SEARCH FOR THE HOLY GRAIL: EVOLVING TARGETED THERAPIES IN BREAST CANCER

Fran Boyle ■ Patricia Ritchie Centre for Cancer Care and Research, Mater Hospital, North Sydney, New South Wales
Email: franb@med.usyd.edu.au

Abstract

Understanding growth factor pathways overactive in subsets of women with breast cancer has enabled the development of agents which target these more precisely, enhancing efficacy of standard therapies and reducing side-effects. The first proof of this principle was the monoclonal antibody trastuzumab, which targets the HER2 receptor, over-expressed in approximately 20% of patients. Its efficacy has been established across the spectrum of clinical settings over the last decade, improving outcomes and synergising with chemotherapy and endocrine therapy. The intracellular HER2 tyrosine kinase inhibitor lapatinib extends this concept and clinical development is progressing rapidly, with adjuvant trials now open. Agents targeting angiogenesis have also found a role in the treatment of metastatic disease, although lack of specific diagnostic tests to identify a subgroup most likely to respond has hampered patient selection. Toxicities of these agents can be predicted by an understanding of their effects on normal cells expressing these pathways, and have generally been reversible. Their economic toxicity has proven more of a challenge and innovative trial designs will be required in future to reduce the cost of bringing them from bench to clinic.

The 'Holy Grail' of anti-cancer therapies is the mythical agent that affects only cancer cells which are marked out by a characteristic inscription, leaving normal tissues unharmed. Such an agent would ideally be oral, active at all sites in the body and able to be individualised in dosing for patients with different metabolic capabilities. Its use would ideally be triggered by a diagnostic test of high reliability, and its efficacy should be able to be monitored by serial testing, allowing individualised discontinuation when the cancer is cured. And it should be inexpensive.

Impossible? The haematologists might say "We've already got one!" as imatinib (Glivec®) in chronic myeloid leukaemia comes close to these specifications, with the exception of its cost and the need for chronic use.[1,2] In breast cancer the quest continues, however progress is being made and will be reviewed here.

There are important factors to consider in assessing the usefulness of targeted therapies.

What makes a good targeted therapy?

- Target molecule is present only in cancer tissues, or is significantly more active in cancer than in normal tissues.
- Frequency of the target is high in the population of patients.
- Target can be measured in histological samples in a reliable manner.
- Target occurs in an important growth pathway to which the cell is "addicted".
- Target is present in early "stem cell like" populations which tend to be resistant to other therapies.
- Targeted therapy can be safely combined with other anti-cancer therapies eg. chemotherapy and endocrine therapy, with synergistic efficacy.
- Oral bioavailability, to allow extended use and reduced administration costs.
- Therapy can reach all body tissues ie. not blocked by blood brain barrier.
- "Off target" toxicities are low and reversible.

Breast cancer targets

Much progress has been made in breast cancer treatment by recognising the responsiveness of the disease in many patients to oestrogen deprivation and the development of endocrine therapies to exploit this vulnerability (reviewed elsewhere in this issue of *Cancer Forum*).[3]

Oestrogen is not the only growth factor for breast cells and a number of other growth pathways are active at different phases of life, and provide potential targets for anti-cancer agents.

Epidermal growth factor family

This family of receptors (HER1,2,3,4 and their dimmers and heterodimers) are transmembrane glycoproteins which trigger tyrosine kinase activation, triggering cell growth and survival, and is important in both growth and repair from injury in many epithelial tissues.

In approximately 20% of women with breast cancer, overactivity of the pathway is conferred by amplification of the HER2 oncogene, leading to over-expression of the HER2 receptor.[4] The trigger of amplification is not known. It appears to occur early in oncogenesis and is often found in high-grade ductal carcinoma in situ. Detection is by immunohistochemistry or in situ hybridisation (summarised in recent American Society of Clinical Oncology guidelines).[5] This form of breast cancer is more likely to be high grade, invasive and associated with neovascularisation. It may be hormone receptor positive or negative, and if positive, may be

associated with poorer responsiveness to endocrine therapies. It may be more responsive to anthracycline based chemotherapy if there is co-amplification of the topoisomerase II gene, which is collocated on chromosome 17.[6] HER2 receptors are present in many normal tissues, including the skin, gut and heart, although the pathway is not usually active in these tissues in adults unless there is tissue injury.

