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Current Perspective

Dual inhibition of ErbB1 (EGFR/HER1) and ErbB2 (HER2/neu)

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ABSTRACT

Targeting of epidermal growth factor receptor (EGFR) and HER2 is a proven anti-cancer strategy. However, heterodimerisation, compensatory 'crosstalk' and redundancy exist in the ErbB network, and there is therefore a sound scientific rationale for dual inhibition of EGFR and HER2. Trials of approved agents in combination, for example trastuzumab and cetuximab, are underway. There is also a new generation of small molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mABs) that target two or more ErbB receptors. Lapatinib, a TKI of EGFR and HER2, has shown clinical benefit in trastuzumab refractory breast cancer and is poised for FDA approval. Other agents include BIBW-2992 and HKI-272, irreversible TKIs of EGFR and HER2, and pertuzumab, a heterodimerisation inhibitor of EGFR and HER2.

1. The ErbB receptor family

The ErbB or epidermal growth factor (EGF) receptors are members of subclass 1 of the receptor tyrosine kinase (RTK) superfamily. There are four ErbB receptor family members: ErbB1 (EGFR, HER1), ErbB2 (HER2/neu), ErbB3 (HER3) and ErbB4 (HER4).[1–3] The receptors are situated at the cell membrane and have an extracellular ligand-binding region, a transmembrane region and a cytoplasmic tyrosine-kinase domain. Ligand binding to the receptors results in receptor homo- and heterodimers, activation of the intrinsic kinase domain and phosphorylation of specific tyrosine residues within the cytoplasmic tail. Proteins dock on these phosphorylated residues, leading to the activation of a variety of intracellular signalling pathways that promote cell growth, proliferation, differentiation, and migration.[1–3] Interactions between ErbB receptors allow ErbB2, which has no identified ligand, and ErbB3, which has no kinase activity, to participate in effective signalling.[1,3,4] ErbB2 is the preferred dimerisation partner for all the other ErbB receptors.

2. ErbB receptors and carcinogenesis

These receptors are profoundly important in human cancer. In particular, EGFR and ErbB2 have been implicated in the development of human cancers.[2] Patients whose tumours have an alteration in ErbB receptors are associated with more aggressive disease and poorer clinical outcome.[5] ErbB receptors undergo various types of alteration in human tumours including gene amplification, receptor overexpression, activating mutations, overexpression of receptor ligands and/ or loss of negative regulatory controls.[2] The most robust example is that of amplification of HER2/neu in breast cancer. Amplification of HER2/neu is seen in 25–30% of breast cancers and is associated with a statistically significant shortening in disease-free and overall survival.[6–8]

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Other examples include the discovery of activating mutations in the tyrosine-kinase domain of EGFR in non-small-cell lung cancer,[9,10] and gene amplification and over-expression of wild-type EGFR in head and neck cancer.[11] A number of agents directed against individual ErbB receptors have been approved for clinical use in human cancer and can broadly be separated into two main groups. Humanised monoclonal antibodies are directed against the extracellular domain of the receptor, *e.g.* trastuzumab (Herceptin™); and small molecule tyrosine kinase inhibitors, *e.g.* gefitinib (Iressa™), bind to the ATP binding site of the intrinsic tyrosine-kinase domain of the receptor.[2]

While these agents have demonstrated safety and clinical efficacy, anti-tumour effects are often not as frequent as might have been predicted from preclinical studies, except in rare instances were tumour pathogenesis is driven by a single molecular abnormality.[12] The modest activity of these agents is not surprising when one considers the complex molecular biology driving cancer. Molecular pathways can be adaptable and redundant. It is therefore unlikely that therapy focusing on a single target will achieve durable disease control for most patients. This is relevant with reference to the ErbB receptor family members that are known to be interdependent, preferentially functioning in concert with each other in signal transduction and malignant transformation.[13] For example, preclinical experiments have demonstrated that ErbB receptors act synergistically to cause malignant transformation in NIH3T3 cells. In this situation, either receptor alone is insufficient to induce cellular transformation.[14,15] Also, other studies have shown that tumour cells can be spared the antiproliferative effect of an agent targeted at a particular ErbB receptor, by the presence of ligand for an alternative receptor. This phenomenon was demonstrated in HER2 driven breast cancer cells. The anti-tumour effect of 4D5, a murine anti-HER2 antibody, was reversed by EGF-related peptides, and the ability of EGF-related peptides to stimulate HER2 driven breast cancer cells was inhibited by PKI-166, a TKI with dual activity against both EGFR and HER2.[16]

