

# The art of prescribing trastuzumab for HER2-positive breast cancer

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## Abstract

The human epidermal growth factor receptor 2 (HER2) is overexpressed in HER2-positive breast cancer. This confers characteristics associated with an overall poor prognosis, with early metastases to major visceral sites and a relative resistance to chemotherapy. Trastuzumab is a humanised monoclonal therapeutic antibody that specifically targets HER2 receptor overexpressing breast cancer cells, inhibiting their growth and proliferation, and inducing their regression. It is licensed for metastatic and early HER2-positive breast cancer, determined by slide-based testing techniques. Trastuzumab dosing regimens are aimed at increasing its efficacy, while minimising its potentially undesirable effects which include cardiotoxicity and the development of resistance.

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## Introduction

Recognising the diversity of tumour receptor subtypes in breast cancer has compelled clinicians to redefine and perfect rational principles of therapy for each of the distinct biological subclasses. Fifteen to 25% of breast cancers are of the human epidermal growth factor receptor 2 (HER2) positive variety, distinguished by their unique genetic, molecular and clinical signatures.<sup>1</sup> Multiple copies of the amplified HER2/*neu* oncogene can be visualised on chromosome 17 in the nucleus of affected cells. HER2/*neu* gene amplification is seen early in the development of invasive breast cancer, even at the stage of ductal carcinoma in situ<sup>2</sup> (Table I). The phenotype is characterised by an excessive production or overexpression of HER2 growth receptors. These 185 kD transmembrane glycoprotein tyrosine kinase receptors form part of the epidermal growth factor receptor family, which in addition to HER2, comprises epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 3 (HER3) and human epidermal growth factor receptor 4 (HER4). The family members work closely in concert to facilitate cell-to-cell or cell-to-stroma communication, chiefly via the process of signal transduction.

Activation of the intracellular tyrosine kinase domains of the HER2 receptors (a process that usually requires binding of an external ligand to a growth receptor,

enabling it to adopt a conformational change conducive to dimerisation, either with itself or with other family members), triggers phosphorylation and activation of intracellular signalling cascades. This ultimately lead to changes in gene transcription with enhanced effects on cellular growth and proliferation, division, differentiation, migration, adhesion and survival.<sup>3</sup> HER2 overexpression is thus strongly linked to poorly differentiated tumours (moderate-to-high tumour grade, a high percentage of S-phase cells, aneuploidy, lack of oestrogen and progesterone receptors, and ductal, rather than lobular features) with high proliferative rates and positive axillary lymph nodes, which are relatively resistant to chemotherapy.<sup>4</sup> Not surprisingly, these characteristics are associated with an overall poor prognosis with early metastases to major visceral sites, including bone marrow, lungs, liver, adrenal glands and ovaries, and an increased risk of disease recurrence and death.<sup>5</sup> Other adverse prognostic variables associated with HER2 receptor overexpression include p53 mutation, topoisomerase IIa gene amplification and alterations in a variety of other molecular biomarkers of breast cancer invasiveness and metastasis.<sup>6-9</sup>

Trastuzumab is a humanised monoclonal antibody, designed to specifically target the overexpressed HER2 receptor.<sup>10</sup> It consists of two antigen-specific sites that bind to the juxtamembrane portion of the extracellular

**Table 1:** HER2 status and breast pathology<sup>23</sup>

Breast pathology	Incidence: HER2 positive	Comments
Ductal carcinoma in situ (DCIS)	24-38%	Higher grades. Extensive forms. Comedo-type necrosis.
Invasive ductal carcinoma (IDC)	15-20%	The invasive carcinoma may not feature HER2. Strongly correlated to tumour grade.
Invasive lobular carcinoma (ILC)	< 10%	HER2 linked exclusively to pleomorphic variant (not in classic ILC). Strongly correlated to tumour grade.
Paget's disease (mammary and extramammary)	A consistent feature ~ 100%	
Male breast cancer	Lower incidence	Responds to trastuzumab.
Mucinous (colloid) breast cancer	Extremely low	Aggressive disease.
Medullary breast cancer	0%	
Tubular carcinoma	Very rare	
Inflammatory breast cancer	Rare	
Hereditary breast cancer (BRCA1 and BRCA2 germline mutations)	Rare	
Breast sarcomas and phylloides tumours	0%	
Benign breast disease	Low-level overexpression	Greater risk for invasive breast cancer.

