EJC SUPPLEMENTS 6, NO. 5 (2008) 25–31

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

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

*Pierre Fumoleau**

Centre G-F Leclerc, Dijon, France

ARTICLE INFO

Keywords:
Breast neoplasms
Lapatanib
Receptor, epidermal growth factor
HER2

ABSTRACT

This article overviews future trends for the treatment of ErbB2 (HER2)-positive breast cancer. It is based on a presentation given at the ECCO 14 congress, September 2007.

Novel ErbB2-targeted agents and/or treatment combinations have shown promise in treating ErbB2-positive metastatic breast cancer. Combinations include two agents that both inhibit ErbB2 and existing/novel ErbB2 inhibitors with chemotherapy and/or vascular endothelial growth factor (VEGF)- and VEGF receptor (VEGFR)-targeted agents. Early data suggest lapatinib (an ErbB1/2 inhibitor that recently received European approval) may be valuable in treating and/or preventing brain metastases secondary to ErbB2-positive breast cancer. Furthermore, based on promising data in metastatic disease, adjuvant and neoadjuvant lapatinib monotherapy and combination therapy trials are ongoing in early disease. Translational research will become increasingly important with new/novel agents to optimize outcomes through individualized treatment.

In summary, novel targeted agents/combinations may fulfill unmet treatment needs in ErbB2-positive breast cancer; ongoing research will confirm therapeutic potential.

1. Introduction

The preceding reviews in this supplement have explored the issues and latest advances relating to the treatment of ErbB2 (HER2)-positive breast cancer. In particular, they have highlighted the unmet needs that must be overcome to improve clinical outcomes in patients with ErbB2-positive breast cancer receiving targeted therapies, and they have also summarized recent advances with novel targeted agents in development that may ultimately represent improved first-line options. These novel treatment options may offer hope to ErbB2-positive breast cancer patients, including those who do not respond to, or who become insensitive to, trastuzumab-based regimens. Improved treatment options in this latter group would be particularly beneficial, as 40–50% of patients with ErbB2-positive metastatic disease do not respond to trastuzumab-containing regimens, and the majority of those who do respond to trastuzumab plus a taxane or vinorelbine develop progressive disease within 1 year after initiation of therapy.[1–4]

As discussed in the accompanying review article in this supplement authored by Dr David Cameron, lapatinib is at the most advanced stage of clinical development of the novel targeted agents for the treatment of ErbB2-positive breast cancer currently in the pipeline. This agent has shown clinical promise in patients who either do not respond to, or who lose response to, trastuzumab. Consequently, lapatinib has been approved in some regions

*Address for correspondence: Pierre Fumoleau. Directeur Général, Centre G-F Leclerc, 1, Rue Professeur Marion – BP 77 980, 21079 Dijon, France.
Tel.: +33 3 80 73 75 01; fax: +33 3 80 73 77 99.
E-mail address: pfumoleau@dijon.fnclcc.fr (P. Fumoleau).

1359-6349/ $ – see front matter

(the USA, the European Union and Switzerland) for the treatment of this patient group. Lapatinib is the first oral, small-molecule dual-targeted therapy that works intracellularly to inhibit ErbB1 (epidermal growth factor receptor [EGFR]) and ErbB2 receptor tyrosine kinases.[5] Lapatinib acts by inhibiting ErbB2-mediated intracellular signalling pathways, resulting in inhibition of tumour growth associated with increased apoptosis.[6,7]

This article will focus on future trends for the targeted treatment of patients with ErbB2-positive breast cancer, which are geared towards further improving treatment options and outcomes for these patients. For metastatic disease, this includes trials to evaluate the efficacy of new combinations of lapatinib and trastuzumab with other targeted agents that inhibit ErbB2 dimerization or are anti-angiogenic. It is hoped that results from these trials will provide valuable first-line treatment options for those patients who have been pretreated with trastuzumab. In addition, trials are planned or ongoing to evaluate the feasibility of preventing the development of secondary brain metastases and/or improving outcomes in patients with brain metastases, which remains a significant management challenge.[8–11] These trials are especially relevant as the incidence of brain metastases has increased, particularly since the advent of trastuzumab.[12] For early stage ErbB2-positive breast cancer, trials to further evaluate lapatinib as a monotherapy or combination therapy in adjuvant/neoadjuvant settings are planned or ongoing; these include definitive, head-to-head comparisons with trastuzumab that should help guide future clinical decision making.