Importantly, cancers that co-overexpress EGFR and HER2 have a worse outcome than do those that overexpress either receptor alone.[17,18] There is therefore increasing evidence to support the concurrent inhibition of two or more receptors. If hitting two or more targets proves more effective than hitting one, a number of questions arise as to the best way to achieve this. For example, is it better to attack multiple receptors with one combined drug or two separate compounds? Can maximal target inhibition be achieved for more than one receptor with a multi-targeted agent? Does the emergence of side-effects preclude achieving maximal target inhibition on different receptors (Table 2)? This review will present the scientific rationale for dual inhibition of ErbB receptors; the therapeutic strategies being employed in the clinic with combinations of single agents, and the experience to date with a new generation of dual-targeting single-agent drugs.

Table 1 – Dual-targeting agents in development

Agent	Target	Sponsor	Stage of development	Irreversible
Tyrosine kinase inhibitors				
Lapatinib (GW-572016)	EGFR, HER2	GlaxoSmithKline	Phase III breast, kidney cancer	No
BIBW-2992	EGFR, HER2	Boehringer-Ingelheim	Phase II prostate	Yes
HKI-272	EGFR, HER2	Wyeth	Phase II breast, non-small-cell lung cancer	Yes
CI-1033	EGFR, HER2, HER4	Pfizer	Phase II breast, non-small-cell lung cancer	Yes
Monoclonal antibodies				
Pertuzumab (2C4, Omnitarg)	EGFR, HER2, HER3	Genentech, San Francisco	Phase II Ovarian, non-small-cell lung cancer, prostate, breast	

EGFR, Epidermal growth factor receptor.

Table 2 – Advantages and disadvantages of a single agent with multiple targets versus combinations of agents targeting individual receptors

	Advantages	Disadvantages
Single agent with multiple targets	(1) Potential to overcome molecular heterogeneity (2) Convenience	(1) Difficulty in achieving maximum potency against several different targets (2) Might have toxicities related to target effects which may not be relevant to every tumour type (3) Difficult to validate a target
Combinations of agents targeting individual receptors	(1) Increased capability to achieve maximal target inhibition (2) Individual targets can be validated (3) May avoid unnecessary toxicities	(1) Multiple drugs, and therefore may be less convenient for patients (2) Might involve clinical trials of efficacy both as a single agent and in combination (3) Legal constraints of combining drugs from different sources

3. Scientific rationale for dual inhibition

HER2 overexpression has been shown to activate and potentiate EGFR signalling, and combined inhibition of EGFR and HER2 results in greater tumour growth inhibition, higher levels of the cyclin dependent kinase inhibitor $p27^{kip1}$ and greater decreases in cyclin dependent kinases than with the blockade of either receptor alone.[19,20] A number of pre-clinical *in vitro* and *in vivo* studies have resulted in superior antitumour activity utilising a dual ErbB approach rather than single receptor targeting.[19,21–25] In six of seven human breast cancer cell lines (SKBR-3, BT-474, MDA- 361, UACC 812, SUM190 and SUM 335) with increased HER2 expression and varying levels of EGFR expression, trastuzumab and erlotinib demonstrated synergistic activity over a range of clinically attainable concentrations.[21] Also, when trastuzmab was combined with gefitinib in BT-474 and SKBR-3 cell lines, additive[23] and synergistic[24] anti-tumour activity was seen. These *in vitro* results translated into positive *in vivo* results in HER2 positive BT-474 breast cancer xenografts, where the combination of trastuzumab and gefitinib produced enhanced antitumour activity when compared with trastuzumab alone.[22] Interestingly, trastuzumab-resistant BT-474 xenografts are sensitive to erlotinib alone or in combination with trastuzumab,[26] and also to lapatinib, a novel agent that targets both EGFR and HER2,[27] suggesting that trastuzumab resistance may be overcome by adding EGFR inhibitors.