domain of the HER2 receptor, inhibiting the growth and proliferation of HER2 overexpressing breast cancer cells and inducing their regression, possibly by reducing the number of HER2 receptors, or as a result of a direct inhibitory effect. These cells undergo arrest during the G1 phase of the cell cycle, presumably by modulation of cyclin-dependent kinase (CDK). Although not fully elucidated, other potential mechanisms of trastuzumab action include antibody-dependent immune mechanisms, diminished receptor signalling, induction of apoptosis, inhibition of angiogenesis, inhibition of DNA repair, altered crosstalk with other signalling pathways, potentiation of the effects of chemotherapy and inhibition of HER2 receptor extracellular domain cleavage and shedding.<sup>11-17</sup>

Trastuzumab was initially granted FDA approval in 1998 for HER2 overexpressing metastatic breast cancer, for use either in combination with paclitaxel, as first-line treatment, or as single agent maintenance therapy following one or more chemotherapy regimens, until disease progression. This was somewhat fitting, given that pivotal studies demonstrated response rates of 34% and objective regressions in 11-26% of patients with HER2 positive metastatic disease.<sup>18</sup> Since trastuzumab's debut, the incidence of progressive visceral metastatic disease has diminished, with the notable exception of clinically significant central nervous system (CNS) metastases. The therapeutic antibody is unable to cross the blood-brain barrier, prompting speculation that

previously occult CNS disease has been unmasked by treatment.<sup>19</sup>

Clinical trials of adjuvant trastuzumab in patients with early HER2-positive breast cancer revealed highly significant reductions in the risk of recurrence, with a projected absolute benefit at four years, of up to 18%. This appeared to surpass all previously reported therapeutic benefits in breast cancer.<sup>5</sup> Pivotal trials showed an improvement in disease-free survival ranging from 7-13% (HERA trial:7%; NSABP B-31 and NCCTG N9831 joint analysis: 13%; BCIRG 006 trial: 9%) with an overall survival benefit ranging from 4% at 35-month follow-up to 5% at five-year follow-up. A decade after it was licensed for metastatic HER2-positive breast cancer, trastuzumab received FDA approval for the adjuvant treatment of HER2 overexpressing node-positive or node-negative (ER/PR negative or any other high risk feature) early breast cancer, either as part of various treatment regimens (including doxorubicin, cyclophosphamide with either paclitaxel or docetaxel, or with docetaxel and carboplatin) or as monotherapy following multimodality anthracycline-based therapy.<sup>20</sup> Many more patients became eligible for trastuzumab treatment. This sparked a measure of controversy, media coverage and litigation, with patients at odds with health care and other funding bodies concerned with the high acquisition costs of the treatment. Currently, the National Institute for Health and Clinical Excellence (NICE) guidelines, which are based on "value

for money” ultimately, support adjuvant trastuzumab use in women with early HER2-positive breast cancer in the United Kingdom.<sup>21</sup>

In the neoadjuvant setting, trastuzumab has demonstrated a significant enhancement in the rate of pathologic complete response (pCR) when used either alone, or in combination with other chemotherapeutic agents prior to surgery.<sup>22</sup> It is yet to be licensed for this indication. However limited, use of trastuzumab in this category, coupled with extensive clinical experience in metastatic and early HER2-positive breast cancer, has to some degree allowed clinicians to address patient eligibility issues, questions pertaining to optimal trastuzumab dosing schedules and regimens, strategies to overcome resistance and other practical aspects of trastuzumab therapy.