2. Future trends in the treatment of metastatic ErbB2-positive breast cancer

Ongoing trials that may impact the treatment paradigm in ErbB2-positive breast cancer include those evaluating novel combinations in heavily pretreated patients with metastatic disease, such as those who have received at least one trastuzumab-containing regimen. These patients have, until recently, had no other recommended treatment options. Other trials include those evaluating the potential of lapatinib in the prevention or treatment of secondary brain metastases and those evaluating the efficacy of this novel targeted agent in early stage ErbB2-positive breast cancer.

2.1. Novel combinations for the treatment of patients who have received at least one line of trastuzumab-containing therapy

Novel combinations of ErbB2-targeted agents, each specific for a target on a distinct signalling pathway, or agents that target more than one molecule, may be required to prevent the continued activation of a bypass/salvage pathway that would otherwise drive tumour growth, and result in treatment failure.[13] Hence, a future challenge for the treatment of ErbB2-positive breast cancer is the identification and optimal use of the most appropriate treatment combinations and/or treatment sequences. These could include combining a targeted agent with either another targeted agent and/or a standard chemotherapy.

A number of trials are currently attempting to determine the optimal use of treatment combinations and/or treatment sequences for patients with ErbB2-positive metastatic breast cancer previously treated with trastuzumab. The ErbB2/ErbB3 dimerization inhibitor pertuzumab (2C4) is a monoclonal antibody (mAb), like trastuzumab, but targets a different region of ErbB2.[14] Preliminary results from the first stage of a Phase II study combining trastuzumab (2 mg/kg once weekly or 6 mg/kg once every 3 weeks [q 3 wk]) with pertuzumab (420 mg q 3 wk) in 33 patients with ErbB2-positive metastatic breast cancer previously treated with trastuzumab, showed an overall response rate (ORR) of 18% (3% complete response, 15% partial response [PR]). At present, patients are being recruited for the second stage of the study.[15] In a separate Phase III, randomized, controlled study in a similar patient population (reviewed in detail by Dr Cameron in this supplement) an ORR of 23.7% was reported in patients administered a combination of lapatinib (1250 mg orally [po] once daily [QD] continuously) and capecitabine (2000 mg/m^2/day po on Days 1–14 q 3 wk).[16] The results of these trials suggest that this lapatinib combination regimen is at least as efficacious as trastuzumab plus pertuzumab in treating metastatic ErbB2-positive breast cancer in patients following one line of a trastuzumab regimen. However, this conclusion should be interpreted with caution due to the limitations associated with cross-study comparisons. Definitive conclusions on the relative efficacy of these two targeted regimens can only be drawn from an appropriately designed head-to-head clinical trial.

2.2. Ongoing trials evaluating combinations targeting ErbB2 and angiogenesis

Several lines of evidence support the use of ErbB2-targeted agents in combination with anti-angiogenic agents that target vascular endothelial growth factor (VEGF) or its receptor (VEGFR): VEGF expression is linked to ErbB2 signalling; overexpression of ErbB2 results in induction of VEGF;[17] and a significant positive association between ErbB2 and VEGF expression has been demonstrated in primary breast tumour tissue lysates from 611 patients.[18] Therefore, there is a strong rationale for the combination of ErbB2 inhibitors with VEGF/VEGFR inhibitors for the treatment of breast carcinoma. For this reason, both trastuzumab and lapatinib are currently under evaluation in combination with anti-VEGF/VEGFR agents.

