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Challenges in the treatment of ErbB2 (HER2)-positive breast cancer

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ABSTRACT

This article reviews the challenges and future options in the treatment of ErbB2-positive metastatic breast cancer. It summarizes a presentation from a symposium that was held at the ECCO 14 congress in 2007.

Despite great progress in the management of ErbB2-positive metastatic breast cancer, significant challenges remain in these patients. Many patients do not respond to trastuzumab-containing regimens or develop progressive disease within 1 year. Continuing trastuzumab in these patients has yet to show proven clinical benefit in prospective studies. Several targeted agents have been developed to overcome the limitations of current targeted therapy for ErbB2-positive breast cancer. One such agent, lapatinib, was recently approved in Europe in combination with capecitabine in patients previously treated with trastuzumab in the metastatic setting. The intracellular site of action of lapatinib may underlie substantial clinical benefit.

Based on available data to date, novel ErbB2-targeted therapies may hold significant promise in the management of ErbB2-positive metastatic breast cancer.

1. Introduction

Breast cancer is the most common neoplasia in women: approximately 430,000 new cases are diagnosed annually in Europe alone, and in 2006 breast cancer represented one in seven (13.5%) of all cancers diagnosed, and 29% of all female cancers.[1] This disease is associated with significant mortality; in Europe, for example, there were 132,000 breast cancer-related deaths in 2006.[1] Up to 30% of breast carcinomas overexpress the ErbB2 (HER2) receptor,[2] with conservative estimates ranging from 15% to 25%.[3,4] Overexpression of ErbB2 is even more prevalent in breast carcinomas that follow an aggressive clinical course, with estimates ranging from 44% to 48% of breast carcinomas in women aged $\leqslant$40 years,[5,6] and in 50–59% of inflammatory breast cancer (IBC) biopsies.[7,8] Overexpression of ErbB2 is clinically relevant, since this is an independent prognostic factor in patients with breast cancer.[3] Indeed, overall survival (OS) is significantly shorter for patients with ErbB2-positive versus ErbB2-negative breast cancer.[3,9] The aggressive nature of ErbB2-positive breast cancer has prompted the suggestion that this should be considered a distinct form of the disease.

The ErbB2 receptor belongs to the ErbB or epidermal growth factor receptor family that, with the exception of ErbB2, have a variety of growth factors as physiological ligands; this topic has been reviewed in detail elsewhere.[10] The first step in the activation of the ErbB-family receptors is ligand binding, triggering dimerization, which leads to phosphorylation of the

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cytoplasmic tyrosine kinase domain and, finally, activation of intracellular signalling pathways associated with growth and cell survival. [10] However, ErbB2 is the only member of the ErbB family with no known natural or physiological ligand. [11] Instead, it is held in a pre-primed conformation similar to ErbB monomers that have already bound ligand, allowing it to readily form homodimers or heterodimers with other ligand-bound ErbB family members, to stimulate intracellular signalling. [10,11] Consequently, ErbB2 is the preferred partner for other ErbB family members, [10] notably ErbB3, which is co-expressed with ErbB2 in aggressive forms of breast cancer, such as IBC. [11] The ErbB3 receptor lacks a functional intracellular tyrosine kinase domain and must, therefore, bind ligand and dimerize with another ErbB member (usually ErbB2) to induce intracellular signalling. [11] The composition of the ErbB heterodimer or homodimer determines the signal transduction pathway that is activated, and the cellular processes affected. [10]

Despite the success of targeted agents such as trastuzumab in the treatment of ErbB2-positive breast cancer, unmet needs still remain, particularly in patients with heavily pretreated metastatic disease. Many patients with ErbB2-positive metastatic breast cancer either do not respond to trastuzumab therapy, [12–14] or progress within 1 year of initiating trastuzumab treatment. [2,12–14] Until recently, these patients have had no available recommended treatment options. [15,16] New, effective and safer targeted alternatives, either as monotherapy or in novel combinations, are needed for these patients.

This review will highlight the current challenges in the treatment of metastatic ErbB2-positive breast cancer, with special focus on those patients who have been pretreated with trastuzumab. The concept of continued or lifelong ErbB2 suppression with a targeted agent in patients no longer sensitive to trastuzumab will also be briefly discussed. The latest advances in the targeted treatment of ErbB2-positive breast cancer, which are now beginning to translate initial preclinical promise into clinical benefit, will be overviewed. Finally, special emphasis will be placed on lapatinib – the first oral, small molecule, dual-targeted therapy that works intracellularly to inhibit both ErbB1 and ErbB2 – as it is at the most advanced stage of the new targeted agents in development for ErbB2-positive breast cancer.