Trastuzumab

The development of mouse monoclonal antibodies to the HER2 receptor allowed diagnostic identification of this subset. These were able to be crafted into therapeutic agents by humanising the antibody, known as trastuzumab (Herceptin). This agent has been widely studied in breast cancer over the past decade, and has activity against both stem and non-stem cell populations, which may account for its better than expected efficacy.[7] It has established roles in the following settings.

Adjuvant trials over the past decade included a variety of strategies (summarised in table 1), all of which appear to improve disease free survival (DFS), and the extended therapies also improve overall survival (OS). Concurrent administration with chemotherapy might theoretically provide greater synergy, particularly in high risk patients. The sequential approach also performed well in the HERA study with lower overall toxicity, however the smaller sequential study PACS-04 failed to achieve statistical significance.

Recent meta-analyses have confirmed benefits in disease free and overall survival, local recurrence and distant disease free survival.[13] A higher rate of brain metastases as first site of relapse was also noted (RR1.6, CI 1.06-2.40), consistent with poor penetration of the blood brain barrier.

Trastuzumab has a low but important incidence of cardiac toxicity, manifest as asymptomatic falls in left ventricular ejection fraction, and rarely, symptomatic left ventricular failure and cardiac death (total events <4.0%). It is more common in women who also receive anthracycline chemotherapy, and is due to the activation of epidermal growth factor receptor (EGFR) pathways in myocardium recovering from anthracycline damage. Other predisposing factors include concurrent use with chemotherapy versus sequential use, increased age and hypertension. Women with more serious underlying cardiac defects were excluded from all of the adjuvant studies, so the safety of Herceptin in such women is unknown. Use of a non-anthracycline chemotherapy, such as Carboplatin and Docetaxel (as in BCIRG 006), with close monitoring and tight blood pressure control, might be the safest approach in such women.[9]

Non cardiac toxicities include allergic reactions and anaphylaxis (usually with the first infusion), diarrhoea, rash, fatigue, nausea and headache. When used in combination with chemotherapy, rates of febrile neutropaenia are higher.

Optimal duration in the adjuvant setting remains a subject of investigation. A further arm of HERA, utilising two years of trastuzumab therapy, is yet to report. A number of other studies are underway investigating shorter durations of therapy, such as six months and nine weeks. Further follow-up data will emerge from the studies noted above, however it will be influenced by crossover of some patients on control arms to delayed trastuzumab. The use of 12 months of adjuvant trastuzumab is now recommended by the National Breast and Ovarian Cancer Centre guidelines and has been subsidised in Australia (if commenced concurrently with chemotherapy post-operatively) since October 2006.[14] This potentially curative approach should pay dividends with falling death rates in the next

Table 1: *Adjuvant trastruzumab trials in operable breast cancer.*

Study	Number analysed	Duration of trastuzumab	Chemotherapy backbone	Strategy	Hazard ratio DFS (CI)	Hazard ratio OS (CI)
N9831 NSABP B31[8]	3351	52 weeks	AC x 4, weekly paclitaxel x 12 or 3 weekly x 4	concurrent paclitaxel	0.48 (0.39-0.59)	0.65 (0.51-0.84)
BCIRG 006[9]	3222	52 weeks	AC Docetaxel or Carboplatin Docetaxel	concurrent	0.61 ACTH (0.48-0.76) 0.67TCH (0.54-0.83)	0.59 ACTH (0.42-0.85) 0.66 TCH (0.47-0.93)
HERA[10]	3401	1 year 3 weekly	Sequential	various	0.64 (0.54- 0.76)	0.66 (0.47-0.91)
FinHer[11]	232	9 weeks	Docetaxel before anthracycline	concurrent	0.42 (0.21-0.83)	Not sig at 3 yrs
PACS 04[12]	528	I year 3 weekly	FEC-Docetaxel or Epirubicin Docetaxel	sequential	0.86 NS (0.61-1.22)	1.27 NS (0.68-2.38)