In addition to pre-clinical work in breast cancer cell lines, evidence exists in other tumour types for dual ErbB inhibition. Cell line work showed that combination therapy with cetuximab and the murine anti-ErbB2 antibody 4D5 had an additive anti-proliferative effect on HER2 overexpressing human ovarian carcinoma cells causing an accumulation of cells in G1 arrest, increase in $p27^{Kip1}$ and decrease in cyclin dependent kinase activities.[19] In MDA PCa 2a prostate cancer cells, the combination of cetuximab and trastuzumab given with the anti-androgen flutamide showed superior activity to flutamide with either antibody alone.[25]

These pre-clinical results provided the scientific rationale to pursue clinical trials of combinations of single target agents directed at EGFR and HER2.

4. Monoclonal antibodies (MAbs)

The two most commonly used have been cetuximab (MAb to the ErbB1/EGFR receptor) and trastuzumab (MAb to ErbB2/HER2 receptor). Cetuximab induces dimerisation, internalisation and downregulation of the EGFR receptor and blocks activation of the tyrosine kinase domain when ligand is bound.[28] This agent has activity either alone, or in combination with cytotoxic chemotherapy[29] in colorectal,[30] lung[31] and head and neck cancers.[32] The main toxicities reported to date are rash and rarely bowel perforation.

Trastuzumab binds to the extracellular domain of ErbB2. It has been shown to induce antibody-dependent cytotoxic responses, accelerate receptor internalisation and degradation. This agent has been used alone and in combination with a range of cytotoxic drugs with beneficial outcome.[33] Its main use has been in breast cancer, but other cancer types are now being investigated, especially those with known overexpression of HER2, such as some gynaecologic cancers.[34] The most serious side-effect for this agent is potential cardiac dysfunction which is reversible, and is seen in a proportion of patients receiving the drug.

5. Tyrosine kinase inhibitors

Gefitinib and erlotinib are reversible small molecule inhibitors of the intracellular tyrosine kinase domain of EGFR. Gefitinib downregulates EGFR signalling and promotes apoptosis, alone and in combination with cytotoxic agents. It has been shown to be active in lung cancer, particularly in a subpopulation of patients with EGFR mutations in the tyrosine kinase domain. Other cancers have also shown some response, such as glioblastoma, cervical, pancreatic and gastric.[35]

Erlotinib is active in a similar tumour subset to gefitinib. The major side-effects of these compounds are acneiform rash and diarrhoea.[36] There are current studies investigating the dose to rash effect, as a significant number of patients experiencing a positive effect of the compound on their tumour developed at least a grade 2 rash.[37]

6. Combinations of single-targeted agents

Phase 1 trials with combinatorial EGFR and HER2 blockade have recently been completed in advanced solid tumours. A phase 1 study of weekly trastuzumab and escalating doses of erlotinib in HER2 positive metastatic breast cancer patients has been reported. Erlotinib dose was escalated from 50 mg to 150 mg with resultant toxicities of grade 1 or 2 diarrhoea and grade 1 rash. Grade 2/3 rash occurred in 2 patients at the 150 mg dose level requiring dose reductions. Two patients had reversible drop in left ventricular ejection fraction.[38]

A phase 1 study of erlotinib and trastuzumab in combination with weekly paclitaxel chemotherapy has also recently been reported. Patients with advanced HER2 positive (immunohistochemistry 1+ to 3+) solid tumours, the majority of whom were breast cancer patients, tolerated the combination well. Responses were seen in patients with taxane and trastuzumab refractory breast cancer, suggesting, as in pre-clinical work, that EGFR inhibition may be able to overcome resistance to trastuzumab.[39]