### HER2 testing techniques and patient eligibility

After HER2/*neu* gene amplification has occurred, the HER2 phenotype is thought to be fixed for the duration of the natural history of the invasive tumour. Therefore HER2 testing can be performed on either the primary tumour, or on a metastatic tumour deposit, generally with similar results. Furthermore, routine retesting of HER2 may not be needed for most patients with metastatic disease.<sup>24</sup> This is in contrast with emerging data hinting that there might be changes in HER2 expression between primary and metastatic disease, particularly after intervening HER2-directed therapy.<sup>25</sup>

Slide-based assays comprise immunohistochemical (IHC) staining which is a quantitative assessment of receptors (see Table II) and which is performed on approximately 80% of newly diagnosed breast cancers, fluorescence in situ hybridisation (FISH) which measures gene amplification and is often, and controversially considered to have greater accuracy and reproducibility than IHC, and chromogenic in situ hybridisation (CISH) which has recently been approved by the FDA. Silver in situ hybridisation (SISH) is currently under review.<sup>26-27</sup>

The 2007 ASCO-CAP guidelines provide recommendations for standardised laboratory procedures, proficiency testing and quality assurance programmes, among others, in order to improve the accuracy of tissue-based HER2 testing (IHC, FISH, CISH).<sup>28</sup> They remain neutral as to the relative superiority of one test over the others. However, what is clear is that women who score 3+ on IHC staining show a response rate of 35% to targeted treatment, compared to women with 2+ IHC who demonstrate no response at all (Table III). Therefore, it is critical that accurate testing of HER2 status be undertaken for optimal patient selection. The most efficient testing algorithm for HER2 determination is achieved by using IHC (HER2

receptor overexpression) as the method of choice, with either FISH or CISH (HER2/*neu* gene amplification) performed for cancers with indeterminate results (2+ score). However, both methods are widely used.<sup>29</sup>

**Table II:** Slide-based HER2 testing techniques<sup>23</sup>

Test	Comments
<b>IHC</b> (immunohistochemistry)	Detects receptor over-expression.
<b>FISH</b> (fluorescent in situ hybridisation)	Detects HER2 gene copy.
<b>CISH</b> (chromogenic in situ hybridisation)	Detects HER2 gene copy.
<b>SISH</b> (silver in situ hybridisation)	Detects HER2 gene copy number and chromosome 17 centromeres.
<b>Chromosome 17 polysamy</b>	Linked to HER2 overexpression.

**Table III:** Standardised immunohistochemical (IHC) scoring system<sup>28</sup>

<b>0</b>	Negative	No staining or membrane staining in < 30% of tumor cells.
<b>1+</b>	Negative	Faint membrane staining in > 30% of tumour cells; only part of membrane is stained.
<b>2+</b>	Weak positive	Weak/moderate complete membrane staining in > 30% of tumour cells.
<b>3+</b>	Strong positive	Strong complete membrane staining in > 30% of tumour cells.

Note: 30% threshold is from ASCO/CAP scheme in 2007, prior threshold was 10%

### Tolerability issues

Trastuzumab specifically targets the HER2 receptor, but is not devoid of unwanted effects. The antibody is a product of mouse origin and although largely humanised, its potential to cause immune reactions persists. In addition, trastuzumab may increase the vulnerability of non-cancerous cells that require normal HER2 receptor expression for growth and survival. Before commencing eligible HER2-positive patients on trastuzumab, the benefits need to be weighed against the risks of treatment, and if possible, precautionary measures should be considered to limit the latter.

The most common adverse effects occur during the initial trastuzumab infusion and consist of a symptom complex characterised by fever and chills, and on occasion include nausea, vomiting, pain (in some

cases at tumour sites), headache, dizziness, dyspnoea, hypotension, rash and asthenia. Most infusion-related reactions are mild to moderate and occur within 24 hours of administration. They may be treated effectively with medications (paracetamol or diphenhydramine) or by temporarily interrupting, or slowing the rate of infusion. Other common adverse effects include fatigue, skin rash, increased cough, nasopharyngitis, diarrhoea, arthralgia, myalgia, neutropenia, anaemia and oedema.<sup>30-33</sup>

