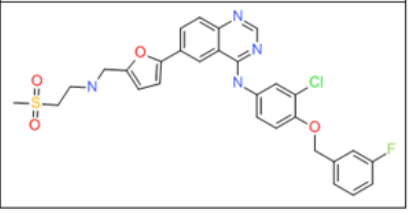
There is a 1 in 8 chance of a woman having invasive breast cancer during her lifetime. Around 12–15% of all breast cancers over-express the cell surface tyrosine kinase receptor human epidermal growth factor receptor 2 (HER2+). These patients have a more aggressive disease than those who are HER2-negative, and a higher chance of developing incurable, life-threatening metastatic disease. The drug trastuzumab (Herceptin) is used to treat such cases, but in most patients, resistance develops and alternative therapies are needed. No such therapies were available before the development of lapatinib.

PUTTING RESEARCH INTO ACTION:
DETAILED ANALYSIS OF TRIAL OF LAPATINIB IN COMBINATION WITH CAPECITABINE IN ADVANCED, HER2+ BREAST CANCER

Professor David Cameron from the Cancer Research UK Edinburgh Centre, as joint global Chief Investigator, undertook the detailed analysis of sub-group outcomes that identified cohort benefit in advanced metastatic breast cancer in the capecitabine and lapatinib HER2+ metastatic breast cancer trial [1]. Crucially, further analyses of the trial data by Cameron and colleagues identified evidence that there might be a subgroup of patients who particularly benefited from the addition of lapatinib. Circulating serum markers and tumour characteristics failed to identify patients who did not benefit from the use of lapatinib [2–4], other than those whose tumours were not centrally confirmed to be HER2-over-expressing.

After preliminary pre-clinical, phase I and phase II studies that confirmed the efficacy of lapatinib in previously treated HER2+ metastatic breast cancer, and the demonstration of an acceptable tolerability profile when combined with the chemotherapy agent capecitabine, it was clear that there was real potential for this combination to be effective in treating metastatic breast cancer that overexpressed HER2 and was no longer responding to trastuzumab (Herceptin). In liaison with colleagues at GlaxoSmithKline (GSK), Cameron (who assumed the role of joint global chief investigator) led a multinational, multicentre randomised phase III trial to test the hypothesis that the combination of lapatinib and the cytotoxic drug capecitabine would be superior to capecitabine alone in patients with HER2+ metastatic breast cancer that had progressed despite trastuzumab treatment. Trial design and execution was closely aligned to FDA (US Food and Drug Administration Agency) requirements to maximise the opportunity to bring a new treatment to the clinic rapidly. Patients were recruited in 2004–2006 and the Independent Data Monitoring Committee (IDMC) reviewed an interim analysis of the study in March 2006, and recommended that the trial be stopped and patients allowed to cross over to the research arm. The interim analysis data were published in late 2006 [1]. The data-set that was used for the European (and many other countries') application for marketing authorisation was the analysis of all enrolled patients that was published in 2008 [2].

CHEMICAL FORMULA AND STRUCTURE
Lapatinib

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Lapatinib	231277-92-2	C29-H26-Cl-F-N4-O4-S	

The trial showed that the time to disease progression (worsening of the cancer) almost doubled in patients with HER2+ advanced breast cancer treated with lapatinib in combination with capecitabine compared with the use of capecitabine alone, with median times to progression significantly better in the combination arm (8.4 months) compared with the single arm (4.4 months) ($p < 0.001$, hazard ratio = 0.47). In addition there was evidence of a higher rate of tumour shrinkage (objective response rate) on the combination therapy with a 22% response rate, while the response to capecitabine alone was 14% ($p = 0.09$).

Data on quality of life for patients on this therapy [5], and a final survival analysis [6] have also been published. These report that there are quality of life benefits, despite the modest toxicity, as well as some evidence of a survival benefit

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for those patients being offered this combination after only one trastuzumab-containing regimen for metastatic breast cancer.

DETAILS OF THE IMPACT

The widespread adoption of lapatinib as a combination agent for advanced breast cancer hinged on the detailed analysis of sub-groups led by Cameron [2–4]. The results of the phase III trial with lapatinib confirmed the clinical efficacy of a small molecular tyrosine kinase inhibitor in patients with HER2+ breast cancer for which trastuzumab was no longer effective. Lapatinib was the first agent to be approved for use in HER2+ breast cancer after trastuzumab.

Impact on health and welfare

There is no robust data available on the number of patients treated with lapatinib, but it is likely to be around 10,000 or more each year, based on the drug costs and average duration of therapy. For women with advanced HER2+ breast cancer, who without effective therapy have a poor prognosis, the use of lapatinib plus capecitabine offers an entirely oral, effective therapy once the disease has become resistant to trastuzumab, which is the first-line therapy. The treatment is not curative — cures are rare in metastatic breast cancer — but it delivers clear clinical benefits for patients. Also, because of the availability of lapatinib, a phase II study compared radiotherapy with capecitabine plus lapatinib, and confirmed that this combination was an equally effective alternative to conventional radiotherapy for treating patients with HER2+ breast cancer metastatic to the brain.

Impact on commerce and the economy

Lapatinib (commercialized as Tykerb/Tyverb) generated sales for the UK-based company (GSK) of £227M in 2010, £231M in 2011, £239M in 2012, £207M in 2013 and £171M in 2014. In addition, but hard to quantify, there are economic benefits of an effective therapy for patients with advanced breast cancer – some are able to continue working because their disease is being better controlled.

Impact on public policy

The positive results of this pivotal, registration phase III trial led to marketing authorisations in 107 countries including the USA, Europe, Australia, India, Brazil, Russia, Turkey, South Korea and other countries around the world. The majority of these authorisations occurred after 1st Jan 2008; for example, the European Commission granted a conditional marketing authorisation for lapatinib in all 27 European Union (EU) member states on June 10, 2008. The option of using lapatinib in combination with capecitabine was recommended within several guidelines (e.g., European School of Oncology, German Gynecological Oncology Group (Arbeitsgemeinschaft Gynaekologische Oncologie, AGO), National Comprehensive Cancer Network (NCCN) guidelines in the USA and European Society for Medical Oncology (ESMO) guidelines). Although it is licensed in the UK, the regimen was not approved by either the National Institute for Health and Care Excellence (NICE) or the Scottish Medicines Consortium (SMC), as it was felt to be insufficiently cost-effective. Denial to fund this treatment led to intensive patient-led campaigning, and the lapatinib-treatment-seeking patient Nikki Blunden, whose case was highlighted in the House of Commons (June 16, 2010), became "the face" of the Government's £50M emergency fund to pay for new cancer drugs for those with life-shortening cancer. From October 2010 until February 2011, 195 patients obtained lapatinib treatment due to the interim cancer drugs funding, and from April until September 2011 more than 350 patients received the drug with support from the Cancer Drugs Fund. Lapatinib used in this indication was one of the top ten drugs within the English Cancer Drugs' fund with an approval rate of 94% (June 2011), reflecting strong UK clinician support for the treatment whose efficacy was confirmed by the phase III trial.

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