A phase I study with gefitinib and trastuzumab in HER2-overexpressing breast cancer has been completed. Treatment was with weekly standard dosing of trastuzumab and increasing doses of once daily gefitinib, up to 500 mg. Dose limiting toxicity was diarrhoea at the 500 mg dose of gefitinib. The treatment was otherwise well tolerated, with the other expected side-effect of rash seen in a subgroup of patients. Maximum tolerated dose of standard dose trastuzumab and 250 mg once daily of gefitinib were taken to phase II in the same patient group.[40] Unfortunately, the initial activity seen in cell lines with gefitinib and trastuzumab has not been borne out in practice, and the phase II trial was terminated early with no effect seen (Dr. C.L. Arteaga, Vanderbilt-Ingram Comprehensive Cancer Centre).

Trials currently recruiting involving dual ErbB inhibition include trastuzumab plus cetuximab in metastatic breast cancer. Other studies use combinations of molecularly targeted agents to produce dual ErbB inhibition plus concomitant chemotherapy such as erlotinib, trastuzumab and paclitaxel in solid tumours, and gefitinib, trastuzumab and docetaxel in metastatic breast cancer patients.

Whilst most interest has been centred on the agents that produce dual inhibition from one molecule such as lapatinib and BIBW-2992, there is still room for work with single agents, in order to attain full blockade of both receptors which might not be efficiently obtained from a single molecule. This is due to the potential to reach dose limiting side-effects from the blockade of one receptor before fully blocking the signalling of the other (Table 2).

7. Novel single agents targeting dual receptors

In addition to combination studies of single-targeting agents, compounds targeting signalling from more than one ErbB receptor have been developed. As with the single agents, these include tyrosine kinase inhibitors and monoclonal antibodies targeting heterodimerisation domains, of which lapatinib, a tyrosine kinase inhibitor, is in the furthest stages of development. These drugs are discussed below (Table 1 and Fig. 1).

8. Pertuzumab (2C4, Omnitarg)

Pertuzumab is a fully recombinant humanised monoclonal antibody that binds to the HER2 receptor at domain II, sterically blocking heterodimerisation of HER2 with EGFR and ErbB3.[41–45] thereby inhibiting intracellular signalling (Fig. 1). In Phase I studies, pertuzumab was well tolerated with principal side-effects of fatigue, nausea and vomiting.[46] The maximum tolerated dose was not reached with dose escalation to 15 mg/kg. Pharmacokinetic studies showed a terminal half-life of ~21 days, supporting three-weekly dosing. Pertuzumab infusions given every 3 weeks at doses $\geqslant$ 5.0 mg/kg maintained serum concentrations in excess of 20 μg/ml. Dose-response studies in non-clinical models have shown 80% tumour growth suppression at steady state through concentrations of 5–25 μg/ml.[47]

The recommended regimen for Phase II testing was fixed at a dose of 420 mg (equivalent to 6 mg/kg for a 70 kg patient) every 3 weeks. However, with this schedule steady-state concentrations were only achieved after 90 days, and a loading dose of 840 mg was therefore recommended.

A number of Phase II trials have been conducted in prostate,[48,49] ovarian,[50] breast and NSCLC.[51] Clinical responses were seen in a Phase II trial of heavily pre-treated ovarian cancer patients, with five partial responses and eight stable diseases for at least 6 months. The overall response rate was 4.3%.[50] There was no clinically significant activity seen in chemotherapy-naïve[49] or chemotherapy-resistant[48] hormone refractory prostate cancer patients. Negative results in the prostate cancer studies may be explained by the effects of intraprostatic androgens in castrate patients, maintaining androgen receptor signalling, and therefore abrogating any anti-proliferative effect from EGFR/HER2 blockade.[52–54] The interim results of a Phase II trial of single-agent pertuzumab in advanced, NSCLC patients, who have progressed through at least one line of chemotherapy, were recently presented. While no complete responses have been observed, 42% of patients had disease stabilisation at 6 weeks.[51]