Potentially fatal infusion reactions and pulmonary toxicity occur in about one per cent of patients. These severe infusion reactions manifest as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary oedema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome and pulmonary fibrosis may occur as sequelae of serious infusion reactions. It appears that patients with either symptomatic intrinsic lung disease, or with extensive tumour involvement of the lungs resulting in dyspnoea at rest, experience greater toxicity.<sup>20</sup>

Severe neutropenia and febrile neutropenia affect approximately 25% of patients, usually in metastatic breast cancer patients receiving trastuzumab in combination with myelosuppressive chemotherapy. The incidence is higher than in those receiving chemotherapy alone. However, the incidence of septic death is not significantly increased.<sup>20</sup>

Post-marketing reports suggest that trastuzumab use during pregnancy increases the risk of oligohydramnios during the second and third trimesters, and it is thus classified as an FDA category D drug and should be avoided if at all possible during the gestational period.<sup>20</sup>

Experimental evidence suggests that adult cardiac myocytes express HER2 receptors, particularly when damaged. These cells may consequently become targets for trastuzumab, leading to failure of cardioprotective survival cues and irreversible loss of cardiac myocytes. Trastuzumab-induced cardiotoxicity usually presents as asymptomatic or symptomatic decreased left ventricular ejection fraction (of between 3-27%, depending on the dosing regimen) or even as overt heart failure (2-16%). This may necessitate interrupting the dosing schedule, stopping trastuzumab altogether and/or commencing patients on lifelong heart failure medication such as angiotensin-converting enzyme (ACE) inhibitors, diuretics and beta blockers. This becomes particularly pertinent for relatively young early breast cancer patients. Patients receiving chemotherapy, particularly the cardiotoxic anthracyclines and trastuzumab concurrently, have the highest risk for developing

cardiotoxicity (27%). Valve dysfunction, hypertension, ischaemia and arrhythmias have also been associated with trastuzumab use.<sup>34</sup> Some clinicians have found that the cardiotoxicity is partially reversible with standard medical therapy.<sup>35</sup> Nonetheless, a suboptimal baseline left ventricular ejection fraction is generally considered a contraindication for trastuzumab treatment and precludes its use in approximately 10% of HER2-positive breast cancer patients. Those patients who remain eligible for trastuzumab should be reassessed every three months with cardiac ultrasound or multigated radionuclide angiography (MUGA). Stringent rules with regard to ceasing trastuzumab should be applied to those whose cardiac function deteriorates to unacceptable levels.<sup>34</sup>

### Trastuzumab dosing regimens

Questions concerning the optimal schedule of trastuzumab pertain predominantly to its potential cardiotoxicity, particularly in patients receiving anthracyclines and trastuzumab simultaneously. Results from trials have suggested that cardiotoxicity is lower after sequential administration, even though simultaneous administration with anthracyclines may be more effective, causing cytotoxicity rather than cytostasis. HER2 overexpression has been associated with enhanced response rates to anthracycline-containing chemotherapy in most studies.<sup>36</sup>

Topoisomerase II $\alpha$  (TOPII $\alpha$ ) gene amplification is almost exclusively restricted to HER2 positive tumours. It is coamplified with the HER2/*neu* oncogene in approximately 35% of HER2-positive breast cancers.<sup>37</sup> Anthracyclines are topoisomerase inhibitors. Thus, it is possible that HER2-positive tumours may serve as surrogate markers for anthracycline sensitivity. However, expression of TOPII $\alpha$  does not necessarily reflect gene amplification status.<sup>38</sup> It cannot be confirmed whether topoisomerase amplification testing can be used for selecting or avoiding anthracyclines in the treatment of HER2-positive breast cancer, but the evidence is becoming overwhelming that HER2 normal breast cancer patients should not receive anthracyclines as part of their adjuvant treatment.<sup>39</sup>