Table 1 – Most frequently reported adverse events in patients with solid tumours administered lapatinib in combination with pazopanib: study VEG10006 (n = 43) [21]

Adverse event (n)	Grade 1	Grade 2	Grade 3	Grade 4	Total
Diarrhoea	10	2	3	0	15
Fatigue	7	5	0	1	13
Nausea	9	2	0	0	11
Anorexia	8	3	0	0	11
Vomiting	9	0	0	0	9
Hair depigmentation	7	0	0	0	7
Rash	6	1	0	0	7
Abdominal cramps	3	2	1	0	6

The humanized mAb bevacizumab binds to VEGF to inhibit VEGFR-mediated intracellular signalling pathways that promote angiogenesis, thus disrupting the tumour vasculature. [19] This agent is in Phase III development for the treatment of ErbB2-positive breast cancer. Preliminary data have been reported from the first 30 of a planned 50 patients enrolled in a Phase II trial evaluating trastuzumab (2 mg/kg once weekly) combined with bevacizumab (10 mg/kg once every 2 weeks). [20] This combination regimen resulted in an ORR of 46% (all PR) in the first-line setting in patients with ErbB2-positive locally advanced or metastatic breast cancer. [20] Stringent cardiac safety surveillance was followed in this trial and six cardiac adverse events (AEs; National Cancer Institute Common Toxicity Criteria version 2) were reported, one of which was symptomatic: two were grade 1, three were grade 2 and one was grade 4.

Pazopanib is an oral, small molecule VEGFR tyrosine kinase inhibitor currently in Phase II clinical development for ErbB2-positive breast cancer and secondary brain metastases. [21] An ongoing Phase II study is evaluating lapatinib (1500 mg po QD) in combination with pazopanib (400–800 mg po QD) versus lapatinib alone, as first-line therapy for ErbB2-positive advanced or metastatic breast cancer (study VEGF20007). A prior Phase I dose escalation study (lapatinib dose range: 750–1500 mg po QD; pazopanib dose range: 200–500 mg po QD) showed that this combination was well tolerated in patients with solid tumours. [21] In the 33 patients evaluated, lapatinib was well tolerated in combination with pazopanib, with the majority of AEs being of grades 1–2 (Table 1). Only one grade 4 event (fatigue) and four grade 3 events were reported (diarrhoea, n = 3; abdominal cramps, n = 1). Diarrhoea, fatigue, nausea, anorexia and vomiting were the most common AEs.

2.3. Potential for lapatinib in the treatment and prevention of secondary brain metastases

Brain metastases affect 25–30% of women with ErbB2-positive breast cancer, [22–26] and are associated with a high burden of care. [27] The management of secondary brain metastases in ErbB2-positive breast cancer remains challenging and outcomes are poor. [8–11] Preliminary data have suggested that lapatinib may have activity in the treatment (study EGF105084) and prevention (study EGF100151) of breast cancer-associated brain metastases as the first site of relapse. An exploratory analysis in the EGF100151 study demonstrated a significantly lower frequency of central nervous system metastases as the first site of relapse with lapatinib (1250 mg po QD continuously) plus capecitabine (2000 mg/m^2/day po on Days 1–14 q 3 wk) versus capecitabine alone (2500 mg/m^2/day po on Days 1–14 q 3 wk; 2% vs 6%; $p = 0.045$). [16] This suggests an associated potential to reduce the incidence of brain metastases as first site of recurrence in metastatic breast cancer.

In the EGF105084 study, 241 patients with ErbB2-positive breast cancer, who had radiographically documented progressive CNS disease and had received prior treatment with cranial radiotherapy, were treated with lapatinib 750 mg po twice daily. The primary endpoint (a 50% volumetric reduction in brain lesion) was achieved by 19 of 241 (7%) patients evaluated. [28] The median absolute volume reduction was 3.1 cm^3 (range 0.17–29.7 cm^3) in these 19 patients. [28] In addition, 46 patients (19%) achieved the secondary endpoint of a 20% reduction in volume of lesion (median absolute volume reduction 1.9 cm^3; range 0.08–29.7 cm^3). [28] Although overall activity was modest, the results demonstrate single-agent activity of lapatinib in patients with recurrent brain metastases from ErbB2-positive breast cancer.