9. Lapatinib (GW572016)

Lapatinib is a novel member of the 4-anilinoquinazoline class of kinase inhibitors. It is a potent, reversible, selective dual inhibitor of EGFR and ErbB2 kinases. In a panel of tumour cell lines that overexpress either EGFR or HER2, the IC50 values for growth inhibition are <0.2 μM. Lapatinib has demonstrated >300-fold selectivity for both tyrosine kinases compared to other related tyrosine kinases evaluated.[55] Lapatinib demonstrated growth inhibition both in *in vitro* and *in vivo* models of EGFR and/or ErbB2 overexpression.[56] Lapatinib has been shown to inhibit downstream signalling effectors such as phospho-Erk1/2, phospho-Akt and cyclin D.[57] Lapatinib given in combination with tamoxifen effectively inhibited cell proliferation and restored tamoxifen sensitivity in ER-positive, breast cancer models resistant to tamoxifen.[58]

A range of toxicology studies supported the oral administration of GW572016 to humans. The first studies with oral lapatinib were conducted in healthy volunteers and showed lapatinib to be safe. In cancer patients, two phase I trials using a dose range from 175 mg up to 1800 mg once daily or 500 mg up to 900 mg twice daily reported no significant toxicity at the maximum doses.[59,60] Most common side-effects were mild and consisted of gastrointestinal and skin toxicity. The maximum tolerated dose study, EGF10003, did not select patients on the basis of ErbB receptor status although receptor status was tested in patients on trial. Clinical activity was demonstrated with one complete response (CR) in an ErbB1 overexpressing head and neck squamous cell carcinoma (HNSCC), and 22 patients with various tumours overexpressing either ErbB1 or ErbB2 with stable disease for a median duration of 4 months (range 1–13 months). Of these 22 patients, one patient with adenocarcinoma of unknown primary with lung metastases, and who had previously progressed on gefitinib, remained on treatment for 8+ months.[60] The phase 1B study, EGF10004, recruited heavily pretreated metastatic cancer patients with biopsiable disease and EGFR or ErbB2 overexpression on immunohistochemistry, ErbB2 overexpression on gene amplification or evidence of activated EGFR and ErbB2 receptors on immunohistochemistry. Significantly, 4 trastuzumab resistant metastatic breast cancer patients, 2 of whom were classified as having inflammatory breast cancer, had partial responses. A further 24 patients with a variety of different carcinomas achieved stable disease for $\geqslant$6 months.[59] Finally, Minami *et al.* conducted a Phase 1 study in which 2 patients with trastuzumab resistant breast cancer and squamous cell carcinoma of lung had partial responses, and 12 patients achieved stable disease. Of the partial responses and stable disease patients, 8 remained on therapy for $\geqslant$3 months.[61]