2. Management of ErbB2-positive metastatic breast cancer – current options and challenges

The treatment of metastatic breast cancer is palliative, with the aim of prolonging survival while maintaining the quality of life of the patient, and typically involves hormone or chemotherapy with or without trastuzumab. [15] Radiation therapy is also an integral part of this palliative treatment. [15] According to the current European Society for Medical Oncology (ESMO) guidelines, trastuzumab with or without non-anthracyline-containing chemotherapy is the only recommended option for the treatment of ErbB2-positive metastatic breast cancer. [15]

2.1. Successes and limitations with trastuzumab in ErbB2-positive metastatic breast cancer

The ESMO recommendations were based on clinical studies that demonstrated prolonged time to progression (TTP) and OS with trastuzumab in combination with a taxane (paclitaxel or docetaxel) versus taxane alone, as first-line treatment in patients with ErbB2-positive metastatic breast cancer. [15] In a subanalysis of the pivotal trial for trastuzumab, the combination of trastuzumab with paclitaxel increased median TTP (7.1 versus 3.0 months; $p < 0.05$) and OS (25 versus 18 months) compared with paclitaxel monotherapy in patients with ErbB2-positive metastatic breast cancer; however, the OS increase was not statistically significant in this subgroup. [14] Also, in a Phase II trial of metastatic breast cancer patients who received trastuzumab in combination with docetaxel, OS was significantly prolonged in the trastuzumab-containing arm compared with docetaxel monotherapy (31.2 versus 22.7 months, respectively; $p = 0.0325$). Further, median TTP was significantly prolonged compared with docetaxel treatment alone (11.7 versus 6.1 months, respectively; $p = 0.0001$). In this study, ErbB2 positivity was defined by immunohistochemistry and, where necessary, confirmatory fluorescence *in situ* hybridization (IHC3+ or IHC2+/FISH+). [12]

The successes with trastuzumab also highlight the unmet needs that remain in the management of ErbB2-positive metastatic breast cancer. A substantial proportion of patients did not respond to the trastuzumab-containing regimens in the Phase II (39% non-responders) and Phase III (51% non-responders) trials described above. [12–14] Furthermore, the median TTP results suggest that the majority of patients with ErbB2-positive metastatic breast cancer who do respond to trastuzumab plus a taxane or vinorelbine will subsequently develop progressive disease within 1 year of initiation of therapy. [2,12–14] Therefore, there is an urgent need for treatment alternatives for these patients.

2.2. Treatment beyond trastuzumab: the need for clinical data to test validity of continued ErbB2 suppression

The current ESMO guidelines do not recommend treatment options for patients with ErbB2-positive metastatic breast cancer pretreated with trastuzumab-containing regimens. [15] Although it is common practice for trastuzumab treatment to be continued in these patients, there is a lack of robust (Level 1) clinical evidence, and no licensed indication, to support this use. [17,18] Clinical trials data are, therefore, required to further

evaluate the validity of continued ErbB2 suppression in patients no longer sensitive to trastuzumab.

2.3. *Trastuzumab cardiac safety profile*

Cardiac safety data are available from several pivotal trials evaluating trastuzumab-containing regimens in patients with ErbB2-positive early breast cancer (HERA; NSABP B-31; NCCTG N9831; and BCIRG 006).[19–22] In these trials, trastuzumab-containing regimens were associated with a 0.4–3.9% incidence of severe congestive heart failure and a 3–18.1% decrease in left ventricular ejection fraction (LVEF).[19–22] Notably, the highest cardiac adverse-event rates were associated with trastuzumab-containing regimens in patients previously treated with anthracycline-based chemotherapy.[19–22] A similar observation was made in earlier trials in the metastatic setting; consequently, anthracycline is not a recommended chemotherapy option for combination with trastuzumab in the current ESMO guidelines, even though this regimen was shown to provide a clinical benefit in terms of significantly prolonged median TTP and OS in the pivotal Phase III trial.[13,14]

2.4. *Management of brain metastases in ErbB2-positive breast cancer*

Brain metastases develop in 25–30% of women with ErbB2-positive breast cancer.[23–27] The 1-year survival rate for breast cancer patients with brain metastases is <20%,[28] and median survival is shorter in patients with ErbB2-positive disease versus ErbB2-negative disease.[29] Worryingly, the incidence of brain metastasis has increased since the advent of targeted treatments for metastatic ErbB2-positive breast cancer.[30] This increasing incidence of brain metastasis is possibly due to longer patient life expectancy with improved treatment of the primary breast tumour.[31]

Therapeutic options (besides radiation) are very limited for the treatment of brain metastases and, since none are curative and all have limited efficacy, prognosis is poor. Novel targeted treatment options are, therefore, urgently required to improve outcomes in these patients.