Taken together, the results of these two studies in ErbB2-positive breast cancer patients suggest that lapatinib may be of value in the management of brain metastases. [16,28,29] On the basis of these promising early data, lapatinib is undergoing further clinical evaluation for the management of brain metastases secondary to ErbB2-positive breast cancer (studies EGF107671 and VEG109909).

3. Why use lapatinib in early stage Erb2-positive breast cancer?

The demonstrated promising efficacy of lapatinib in the treatment of ErbB2-positive breast cancer in the

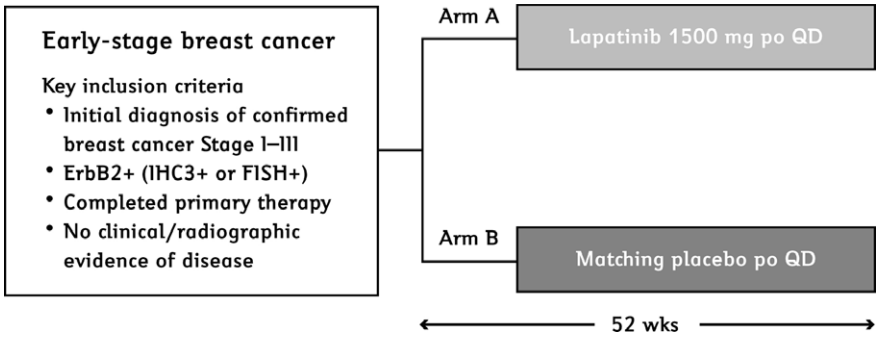

Fig. 1 – TEACH (Tykerb Evaluation After Chemotherapy) study design: evaluating lapatinib in the adjuvant setting. FISH = fluorescence *in situ* hybridization; IHC = immunohistochemistry; po = oral; QD = once daily.

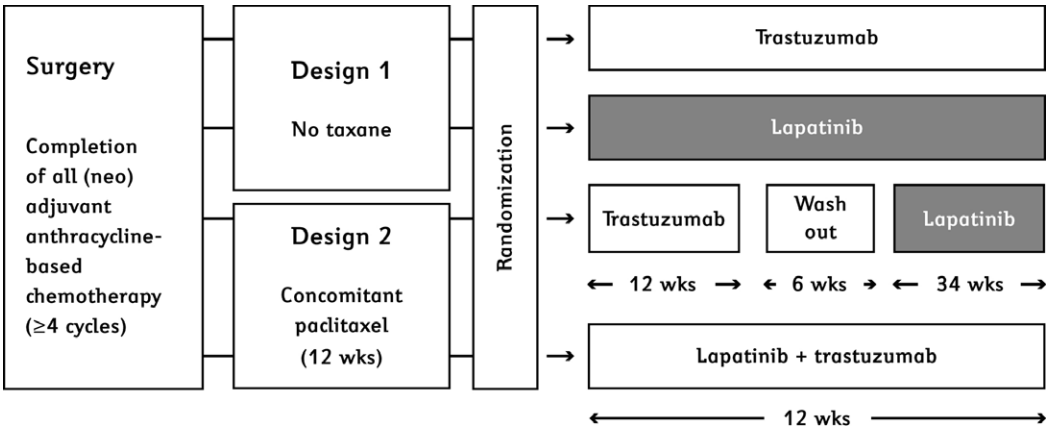

Fig. 2 – ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study design: definitive head-to-head comparison of lapatinib with trastuzumab in the adjuvant setting. N = 8000 (2000 per treatment arm).

metastatic setting warranted further evaluation of this agent in earlier stages of disease. Thus, a clinical development programme was designed to include evaluation of lapatinib as a monotherapy or combination therapy in the adjuvant and neoadjuvant treatment of ErbB2-positive early breast cancer.

The Tykerb Evaluation After Chemotherapy (TEACH) study is a Phase III, two-armed, randomized, double-blind, placebo-controlled study of single-agent lapatinib (1500 mg po QD) in the adjuvant treatment of ErbB2-positive invasive breast cancer in patients without prior trastuzumab treatment (Figure 1).[30] It represents the first study to evaluate lapatinib in the adjuvant setting and aims to determine whether adjuvant lapatinib therapy for 1 year improves disease-free survival. Planned enrolment for the TEACH trial is 3000 patients; to date, more than 1500 patients have been enrolled. Key inclusion criteria include: initial diagnosis of confirmed breast cancer Stage I–III; ErbB2-positive (i.e., by immunohistochemical staining [intensity of 3+] or fluorescence *in situ* hybridization); completed primary therapy; and no clinical/radiographic evidence of disease.