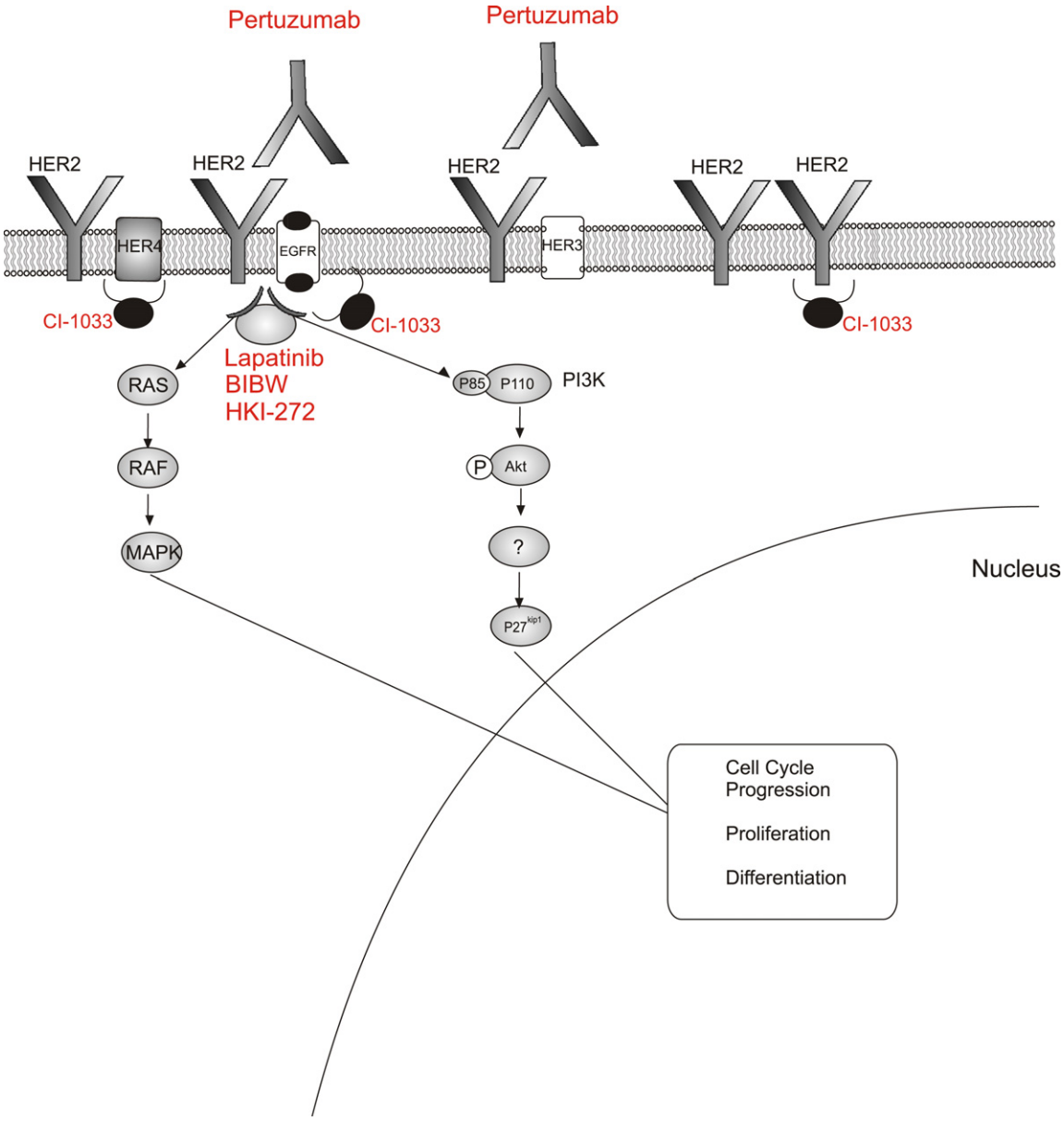

Fig. 1 – The ErbB receptor family and novel dual-targeting agents. The ErbB receptor family is composed of four members: ErbB1/HER1, Epidermal Growth Factor Receptor (EGFR); ErbB2/HER2; ErbB3/HER3; ErbB4/HER4. On ligand binding, the receptors homodimerise or heterodimerise with each other resulting in tyrosine-kinase activity within the cytoplasmic domains of the receptors. These events activate downstream signalling pathways, in particular the PI3K/Akt pathway. Drugs targeting individual receptors include: cetuximab, monoclonal antibody to EGFR; trastuzumab, monoclonal antibody to HER2; and gefitinib and erlotinib, small molecule tyrosine kinase inhibitors of EGFR. Novel dual-targeting agents (pictured above) include lapatinib, a reversible EGFR/HER2 tyrosine kinase inhibitor; BIBW, an irreversible EGFR/HER2 tyrosine kinase inhibitor; CI-1033, a pan-ErbB tyrosine kinase inhibitor; HKI-272 an irreversible EGFR/HER2 tyrosine kinase inhibitor; and pertuzumab, a HER2-targeted antibody that disrupts heterodimerisation between EGFR/HER2 and HER2/ErbB3. HER, human epidermal growth factor receptor; PI3K, phosphatidylinositol 3-kinase; P, phosphorylated; MAPK, mitogen-activated protein kinase.