### Metastatic HER2-positive breast cancer

Trastuzumab should be considered for the management of all metastatic breast cancers with HER2 receptor overexpression as identified by 3+ HER2 immunoassaying or gene amplification on FISH or CISH.<sup>20</sup> Patients with moderate-to-high risk, rapidly progressive cancer characterised by a negative hormone-receptor status, extensive visceral metastases and a short disease-free interval (less than two years) are candidates for immediate

treatment with chemotherapy and should receive the appropriate agent in combination with trastuzumab. The chemotherapy regimen should take into account previous adjuvant therapy and coexisting conditions.<sup>11</sup> Although trastuzumab is currently indicated either in combination with paclitaxel (as first-line treatment) or as a single agent in patients who have already received one or more chemotherapy regimens for metastatic disease (Table IV), a number of additional approaches have gained favour in clinical practice (Table V).<sup>40</sup>

Recently carboplatin-based strategies have become popular because of their apparent boost in efficacy, (as measured by higher overall response rate and the longer progression-free survival time), and cardioprotective benefits gained by avoiding an anthracycline-containing regimen.

For the subgroup of HER2-positive patients who are also hormone-receptor positive, it is not clear whether trastuzumab should precede, follow, or be added to hormonal therapy. The expression of HER2 appears to be inversely related to the quantitative expression of oestrogen receptors (ER) and progesterone receptors (PR).<sup>41-42</sup> Continued studies of gene expression have revealed considerable crosstalk between the HER2 and ER receptor pathways in metastatic breast cancer.<sup>43</sup> Some have suggested that ER-positive, HER2-positive patients have a superior response to aromatase

inhibitors compared to tamoxifen.<sup>44</sup> Some have even suggested that tamoxifen has an adverse impact on the prognosis of HER2-positive patients.<sup>45</sup> The consensus is that HER2-positive status confers resistance of breast cancer tumour cells to hormonal therapy, but whether HER2 status can be used to select individualised approaches to hormonal therapies in ER-positive patients has not been properly validated.<sup>46</sup>

As trastuzumab monotherapy appears to be effective for the treatment of metastatic breast cancer, its use as a single agent for newly discovered metastatic disease can be considered. This strategy delays the initiation of chemotherapy, with its attendant side-effects for eight to sixteen weeks and allows the clinician to assess whether trastuzumab is effective when used alone.<sup>23</sup> Studies also suggest that HER2-positive tumours treated with trastuzumab-based neoadjuvant therapy, combined with external beam radiation, show a favourable response in locally advanced breast cancer. Notable too is that HER2-positive brain metastases appear to be more sensitive to local radiation than HER2-negative tumours.<sup>23</sup>

The continued use of trastuzumab after disease progression remains controversial. Except in the case of progression within weeks of initiating trastuzumab (possibly reflecting inadequate drug exposure), continued use after its apparent failure would be ineffective if

**Table IV: Trastuzumab: licensed dosing schedules for HER2-positive breast cancer<sup>20</sup>**

Type	Trastuzumab combination	Trastuzumab monotherapy	Loading dose over 90 minutes	Maintenance dose over 30-90 minutes	Dosing interval	Duration
<b>Metastatic<sup>a</sup></b>	Paclitaxel		4 mg/kg	2 mg/kg	Weekly	Disease progression
		Single agent following AC regimen	4 mg/kg	2 mg/kg	Weekly	Disease progression
<b>Early breast cancer<sup>b</sup></b>	Paclitaxel or Docetaxel (following AC regimen <sup>c</sup> )		4 mg/kg	2 mg/kg	Weekly	12 weeks
	Docetaxel-carboplatin		4 mg/kg	2 mg/kg	Weekly	18 weeks
		One week after combination	6 mg/kg	6 mg/kg	3 weekly	52 weeks
		Single agent Following AC regimen <sup>c</sup>	8 mg/kg	6 mg/kg	3 weekly	52 weeks

<sup>a</sup>Trastuzumab is administered at an initial dose of 4 mg/kg over 90 minutes as an intravenous infusion, followed by subsequent weekly doses of 2 mg/kg as 30-minute IV infusions until disease progression.

<sup>b</sup>Trastuzumab is administered at an initial dose of 4 mg/kg if given in combination with chemotherapy, or at an initial dose of 8 mg/kg if used as a single agent, followed by subsequent 2 mg/kg weekly doses or 6 mg/kg three-weekly doses for a total duration of 52 weeks.