3. Meeting the challenges of current unmet needs in ErbB2-positive breast cancer

There are broadly two types of targeted agent, either already available in the clinic (trastuzumab and lapatinib) or in development, for the treatment of ErbB2-positive breast cancer – monoclonal antibodies (mAb) and small molecule targeted agents.

3.1. *Monoclonal antibodies*

Monoclonal antibodies, approved or in development, include those that target the ErbB2 receptor (trastuzumab and pertuzumab) or the vascular endothelial growth factor (VEGF; bevacizumab) pathway (Figure 1). Trastuzumab, which is approved for the treatment of ErbB2-positive breast cancer, and pertuzumab, which is in Phase II development for ErbB2-positive breast cancer, recognize distinct epitopes on the extracellular domain of the ErbB2 receptor.[32] Trastuzumab appears to act in different ways preclinically and clinically, and its precise mechanism of action is not well defined. Preclinically, trastuzumab inhibits activation of downstream signalling pathways that are involved in cellular proliferation (Ak transforming factor [Akt] and cyclin dependent kinase-2 [CDK2]).[33] However, increasing evidence suggests that trastuzumab may act clinically by stimulating lymphoid and natural killer (NK) cell tumour infiltration and subsequent antibody-mediated cellular cytotoxicity (ADCC).[34,35] In contrast, pertuzumab appears to act by preventing ligand-bound ErbB2 receptor monomers from forming dimers, thereby inhibiting receptor tyrosine kinase activation and blocking downstream signalling (Figure 1).[32]

The humanized mAb bevacizumab binds to VEGF to inhibit VEGF receptor (VEGFR)-mediated intracellular signalling pathways that promote angiogenesis, thus disrupting the tumour vasculature (Figure 1).[36] This agent is in Phase III development for the treatment of ErbB2-positive breast cancer. Trastuzumab-DM1 is a novel chemotherapy agent conjugated with trastuzumab.[37] Conjugation to trastuzumab enables the chemotherapy to be delivered specifically to the ErbB2-overexpressing breast tumour cell. This agent is in Phase I development for the treatment of ErbB2-positive breast cancer.[37]

3.2. *Small molecule targeted agents*

Several small molecule targeted agents (gefitinib, erlotinib, lapatinib, HKI-272, sunitinib and pazopanib) are in development or approved for the treatment of ErbB2-positive breast cancer. Erlotinib and gefitinib are ErbB1-targeted agents (Figure 1),[38,39] while lapatinib is the first oral, small molecule, dual-targeted therapy that works intracellularly to inhibit both ErbB1 and ErbB2.[40] HKI-272 is also a dual inhibitor of ErbB1 and ErbB2, but unlike lapatinib, which binds reversibly to its targets, HKI-272 is an irreversible inhibitor, and is currently in Phase I development.[41] Erlotinib is in Phase II development for ErbB2-positive breast cancer, whereas lapatinib has been approved in Switzerland, the European Union (EU) and the USA.

The multi-targeted agent sunitinib inhibits several receptor kinases to exert an antiangiogenic and antiproliferative effect on tumour cells.[42] It is in Phase III development for ErbB2-positive breast cancer. Pazopanib is an oral, small molecule VEGFR-targeted agent (Figure 1)[43] in Phase II clinical development for ErbB2-positive breast cancer and secondary brain metastases.