AC = Adriamycin and cyclophosphamide FEC = 5-Flurouracil, Epirubicin, and cyclophosphamide

decade. As Dennis Slamon has observed: "This is proof of the principle that we can identify what's wrong in a cancer cell and fix it".[15]

A randomised Phase III study showed that adding trastuzumab to neoadjuvant chemotherapy increased the proportion of women obtaining a pathological complete response.[16] This effect does not appear to be influenced by hormone receptor status. This approach is not funded in Australia, and is being evaluated in further Phase II studies (including ANZ 0502 – Neo Gem) in Australia.

Targeted therapy might be of particular benefit in women with locally advanced or inflammatory breast cancer, which has a high rate of HER2 positivity. A Phase II study showed feasibility of combination with non-anthracycline based chemotherapy in this setting.[17]

Of great interest when first presented, this study was a collaborative effort of researchers and advocates, who worked to improve recruitment in the US, proving many principles along the way.

The original study identified additive benefit for DFS and OS (25.1 versus 20.3 months) combining trastuzumab with either anthracycline or paclitaxel chemotherapy.[18] The unacceptable incidence of cardiac toxicity has led to the avoidance of anthracycline combinations in subsequent usage.

Efficacy of trastuzumab in improving DFS and OS (31.2 versus 22.7 months) in combination with docetaxel given three weekly was subsequently reported.[19] Concurrent use of either weekly or three weekly trastuzumab with either taxane has been funded in Australia since 2001 via a separate Health Insurance Comission scheme after repeated Pharmaceutical Benefits Scheme (PBS) rejection.

Trastuzumab is also effective in combination with Vinorelbine in the metastatic setting, although this combination has never been approved in Australia.[20] This study also identified that lack of an early fall in serum levels of HER2 extracellular domain predicted for lack of response. Given the number of women who now receive a taxane as part of their adjuvant therapy, those who relapse would benefit from greater availability of this approach. In vitro synergy is observed with many cytotoxic agents and other combinations are under investigation.[21]

Combination with the aromatase inhibitor anastrazole also improved DFS compared with AI alone, and for patients with ER positive and lower risk metastatic disease, this offers a low toxicity approach to therapy.[22]

Controversy surrounds the issue of whether progression while on trastuzumab therapy should lead to the reintroduction of chemotherapy with maintained trastuzumab, or a switch to other agents. A German breast group study with capecitabine as a second line agent showed additional benefit to continuing trastuzumab.[23] The higher incidence of central nervous system metastases in these women has also been noted, leading to therapy with radiotherapy and/or surgery. A search for targeted agents with the potential to cross the blood brain barrier has emerged as a clear priority.

Lapatinib

The orally active tyrosine kinase inhibitor lapatinib (Tykerb) binds to the intracellular portion of the HER2 receptor and blocks signal transduction.[24] It has the potential to overcome trastuzumab resistance due to loss of the extracellular binding site (truncated p95 receptor).[25] To date it has been associated with lower levels of cardiotoxicity, although most patients studied have not had recent anthracyclines.[26] Some other common side-effects relate to its blockade of the EGF receptor (which does not correlate with clinical activity), including rash and diarrhoea.[27,28] It has established use in the second line metastatic setting in combination with capecitabine and is under investigation in a number of other clinical settings.

The pivotal study EGF 100151 compared capecitabine alone with capecitabine plus lapatinib in women whose disease had progressed after chemotherapy and trastuzumab. Improved progression free survival was demonstrated of 27.1 versus 18.6 weeks (CI 0.43-0.77). There was a higher response rate in the combination arm, and a 22% reduction in the risk of death.[29] Lapatinib was approved for PBS subsidy in this patient population in May 2008.