<sup>c</sup>AC = anthracycline and cyclophosphamide

the tumour has developed resistance to the antibody. Equally, the addition of synergistic chemotherapy at this point may well overcome this barrier and render the trastuzumab clinically beneficial.<sup>47</sup> To date, the argument for continued treatment relies heavily on preclinical studies and anecdotal reports and there are insufficient data to provide evidence for, or against, this approach. Because of the lack of this evidence base, the South African Oncology Consortium (SAOC) currently recommends that trastuzumab be permanently discontinued when there is objective radiological evidence of disease progression, unless there is isolated evidence of progression within the central nervous system, i.e. brain metastases, where trastuzumab may have a boost of efficacy if used in combination with lapatinib and systemic chemotherapy.<sup>48</sup>

If considering continuing therapy beyond disease progression, the theoretical gains of trastuzumab should be weighed against its high acquisition cost and its potential for adverse effects. It should also be noted that the activity of newer anti-HER2 therapies, including oral lapatinib and intravenous 17-allylamino-17-demethoxygeldanamycin in patients with trastuzumab refractory HER2-positive tumours, suggests that the observed resistance is drug-specific, rather than receptor target-specific.<sup>49</sup>

**Adjuvant therapy of HER2-positive early-stage breast cancer**

All HER2-positive patients with positive lymph nodes should ideally receive trastuzumab as part of adjuvant

systemic therapy, unless there are compelling reasons not to do so. Patients who are node-negative should also receive the antibody if they have increased risk of recurrence after optimal surgery, chemotherapy and endocrine therapy.<sup>50</sup>

Trastuzumab is given at an initial dose of 4 mg/kg as an intravenous infusion over 90 minutes, then as a 2 mg/kg dose weekly over 30 minutes during chemotherapy, either for the first 12 weeks (if given with paclitaxel or docetaxel) or for the first 18 weeks (if given with docetaxel-carboplatin). The week after the weekly doses of trastuzumab, trastuzumab is administered at 6 mg/kg as an intravenous infusion over 30-90 minutes, and then three weekly at the same dose for a total duration of 52 weeks.<sup>20</sup> As a single agent, within three weeks following completion of anthracycline-based chemotherapy regimen, it is given at an initial dose of 8 mg/kg as an intravenous infusion over 90 minutes, followed by subsequent three-weekly doses of 6 mg/kg for a total duration of 52 weeks.<sup>20</sup>

The licensed indications and dosage regimens for trastuzumab are based primarily on the pivotal trial usage. Although there is a choice of several adjuvant trastuzumab approaches, head-to-head comparisons of these are not available. Therefore, cross-trial comparisons are made by necessity which confound the data because of different trial designs, dosing schedules and patient populations.<sup>50</sup> Questions persist pertaining to the optimal adjuvant trastuzumab therapeutic approach.

**Table V:** Preferred chemotherapy regimens for recurrent or metastatic HER2-positive breast cancer: National Comprehensive Cancer Network practical guidelines in oncology 2009<sup>40</sup>

Preferred first-line agents with trastuzumab for HER2-positive disease			
Agent 1	Agent 2	Agent 3	Trastuzumab schedule
Trastuzumab	Paclitaxel		Every 3 weeks or weekly
Trastuzumab	Docetaxel		Every 3 weeks or weekly
Trastuzumab	Vinorelbine		Every 3 weeks or weekly
Trastuzumab	Capecitabine		Every 3 weeks or weekly
Trastuzumab	Paclitaxel	Carboplatin	Every 3 weeks or weekly
Trastuzumab	Docetaxel	Carboplatin	Every 3 weeks or weekly
Preferred agents for trastuzumab-exposed HER2 positive disease			
Agent 1	Agent 2		Trastuzumab schedule
Trastuzumab	Other first-line agents as above		Every 3 weeks or weekly
Trastuzumab	Capecitabine		Every 3 weeks or weekly
Trastuzumab	Lapatinib		Every 3 weeks or weekly
Lapatinib	Capecitabine		N/A

Trastuzumab is given by slow intravenous infusion until disease progression.  
 If given weekly: 4 mg/kg loading dose, followed by 2 mg/kg maintenance dose.  
 If given every 3 weeks: 8 mg/kg loading dose, followed by 6 mg/kg maintenance dose.