Of the targeted agents in the pipeline for the treatment of ErbB2-positive disease, lapatinib is at the most

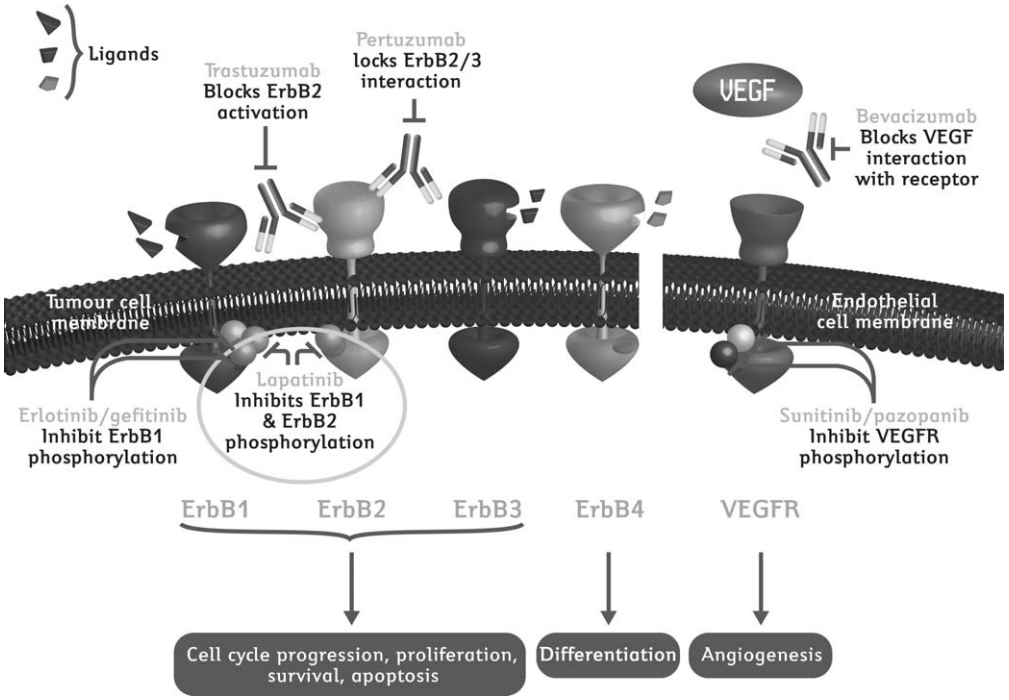

Fig. 1 – Targeted agents currently in development or approved for the treatment of ErbB2-positive breast cancer: sites of action and molecular targets. VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.

advanced stage of clinical development, and recently received approval in the EU. Therefore, the remainder of this article will focus on this novel targeted agent.

4. Lapatinib: molecular targets and distinct mechanism of action from trastuzumab

Lapatinib is a small molecule that is a potent and reversible inhibitor of the adenosine triphosphate (ATP) binding site at the intracellular tyrosine kinase domains of ErbB1 and ErbB2 (Figure 1).[44,45] It blocks receptor phosphorylation and activation, thereby preventing subsequent downstream signalling events.[46] Specifically, lapatinib inhibits activation of extracellular signal-related kinase (ERK)-1/2 and phosphatidylinositol 3′ kinase (PI3K)/Akt pathways;[47,48] this results in cell growth arrest and/or apoptosis.[46,48]

Preclinically, lapatinib markedly downregulates *Akt* and *mitogen-activated protein kinase* (*MAPK*) genes 7–25-fold, an effect associated with potent inhibition of tumour cell proliferation (IC_{50} [the concentration required to achieve 50% of maximal inhibition of cell proliferation]: BT474 cells, 25 nmol/L; SKBr3 cells, 32 nmol/L).[47] Lapatinib also upregulates genes associated with inducing apoptosis.[47] Importantly, this holds true in the clinical setting, where clinical response to lapatinib in four patients with ErbB2-positive metastatic breast cancer was shown to be associated with increased tumour apoptosis (Figure 2).[46]

Due to its intracellular site of action, lapatinib may have a mechanism of action distinct from the mAb trastuzumab, which acts extracellularly. Preclinically, trastuzumab has diverse effects on intracellular signalling pathways; however, its effects depend on the tumour cell line evaluated. Trastuzumab induces G1