The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) study is a Phase III, four-armed, randomized, open-label, multi-centre study comparing the activity of lapatinib alone, versus trastuzumab alone, versus trastuzumab followed by lapatinib, versus lapatinib concomitantly with trastuzumab in the adjuvant treatment of patients with ErbB2-positive breast cancer.[31] The study design is shown in Figure 2. The ALTTO trial represents the largest global adjuvant study to date, encompassing the most comprehensive translational research programme in cancer research. It is a pioneering, collaborative group study with a planned enrolment of 8000 patients (2000 patients per treatment arm).

In addition to these two adjuvant studies, lapatinib is also being evaluated in the neoadjuvant setting. The NEO-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NEO-ALTTO) study is a three-armed, randomized, Phase III neoadjuvant trial comparing trastuzumab plus lapatinib with single-agent trastuzumab or lapatinib in patients with operable or palpable ErbB2-positive breast cancer.[32] The study design is shown in Figure 3. All arms will include a 12-week period of weekly paclitaxel prior to surgery. The NEO-ALTTO study represents the first trial to evaluate the combination of trastuzumab plus lapatinib in the neoadjuvant setting.

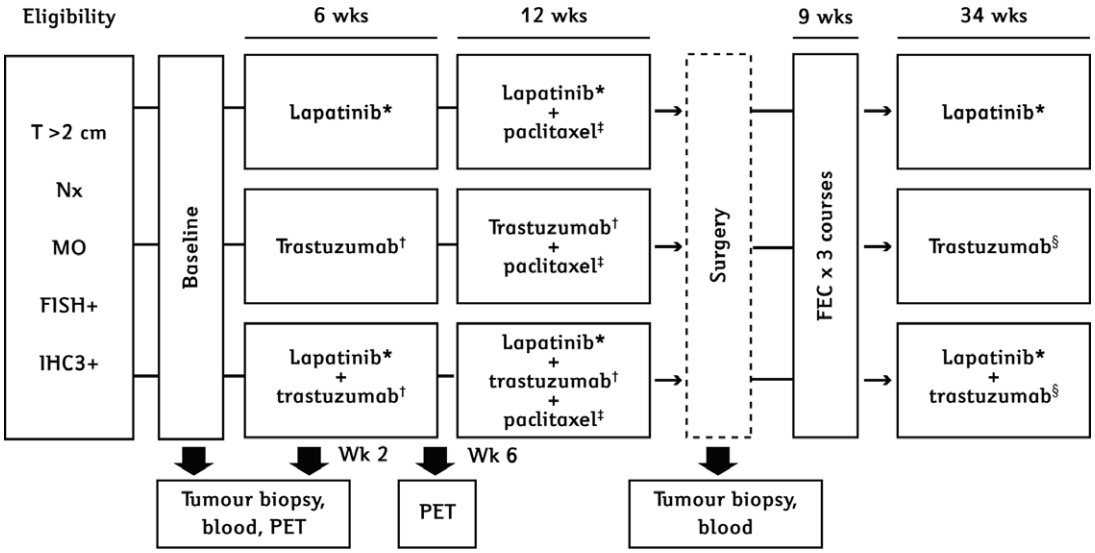

Fig. 3 – NEO-ALTTO (NEO-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study design: evaluating the use of lapatinib in the neoadjuvant setting. *1500 mg/day; †2 mg/kg q wk; ‡80 mg/m^2 q wk; §6 mg/kg q 3 wk. FEC = 5-fluorouracil, epirubicin, cyclophosphamide; FISH = fluorescence *in situ* hybridization; IHC 3+ = immunohistochemical staining intensity of 3+; MO = no distant metastasis; Nx = regional lymph nodes cannot be assessed; PET = positron emission tomography; q (3) wk = every (three) weeks; T = tumour.