The advantages of concurrent administration of trastuzumab with paclitaxel include clear efficacy and a demonstrated survival advantage. The downside of this combination is one of the highest reported risks of New York Heart Association (NYHA) class III/IV heart failure (3.5-4.1%). Potential benefits for concurrent administration of trastuzumab with docetaxel are early integration of trastuzumab with potentially synergistic chemotherapy and a shorter duration of infusion therapy (12 months). The risk of cardiotoxicity appears to be lower than with paclitaxel. Administering trastuzumab sequentially, after chemotherapy, affords a lower risk of NYHA class III/IV cardiotoxicity (0.5-2.5%), but the possible drawback of this approach is the theoretical risk of early relapse, and the possible loss of the synergistic or additive interactions that are found when combining chemotherapy with trastuzumab.<sup>51</sup>

Different treatment durations have been studied, ranging from nine weeks (the FinHer study used a short course of trastuzumab concurrently with chemotherapy) to two years, creating debate over the optimal duration of trastuzumab treatment.<sup>52</sup> The short course is enticing as theoretically it is less cardiotoxic. Nonetheless, a total of 52 weeks is currently recommended by the manufacturers.<sup>20</sup>

### Strategies to overcome trastuzumab resistance

The majority of HER2-positive breast tumours in metastatic breast cancer demonstrate primary resistance to single-agent trastuzumab. Objective response rates range from 12-34% for a median duration of nine months.<sup>30-32</sup> Moreover, the majority of patients with metastatic breast cancer, who initially respond to trastuzumab, eventually acquire resistance and suffer disease progression within one year of treatment initiation.

Potential molecular mechanisms that could contribute to the development of trastuzumab resistance include altered receptor-antibody interactions, inhibition of immune recognition of cancer cells, suppression of apoptosis, promotion of tumour progression (all possibly attributable to interference by elevated levels of the mammary epithelial protective glycoprotein, mucin-4), decreased expression of the targeted HER2 receptors, continued intracellular signalling and crosstalk achieved by other receptors such as EGFR, HER-3, HER-4 and insulin-like growth factor receptor (IGFR), and loss of function of the tumour suppressor phosphatase and tensin homolog (PTEN) gene that leads to decreased sensitivity to trastuzumab.<sup>53-62</sup> Strategies to overcome trastuzumab resistance in HER2-positive breast cancer and to increase the degree and duration of response to treatment generally entail combining trastuzumab with other biologic agents,

as well as driving research into alternative therapeutic agents to target the HER2 receptor.<sup>63</sup>

Lapatinib is a small molecule dual tyrosine kinase inhibitor (TKI) that inhibits both HER2 and its family member, EGFR. Because of its slow dissociation, it causes protracted downregulation of intracellular receptor tyrosine phosphorylation in tumour cells and inhibits downstream cascades that are responsible for cellular proliferation and survival.<sup>64</sup> Combinations of lapatinib and anti-HER2 antibodies have demonstrated improved apoptosis of HER2 overexpressing breast cancer cells.<sup>65</sup> A number of clinical trials have examined the potential synergy of using trastuzumab and lapatinib for HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings.<sup>66-68</sup> More recently, in a heavily pretreated population of HER2 positive metastatic breast cancer patients who progressed on trastuzumab-based regimens, significant synergy (measured by progression-free survival) was shown with the combination of trastuzumab and lapatinib.<sup>49</sup> Lapatinib currently has FDA approval for use in combination with capecitabine for metastatic HER2-positive breast cancer.