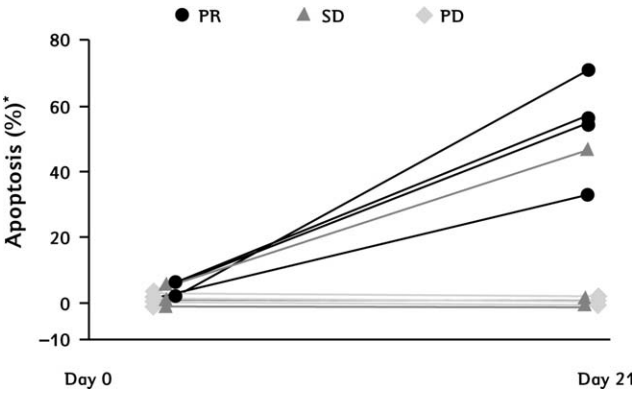

Fig. 2 – Clinical response (partial response) to lapatinib in patients with ErbB2-positive breast cancer is associated with increased apoptosis within tumour biopsies.[46] Reprinted from Spector NL, Xia W, Burris 3rd H, et al. Study of the biologic effects of lapatinib, a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. *J Clin Oncol* 2005;23(11):2502–12 with permission from the American Society of Clinical Oncology. *By TUNEL. PD = progressive disease; PR = partial response; SD = stable disease.

cell cycle arrest of several breast cancer cell lines overexpressing ErbB2, an effect associated with down-regulation of CDK2 and Akt, to upregulate the CDK inhibitor $p27^{kip1}$. [33] In contrast, in MCF-7 breast cancer cells co-expressing ErbB2 and ErbB3, trastuzumab was unable to inhibit ligand-activated receptor tyrosine kinase phosphorylation of ErbB2–ErbB3 heterodimers or the subsequent downstream activation of Akt or MAPK signalling pathways. Consistent with these observations, trastuzumab had no inhibitory effect on the growth of MCF-7 breast tumour xenografts. [32]

In contrast to the preclinical data described above, little evidence from tumour biopsies is available to suggest that the primary clinical mechanism of action of trastuzumab is inhibition of ErbB2-mediated intracellular signalling. Indeed, in recent years, an increasing body of evidence has suggested that the clinical effects of trastuzumab are primarily associated with stimulation of ADCC in tumour-infiltrating lymphoid cells. [34,35] This is mediated through the Fc region of the trastuzumab molecule: the Fc portion remains exposed once trastuzumab binds to the extracellular domain of ErbB2, and is recognized by the Fc receptors of immune effector cells (including lymphoid cells and NK cells) infiltrating the tumour. [35] These then secrete proteins, such as granzyme, that perforate the tumour cell membrane, resulting in tumour cell death. [35] Supporting evidence for this mechanism of action comes from two small neoadjuvant studies of trastuzumab in ErbB2-positive breast cancer. [34,35] In one of these trials, response to trastuzumab was associated with extensive tumour infiltration by lymphoid cells with a significantly raised capacity for ADCC ($p < 0.01$); furthermore, the percentage reduction in tumour diameter correlated with the extent of ADCC ($r = 0.89$; $p = 0.0005$). [34] In the other small trial, responders to trastuzumab treatment (in combination with docetaxel) were found to have significantly increased numbers of tumour-associated NK cells and increased expression of granzyme compared with responders treated with docetaxel alone. [35] In these clinical studies, no evidence of inhibition of tumour signalling pathways (i.e., no antiproliferative or antiangiogenic effect on the tumour) was found in responders to trastuzumab. [34,35]

In contrast to the findings with trastuzumab, and as already discussed, the preclinical and clinical effects of lapatinib have been shown to be associated with inhibition of downstream ErbB2-mediated intracellular signalling through Akt and ERK-1/2, resulting in tumour growth inhibition and apoptosis (Figure 2). [44,45,49,50]

5. Benefits of intracellular versus extracellular site of action with lapatinib

The intracellular site of action of lapatinib and/or its effects on cell signalling may translate into clinical benefits in patients who do not respond to treatment with trastuzumab. Breast carcinomas expressing a truncated variant of the ErbB2 receptor ($p95^{ErbB2}$), for example, lack the extracellular trastuzumab-binding domain and follow a more aggressive clinical course. [52–54] Consequently, trastuzumab lacks activity against $p95^{ErbB2}$, preclinically, [55] and patients with $p95^{ErbB2}$-positive breast cancer respond poorly to trastuzumab (11% overall response rate [ORR] versus 51% with ErbB2-positive breast cancer). [51]

Unlike trastuzumab, lapatinib has been shown to inhibit $p95^{ErbB2}$ phosphorylation, downstream phosphorylation and cell growth *in vitro*, and to inhibit $p95^{ErbB2}$-expressing tumour growth *in vivo*. [51] Lapatinib treatment of the MCF-7 breast cancer cell line expressing $p95^{ErbB2}$ resulted in a long-lasting (48 hours) inhibition of phosphorylation of $p95^{ErbB2}$, while no such inhibition was seen with trastuzumab. [51] Lapatinib also inhibited phosphorylation of the downstream signalling proteins