4. The role of translational research in the evolving management of ErbB2-positive breast cancer

Translational research is critical in advancing the management of breast cancer. With the increasing number of targeted agents available, this type of research is essential to identify biomarkers that will determine which patients will respond best to a given agent. This includes both response prediction and toxicity reduction, with the ultimate goal of individualized treatment for optimal clinical outcomes in each patient. As noted above, the ALTTO study encompasses a comprehensive translational research component, which it is hoped will provide a substantial amount of data in this respect.

5. Conclusions

This is an exciting time in the management of ErbB2-positive breast cancer, with numerous novel agents currently in development and new combinations being tested in comprehensive clinical development programmes. These novel agents and combinations have the potential to fulfill the unmet needs that exist in these patients. Indeed, it is hoped that a breakthrough in the treatment of ErbB2-positive metastatic breast cancer could be determined from investigating new agents and new regimens in the adjuvant setting, and through the power of the associated translational research. The combination of novel agents, novel combinations and a more individualized approach to treatment are likely to have a significant impact on the ErbB2-positive breast cancer treatment paradigm; the exact nature of this change will depend on the outcomes of ongoing research.

Acknowledgments

The author would like to thank Yasamin Mir-Shekari, DPhil, Medicus International, for her editorial assistance. Editorial support and publication of this supplement was funded by an unrestricted educational grant from GlaxoSmithKline.

Conflict of interest statement

The author has received honoraria for consulting for GlaxoSmithKline, sanofi-aventis, Johnson and Johnson and Roche.

Role of the funding source

GlaxoSmithKline had no editorial control in respect of this article and the views expressed are solely those of the author.

References

1. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;23(19):4265–74.

2. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344(11):783–92.
3. Smith IE. Efficacy and safety of Herceptin in women with metastatic breast cancer: results from pivotal clinical studies. *Anticancer Drugs* 2001;12(Suppl 4):S3–10.
4. Burstein HJ, Kuter I, Campos SM, et al. Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2001;19(10):2722–30.
5. Konecny GE, Pegram MD, Venkatesan N, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. *Cancer Res* 2006;66(3):1630–9.
6. 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.
7. Hegde PS, Rusnak D, Bertiaux M, et al. Delineation of molecular mechanisms of sensitivity to lapatinib in breast cancer cell lines using global gene expression profiles. *Mol Cancer Ther* 2007;6(5):1629–40.
8. Mahmoud-Ahmed AS, Suh JH, Lee SY, Crownover RL, Barnett GH. Results of whole brain radiotherapy in patients with brain metastases from breast cancer: a retrospective study. *Int J Radiat Oncol Biol Phys* 2002;54(3):810–7.
9. Tsao MN, Sultanem K, Chiu D, et al. Supportive care management of brain metastases: what is known and what we need to know. Conference proceedings of the National Cancer Institute of Canada (NCIC) Workshop on Symptom Control in Radiation Oncology. *Clin Oncol (R Coll Radiol)* 2003;15(7):429–34.
10. Palmieri D, Smith QR, Lockman PR, et al. Brain metastases of breast cancer. *Breast Dis* 2006;26:139–47.
11. Tham YL, Sexton K, Kramer R, Hilsenbeck S, Elledge R. Primary breast cancer phenotypes associated with propensity for central nervous system metastases. *Cancer* 2006;107(4):696–704.
12. Tosoni A, Ermani M, Brandes AA. The pathogenesis and treatment of brain metastases: a comprehensive review. *Crit Rev Oncol Hematol* 2004;52(3):199–215.
13. Patyna S, Laird AD, Mendel DB, et al. SU14813: a novel multiple receptor tyrosine kinase inhibitor with potent antiangiogenic and antitumor activity. *Mol Cancer Ther* 2006;5(7):1774–82.
14. Agus DB, Akita RW, Fox WD, et al. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell* 2002;2(2):127–37.
15. Baselga J, Cameron D, Miles D, et al. Objective response rate in a phase II multicenter trial of pertuzumab (P), a HER2 dimerization inhibiting monoclonal antibody, in combination with trastuzumab (T) in patients (pts) with HER2-positive metastatic breast cancer (MBC) which has progressed during treatment with T. *J Clin Oncol ASCO Annual Meeting Proceedings* 2007;25(18S): Abstract #1004.
16. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat* 2008 Jan 11; Epub ahead of print.
17. Yen L, You XL, Al Moustafa AE, et al. Heregulin selectively upregulates vascular endothelial growth factor secretion in cancer cells and stimulates angiogenesis. *Oncogene* 2000;19(31):3460–9.
18. Konecny GE, Meng YG, Untch M, et al. Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients. *Clin Cancer Res* 2004;10(5):1706–16.
19. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349(5):427–34.
20. Pegram M, Chan D, Dichmann RA, et al. Phase II combined biological therapy targeting the HER2 proto-oncogene and the vascular endothelial growth factor using trastuzumab (T) and bevacizumab (B) as first line treatment of HER2-amplified breast cancer. *Breast Cancer Res Treat* 2006;100(Suppl 1): Abstract #301.
21. Dejonge M, Savage S, Verweij J, et al. A phase I, open-label study of the safety and pharmacokinetics (PK) of pazopanib (P) and lapatinib (L) administered concurrently. *J Clin Oncol ASCO Annual Meeting Proceedings* 2006;24(18 Suppl): Abstract #3088.
22. Alltaha R, Cromwell E, Ducatman B, Higa G, Abraham J. Risk of brain metastases in HER2/neu-positive breast cancer. *J Clin Oncol, 2004 ASCO Annual Meeting Proc* 2004;22(14S): Abstract #682.
23. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* 2003;97(12):2972–7.
24. Clayton AJ, Danson S, Jolly S, et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer* 2004;91(4):639–43.
25. Stemmler HJ, Kahlert S, Siekiera W, Untch M, Heinrich B, Heinemann V. Characteristics of patients with brain metastases receiving trastuzumab for HER2 overexpressing metastatic breast cancer. *Breast* 2006;15(2):219–25.
26. Yau T, Swanton C, Chua S, et al. Incidence, pattern and timing of brain metastases among patients with advanced breast cancer treated with trastuzumab. *Acta Oncol* 2006;45(2):196–201.
27. Pelletier EM, Shim B, Goodman S, Amonkar MM. Epidemiology and economic burden of brain metastases among patients with primary breast cancer: results from a US claims data analysis. *Breast Cancer Res Treat* 2008;108(2):297–305.
28. Lin NU, Dieras V, Paul D, et al. EGF105084, a phase II study of lapatinib for brain metastases in patients (pts) with HER2+ breast cancer following trastuzumab (H) based systemic therapy and cranial radiotherapy (RT). *J Clin Oncol ASCO Annual Meeting Proceedings* 2007; 25(18S): Abstract #1012. Presentation available at: http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=35084.
29. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with HER2+ breast cancer. *J Clin Oncol ASCO Annual Meeting Proceedings* 2006;24(18S): Abstract #503.
30. Moy B, Maltzman JD, Goss PE. Phase III study of lapatinib after completion of adjuvant chemotherapy in trastuzumab-naive women with ErbB2-overexpressing breast cancer: Tykerb evaluation after chemotherapy

(TEACH) study. *Breast* 2007;16(Suppl 1):S47 (Abstract P119).
31. Piccart-Gebhart MJ, Perez EA, Baselga J, et al. ALTTO (adjuvant lapatinib and/or trastuzumab treatment optimisation) study [BIG 206/N063D/EGF106708]: a phase III study for HER2-overexpressing early breast cancer (BC). *Breast* 2007;16(Suppl 1):S46 (Abstract P118).
32. Baselga J, Piccart-Gebhart MJ, Gelber RD, et al. neo-ALTTO (neoadjuvant lapatinib and/or trastuzumab treatment optimisation) study [BIG 106/SOLTI/EGF106903]: a phase III translational study for Her2-overexpressing early breast cancer (BC). *Breast* 2007;16(Suppl 1):S48 (Abstract P124).