Lapatinib has the potential to cross the blood brain barrier and has demonstrated activity in animal models of brain metastases. Clinical responses with monotherapy lapatinib were observed in patients progressing after trastuzumab, radiotherapy +/- surgery.[30]

The head to head comparison study of trastuzumab versus lapatinib in combination with taxane chemotherapy has just opened internationally (Promise, MA31, NCIC). Translational studies will attempt to identify subgroups with higher responsiveness to either agent.

High response rates as monotherapy have been reported with lapatinib in inflammatory breast cancer, and combination studies are underway with taxanes and the antiangiogenic tyrosine kinase inhibitor pazopanib.[31]

Combination studies in metastatic disease with aromatase inhibitors are due to report in the next year. This offers an all oral approach to restoring endocrine sensitivity in dual positive breast cancer.

The ALTTO clinical trial is underway as a global cooperation to evaluate lapatinib alone, in combination or in sequence after trastuzumab in the adjuvant setting. Predetermined translational studies assessing Topo II, c myc, and the presence of p95 receptor will also be relevant to treatment choice in the future.

Many HER2 positive women worldwide have not had access to adjuvant trastuzumab, yet remain at increased risk of relapse for up to 10 years. The TEACH study has accrued 3165 patients to investigate the role of one year of lapatinib given at some distance from original treatment. Results are anticipated in 2010.

Angiogenesis inhibitors

Growth of tumours beyond approximately 4mm requires the development of new blood vessels to

supply nutrients. The process of new vessel formation, angiogenesis, is triggered by tumour hypoxia. Growth factors including vascular endothelial growth factor (VEGF) are released to stimulate endothelial proliferation and migration.[32] Targeting of this pathway has the potential to interrupt tumour growth, reduce metastatic potential, enhance penetration of chemotherapy and reduce recovery from sublethal damage.

Bevacizumab

This monoclonal antibody to VEGF reduces available ligand for binding to the VEGF receptor and inhibits angiogenesis.[33] It is administered intravenously on a variety of schedules.[34] Its related toxicities include impaired wound healing and renal impairment, proteinuria and hypertension. Anaphylactic reactions have also been described.

Two trials have addressed bevacizumab's combination with first line chemotherapy in metastatic breast cancer. The E2100 study investigated combining bevacizumab 10mg/kg 2nd weekly with weekly paclitaxel, showing significantly improved progression free survival (PFS) from 5.9 to 11.8 months (HR 0.60).[35] Overall survival was similar in the two groups. More recently, the AVADO study utilised three weekly docetaxel and two doses of bevacizumab (7.5 and 15 mg/kg 3 weekly) and showed a modest increase in PFS with both doses.[36] Overall survival data is not yet mature. Hypertension rates were lower and infection rates higher than E2100. It is possible that the anti-angiogenic activity of paclitaxel itself is a factor in the results of E2100, and the optimal chemotherapy backbone remains a subject for investigation. There is also cross-talk between HER2 and VEGF pathways, and double targeting approaches are under investigation in HER2 positive patients.

Pharmaceutical Benefits Scheme funding for this approach has not been secured in Australia to date and although bevacizumab has Therapeutic Goods Administration approval, the significant expense has inhibited implementation. The lack of a diagnostic test to identify patients most likely to respond prevents optimal targeting.

Global clinical trials have opened in 2008 (B020289: BEATRICE) focused on this high risk group, and will explore the benefits of adding 12 months of bevacizumab to standard adjuvant chemotherapy (including anthracyclines and taxanes).

Other angiogenesis and growth factor inhibitors

Multikinase inhibitors including pazopanib (which targets VEGF receptor signalling along with PDGF and C-KIT)[37] and sunitinib[38] are under investigation, and other monoclonal antibodies targeting the VEGF receptor-2 will enter trial in the next year.

Other important receptor mediated pathways active in some breast cancer patients include insulin-like growth factor and growth hormone. Many of these pathways are engaged in cross-talk with each other, with HER2, VEGF and ER. Many agents targeting ligands, receptors and downstream signalling molecules are in development.