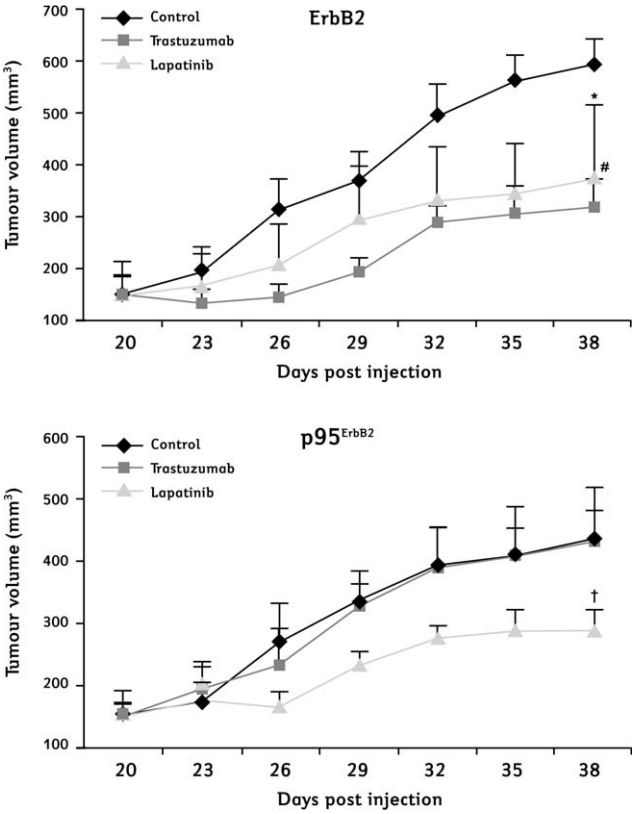

Fig. 3 – Lapatinib and trastuzumab antitumour activity against (top) ErbB2-overexpressing breast tumour xenografts and (bottom) breast xenografts expressing the $p95^{ErbB2}$ mutation. [51] Reprinted from Scaltriti M, Rojo F, Ocaña A, et al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. *J Natl Cancer Inst* 2007;99(8):628–38, by permission of the National Cancer Institute. $^{*}p = 0.003$, $^{\#}p < 0.001$ versus ErbB2 control; $^{\dagger}p = 0.002$ versus $p95^{ErbB2}$ control.

Akt and MAPK (by two- and four-fold at 2 hours, respectively).[51] Furthermore, although both lapatinib and trastuzumab inhibited the growth of MCF-7 tumour xenografts expressing ErbB2, only lapatinib inhibited the growth of MCF-7 tumour xenografts expressing $p95^{ErbB2}$ (mean tumour size: 288.8 versus 435 mm^3 in control after 18 days of treatment; $p = 0.002$) (Figure 3). Trastuzumab had no such inhibitory effect on MCF-7 tumour xenografts expressing $p95^{ErbB2}$.[51]

6. Conclusions

In summary, despite great progress since the advent of targeted therapy for difficult-to-treat patients with ErbB2-positive metastatic breast cancer, the management of ErbB2-positive breast cancer remains challenging. New options are needed for the significant proportion of patients with ErbB2-positive metastatic breast cancer who remain insensitive to, or who develop progressive disease on, trastuzumab-containing regimens. In addition, effective treatments are needed to improve outcomes in those patients who develop brain metastases. Novel targeted agents, such as lapatinib (which is now licensed in the USA, EU and Switzerland), have mechanistic characteristics that, if translated to the clinic, could begin to address these unmet needs.

Possibly the most important differentiating mechanistic feature of lapatinib compared with trastuzumab is the site of action of this agent (intracellular rather than extracellular), which may be responsible for its distinct clinical mechanism of antitumour effect versus trastuzumab (inhibition of ErbB2-mediated signalling to promote apoptosis rather than induction of ADCC). This may translate into clinical benefits, as evidenced by the activity of lapatinib in aggressive tumours insensitive to trastuzumab, such as those expressing the truncated $p95^{ErbB2}$ variant. The clinical efficacy and safety data for lapatinib are reviewed in detail in an accompanying article in this supplement, authored by Dr David Cameron.

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