A Phase I trial in 48 metastatic breast cancer patients with overexpression of the ErbB2 protein 2+ or 3+ on immunohistochemistry (IHC) tested escalating doses of lapatinib (750–1500 mg/d) in combination with weekly, standard dosing of trastuzumab. Diarrhoea and rash were the principle toxicities. Twenty-seven patients were evaluable for response with 1 CR, 5 PR and 10 SD. A lapatinib dose of 1000 mg daily was chosen as the recommended dose in combination with trastuzumab.[62]

Phase II studies have been completed in advanced or metastatic breast cancer. Lapatinib was generally well tolerated at 1250 mg OD and 1500 mg OD as monotherapy. The most

common adverse events were gastrointestinal toxicities (diarrhoea, nausea, vomiting, anorexia), rash and asymptomatic LVEF. The first phase II trial recruited forty-four trastuzumab refractory metastatic breast cancer patients overexpressing ErbB2 on immunohistochemistry.[63] The response rate for the first evaluated 36 patients was 22% (3 PR + 5SD). A second phase II trial of lapatinib, this time as first line treatment in metastatic breast cancer patients with HER2 amplification detected by FISH, demonstrated a response rate of 38%.[64] In another phase II study, presented at ASCO 2006, Spector et al. showed that patients with ErbB2 overexpression (ErbB2 2/3+ IHC or FISH +ve) alone and not patients with ErbB1 overexpression alone predicted for sensitivity to lapatinib in relapsed/refractory inflammatory breast cancer.[65] This study underlines the importance of selecting patients on the basis of the biology of their disease.

Recent data from another phase II trial have demonstrated preliminary activity with lapatinib against brain metastases from trastuzumab refractory breast cancer patients.[66] However, despite two partial responses, the study failed to reach the four objective responses required to reject the null hypothesis.

Following these results, other phase II and III trials with lapatinib and chemotherapy and/or hormonotherapy are underway.[67] Trials are being initiated not only in the metastatic breast cancer setting but also in the adjuvant setting. The HERA replacement trial 'Aphrodite' will examine various schedules of trastuzumab and lapatinib and is poised for recruitment; the neo-adjuvant 'Neo- Aphrodite' trial will incorporate tissue acquisition prior to and at surgery providing crucial information regarding target modulation with respect to these therapies.

While the majority of work to date has been conducted in breast cancer, several phase II studies have been performed in other solid tumours including metastatic colorectal, lung, renal, and bladder. Responses rates were low, similar to the response rates obtained with other TKI.[68,69] Results from a phase III randomised study in metastatic renal cell cancer with lapatinib *versus* hormonal therapy in patients who expressed EGFR and/or ErbB2 by immunohistochemistry showed statistically significant prolonged median overall survival for the group of EGFR 3+ patients treated with lapatinib.[70]

With the success of lapatinib, it remains to be seen whether other dual targeting agents can find a therapeutic niche. A real need exists for drugs capable of crossing the blood brain barrier, with significant activity against brain metastases.

10. Irreversible inhibition

An attractive feature of a number of novel dual-targeting agents is irreversible binding to the target receptor (Table 1). Irreversible binding should provide benefit in terms of target suppression and *in vivo* pharmacodynamics. Prolonged suppression of the target is likely necessary to achieve maximal anti-tumour activity. Therefore, irreversible inhibitors can permanently eliminate kinase activity until new receptor is synthesised. BIBW-2992 and HKI-272 are examples of irreversible dual inhibitors and are discussed below.

11. BIBW-2992

BIBW-2992 is a potent oral, irreversible combined EGFR/HER2 inhibitor both *in vitro* and *in vivo*. The potency of BIBW-2992 on the EGFR and HER2 kinases revealed IC_{50} values of 0.5 nM and 14 nM, respectively. BIBW-2992 is highly selective for these kinases and no additional inhibition of other kinases has been observed.