Further development of the plethora of targeted agents will require changes to clinical trial design, perhaps to greater use of short periods of pre-operative therapy, with serial analysis of biomarkers of response and genetic predictors. More rapid progress should be able to be made as side-effects are often able to be predicted by understanding of pathway interruption. There is hope that this will reduce the overall cost of bringing these agents to the clinic and allow the identification of patients most likely to benefit. The search for the Holy Grail continues…and it won't be inexpensive.

References

1. Gilliam T, Jones T. Monty Python and the quest for the Holy Grail. 1996.
2. Soverini S, Marinelli G, Iacobucci I, Baccarani M. Imatinib mesylate for the treatment of chronic myeloid leukemia. Expert Rev Anticancer Ther. 2008;8:853-64.
3. Jordan VC, Brodie AM. Development and evolution of therapies targeted to the estrogen receptor for the treatment and prevention of breast cancer. Steroids. 2007;72:7-25.
4. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human Breast Cancer, Correlation of relapse and survival with amplification of Her-2/neu oncogene. Science. 1987;235:177-82.
5. Wolf AC, Hammond EH, Schwarz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology /College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor Testing in Breast Cancer. Arch Pathol Lab Med. 2007;131:18-43.
6. Harris LN, Yang L, Liotcheva V, Pauli S, Dirk Iglehart J, Michael CO, et al. Induction of topoisomerase II activity after Erb B2 activation is associated with differential response to breast cancer chemotherapy. Clin. Cancer Res. 2001;7:1497-1504.
7. Kakarala M, Wicha MS. Implications of the cancer stem-cell hypothesis for breast cancer prevention and therapy. J Clin Oncol. 2008;26:2813-2820.
8. Romond ER, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable Her2 positive breast cancer. N Engl J Med. 2005;353:1673-1684.
9. Slamon D, Eiermann W, Robert N, et al. BCIRG 006: 2nd interim analysis. Breast Cancer Res Treat. 2006;Suppl 1:abstract 52.
10. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2 positive breast cancer. N Engl J Med. 2005;353:1659-1672.
11. Joensuu H, Kellolumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, et al. Adjuvant Taxotere or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354:809-820.
12. Spielmann M, Roche H, Humblet Y, et al. Three year follow-up of trastuzumab following adjuvant chemotherapy in node positive HER2 positive breast cancer patients:results of the PACS-04 trial. Breast Cancer Res Treat. 2007;Suppl 1, abstract 72.
13. Dahabreh IJ, Linardou H, Siannis F, Fountzilas G, Murray S, et al. Trastuzumab in the adjuvant treatment of early stage breast cancer: a systematic review and meta-analysis of randomised controlled trials. Oncologist. 2008;13:620-630.
14. National Breast Cancer Centre. Recommendations for the use of Trastuzumab (Herceptin). Camperdown (Australia); 2007.
15. Bazell R. HER2 – the making of Herceptin. New York: Random House; 1998.
16. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathological complete remission rate after neoadjuvant therapy with trastuzumab, pclitaxel, and epirubicin chemotherapy: results of a randomised trial in human epidermal growth factor receptor 2-positive breast operable breast cancer. J Clin Oncol. 2005;23:3676-3685.
17. Hurley J, Doliny P, Reis I, Silva O, Gomez-Fernandez C, Velez P, et al. Taxotere, Cisplatin and Trastuzumab as primary systemic therapy for human epidermal growth factor receptor-2positive locally advanced breast cancer. J Clin Oncol. 2006;24:1831-1838.
18. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783-792.

19. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomised phase II trial of the efficacy and safety of trastuzumab combined with Taxotere in human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first line treatment. J Clin Oncol. 2005;23:4265-4274.
20. Burstein HJ, Harris LN, Marcom PK, Lambert-Falls R, Havlin K, Overmoyer B, et al. Trastuzumab and vinorelbine as first line therapy for HER-2 overexpressing metastatic breast cancer: multicentre phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm. J Clin Oncol. 2003;21:2889-2895.
21. Pegram M, Hsu S, Lewis G, Pietras R, Beryt M, Sliwkowski M, et al. Inhibitory effects of combinations of Her-2/neu antibody and chemotherapeutic agents used for the treatment of human breast cancers. Oncogene. 1999;18:2241-2251.
22. Mackey J, Kaufman B, Clemens M et al. Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. Breast Cancer Res Treat. 2006;SABCS Abstract.
23. Von Minckwitz G. Vogel P, Schmidt M et al. Trastuzumab beyond progression in patients with Her-2 positive metastatic breast cancer. The TBP study. Breast Cancer Res Treat. 2007;SABCS Abstract No.4056.
24. Spector NL, Wenle X, Burris H, Hurwitz H, Dees EC, Dowlati A, et al. Study of the biological effects of lapatinib, a reversible inhibitor of Erb B1 and Erb B2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. J Clin Oncol. 2005;23:2505-2512.
25. Xia W, Liu LH, Ho P, Spector NL. Truncated ErbB2 receptor (p95Erb B2) is regulated but heregulin through heterodimer formation with ErbB3, yet remains sensitive to the dual EGFR/ErbB2 kinase inhibitor GW572016. Oncogene. 2004;23:646-653.
26. Perez EA, Koehler M, Byrne AJ, Preston J, Rappold AJ, Ewer E, et al. Cardiac safety of lapatinib:pooled analysis of 3689 patients enrolled in clinical trials. Mayo Clinic Proc. 2008;83:679-686.
27. Lacouture M, Laabs SM, Koehler M, Sweetman RW, Preston AJ, Di Leo A, et al. Analysis of dermatological events in patients with cancer treated with lapatinib. Breast Cancer Res Treat. E-pub 2008 Jul 4.
28. Crown J, Burris H, Boyle F, Jones S, Koehler M, Newstat B, et al. Pooled analysis of diarrhea events in patients with cancer treated with lapatinib. Breast Cancer Res Treat. E-pub 2008 Jan 20.
29. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355:2733-2743.
30. Lin NU, Carey LA, Liu MC, Younger J, Come SE, Ewend M, et al. Phase II trial of lapatinib for brain metastases in patients with epidermal growth factor receptor2-positive breast cancer. J Clin Oncol. 2008;26:1993-1999.
31. Johnston S, Trudean M, Kaufman B, Boussen H, Blackwell K, LoRusso P, et al. Phase II study of predictive biomarker profiles for response targeting human epidermal growth factor receptor 2(HER-2) in advanced inflammatory breast cancer with lapatinib monotherapy. J Clin Oncol. 2008;26:1066-1072.
32. FolkmanJ. Angiogenesis in cancer, vascular, rheumatoid and other diseases. Nat Med 1995;1:27-31.
33. Kim KJ, Li B, Winer J, Armanini M, Gillett N, Phillips HS, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature. 1993;362:841-844.
34. Cobleigh MA, Langmuir VK, Slegde GW, Miller KD, Haney L, Novotny WF, et al. A phase I/II dose-esclation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol. 2003;30:117-124.
35. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007;357:2666-2676.
36. Miles D, Chan A, Romieu G et al. Randomised, double-blind placebo-controlled, phase III study of bevacizumab with Taxotere or Taxotere with placebo as first line therapy for patients with locally recurrent or metastatic breast cancer : AVADO. J Clin Oncol. 2008; 26:LBA 1011.
37. Harris PA, Boloor A, Cheung M, Kumar R, Crosby RM, Davis-Ward RG, et al. Discovery of pazopanib, a novel and potent vascular endothelial growth factor receptor inhibitor. J Med Chem. 2008;51:4632-4640.
38. Burstein H,J, Elias AD, Rugo HS, Cobleigh MA, Wolff AC, Eisenberg PD, et al. Phase II study of sunitinib maleate, and oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2008;26:1810-1816.