The therapeutic antibody directed at vascular endothelial growth factor (VEGF), bevacizumab, has also shown additive effects with trastuzumab. Bevacizumab was granted an accelerated approval by the FDA in 2008 for metastatic breast cancer, but the license for this indication is now in the process of being revoked, principally because it shows a limited progression-free survival which is outweighed by the risks of treatment. The European licensing authority, European Medicines Agency (EMA), recently elected to support the use of bevacizumab in the metastatic breast cancer setting, but only if used in combination with paclitaxel.<sup>69-70</sup>

Two other targeted agents used in combination with trastuzumab, which hint at synergistic efficacy, include everolimus, an inhibitor of mammalian target of rapamycin (mTOR) designed to overcome resistance in phosphatase and tensin homolog (PTEN) deficient breast cancers, and geldanamycin, which is a chaperone heat shock protein 90 (HSP90) inhibitor that causes increased endocytic recycling and downregulation of the overexpressed HER2 receptor.<sup>23</sup>

Promising newer biological anti-HER2 targeted therapies include a variety of monoclonal antibodies and tyrosine kinase inhibitors (TKIs), antibody-toxin conjugates and vaccines (Table VI).

### Conclusion

If art is considered a human attempt to alter or counteract the efforts of nature, then trastuzumab

Table VI: Newer approaches to HER2-positive breast cancer<sup>23</sup>

Agent	Mechanism of Action	Comments
<b>HER2 vaccines</b>	Boost HER2 immunity.	DNA- and peptide-based vaccine strategies designed to specifically boost HER2 immunity. They have a variety of implications for the treatment and prevention of HER2 breast cancer. <sup>71-73</sup>
<b>Pertuzumab</b>	Anti-HER2 monoclonal antibody, prevents dimerisation with other receptors such as HER3 <sup>a</sup> and IGF1R <sup>b</sup> . Blocks signalling by other family members.	40% clinical benefit suggested with trastuzumab in HER2- positive metastatic disease. Positron emission tomography (PET) metabolic response in HER2-negative patients has aroused interest. <sup>74-76</sup>
<b>Ertumaxomab</b>	Trifunctional bispecific antibody targeting HER2 on tumour cells and CD3 <sup>c</sup> on T-cells.	Redirects T-cells, macrophages, dendritic cells and natural killer cells to the sites of tumour metastases. <sup>77,78</sup>
<b>MDX-H210</b>	Bispecific antibody against HER2 and Fc RI combined with G-CSF <sup>d</sup> .	Limited clinical response to date. <sup>79</sup>
<b>Trastuzumab conjugates (DM1)</b>	Antibody conjugated with fungal toxin: maytansine DM1.	Toxins can be delivered safely at effective doses and may penetrate tumours more effectively than trastuzumab alone. Immune response may be triggered. 40% response rate suggested. <sup>80-81</sup>
<b>Novel tyrosine kinase inhibitors (TKIs)</b>	HER1/HER2 dual kinase inhibitors; panHER TKIs; dual HER2/VEGF TKIs	In various stages of clinical development. <sup>82,83</sup>

<sup>a</sup>HER-3 = human epidermal growth factor receptor 3  
<sup>b</sup>IGF1R = insulin growth-like factor receptor 1  
<sup>c</sup>CD3 = cluster of differentiation 3  
<sup>d</sup>G-CSF = granulocyte colony stimulating factor

could be viewed by perhaps a discerning few as a work of art; over the past decade, the therapeutic targeted antibody has significantly altered the treatment and, more crucially, the prognosis of metastatic and early HER-2 positive breast cancer patients. Trastuzumab may not be universally appealing, particularly if its potential undesirable effects such as infusion reactions, neutropenia and cardiotoxicity become intolerable, or if primary and acquired resistance develop. However, where art disturbs, science is supposedly meant to reassure. Researchers have persisted in trying to enhance the efficacy of trastuzumab whilst minimising its potential for harm. Basic scientists have contributed significantly to the understanding of the HER-2 receptor, the mechanism of action of trastuzumab and the rationale for its adverse effects. In the clinical setting, various trastuzumab dosing regimens have been practised, studied and honed, allowing clinicians to acquire greater familiarity with the agent and to refine their skills. The art of prescribing trastuzumab for HER-2 positive breast cancer lies in balancing the scientific evidence with clinical judgement.

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