Several phase I trials have explored different schedules. A phase I trial of BIBW-2992 given for 21 days followed by 7 days break defined the recommended dose at 40 mg. Limiting toxicities consisted of diarrhoea and skin rash.[71] A parallel phase I trial demonstrated that BIBW-2992 at 70 mg daily could be administered safely in a 2 week on and 2 week off schedule.[72] Two phase I trials of BIBW-2992 given once daily in a continuous schedule have defined the recommended dose at 50 mg.[73,74] Dose-limiting toxicity was reached at 60 mg daily with grade 3 diarrhoea. Two patients with adenocarcinoma of the lung and mutated EGFR had partial responses lasting more than 24 months.[74]

A phase II study of BIBW-2992 in combination with an anti-angiogenic agent is underway in hormone refractory prostate cancer and the combination of BIBW-2992 with docetaxel is currently being evaluated in two other trials.

12. HKI-272

HKI-272 is a highly selective inhibitor of HER2 and EGFR. HKI-272 reduced HER2 and EGFR kinase activity by 50% (IC_{50}) at a concentration of 59 nM and 92 nM, respectively. HKI-272 inhibits HER2 and EGFR in an irreversible manner due to its improved chemical scaffolding.[75]

HKI-272 has proved to be highly active against HER2-overexpressing human breast cancer cell lines *in vitro*. It has demonstrated blockade of downstream signal transduction of MAPK and Akt and cell cycle regulatory pathways. HKI-272 also inhibits the proliferation of cultured cells that contain sensitising and resistance-associated EGFR mutations, including tumour cells that have become resistant to gefitinib or erlotinib.[76] *In vivo*, HKI-272 is active in HER2- and EGFR-dependent tumour xenograft models when dosed orally on a once daily schedule.[77]

Recent data from the phase I trial of HKI-272 given as a continuous, once-daily, oral treatment confirmed its safety. Seventy-three patients with a variety of solid tumours expressing HER2 and/or EGFR were included. The MTD was reached at 320 mg/day, with diarrhoea as the most frequently associated symptom. Preliminary data for 51 patients showed antitumour activity in HER2-positive breast cancer patients refractory to trastuzumab. Two phase 2 studies of HKI-272 in HER2 overexpressing breast cancer and advanced non-small cell lung cancer (NSCLC) are ongoing.

13. CI-1033

CI-1033 is an irreversible pan-ErbB tyrosine kinase inhibitor. Targeting all four ErbB receptors has the theoretical advantage of blocking redundant signalling that might be used to bypass more specific ErbB tyrosine kinase inhibitors; such

agents could be more effective at preventing the emergence of drug resistance. CI-1033 was relatively well tolerated in Phase 1 studies, although thrombocytopaenia and allergic rashes were reported.[78,79] Phase II studies have, however, been largely disappointing, and have precluded this agent's further development.[80]

14. Future directions

Increased understanding of the molecular biology of cancer and in particular the ErbB receptor tyrosine kinase family and related downstream pathways has been crucial for the development of drugs inhibiting these targets. As discussed, monoclonal antibodies and TKIs have shown efficacy and are in clinical use. A key future aim will be identifying accurate predictors of clinical response to these agents. Clinical trial design can then be tailored to the drug or drugs being tested, and patients most likely to benefit be accurately selected. This, in turn, should lead to more rapid approval of novel therapeutics. The identification of accurate biomarkers is also critically important. In some studies, the incidence of skin rash has been positively correlated to tumour response and survival.[81,82] Skin may therefore prove to be a surrogate tissue for determination of molecular response to ErbB inhibitors. Increased efforts in developing biomarkers will aid accurate assessment of drug combination effects. Continued research into the interactions of the ErbB receptors, both with each other and in their interactions with other key pathways, will lead to new drug development, and the optimisation of the use of approved drugs.

Conflict of interest statement

Dr. Johann De-Bono is an advisory consultant to Boehringer Ingelheim.

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