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Evolving options and future challenges for targeted therapies in ErbB2 (HER2)-positive breast cancer

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ABSTRACT

This article provides an overview of the rationale and advent of targeted therapies for ErbB2-positive breast cancer. It summarizes a presentation from a symposium held at the ECCO 14 congress.

The concept that oncogenic phenotype arises from several activated oncogenes but tumour growth is frequently highly dependent on a single oncogene (oncogene addiction) underlies the success of targeted cancer therapy. This has been effectively demonstrated in breast cancer, with the advent of ErbB2-targeted therapy. The first such agent used in treating patients with ErbB2-positive breast cancer, trastuzumab, heralded a major advance in this patient group. A wealth of novel targeted agents designed to further improve treatment in this setting are currently in development, including small molecule kinase inhibitors such as lapatinib, and anti-angiogenic agents that starve the growing tumour and limit metastasis.

In conclusion, novel targeted therapies could further improve outcomes in patients with ErbB2-positive breast cancer beyond that seen to date.

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1. In pursuit of novel targeted therapies for breast cancer

Breast cancer is a complex disease involving the dysregulated activation of multiple intracellular signalling cascades, leading to uncontrolled cellular proliferation, prolonged cell survival, angiogenesis, invasion and metastasis.[1,2] In particular, dysregulated signalling through the phosphatidylinositol-3-kinase (PI3K)/Ak transforming factor (Akt) and Raf/mitogen activated protein kinase (MAPK or MEK)/extracellular signal regulated kinase (ERK) pathways is implicated in breast tumorigenesis, progression and response to treatment.[3–7] Both of these signalling pathways are downstream of, and activated by, ligand binding to growth factor receptors, such as the ErbB2 (HER2) receptor.[5,7] Overexpression of the ErbB2 receptor, which belongs to the ErbB or epidermal growth factor receptor (EGFR) family of receptors, is highly prevalent in breast cancer, and is associated with clinically aggressive disease and reduced survival.[8,9] Indeed the aggressive nature of this form of breast cancer has led some to suggest that it should be viewed as a distinct entity within the umbrella of breast cancer.

In order to identify novel potential therapeutic molecular targets for the treatment of breast cancer, with the ultimate goal of developing more effective targeted therapies, an understanding of the complexities of these aberrant signalling pathways is essential. It is clear that several acquired mutations and/or epigenetic events resulting in loss of function of tumour suppressor

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Table 1 – Oncogenes and tumour suppressor genes implicated in the aetiology of breast cancer [8,9,11–20]

Gene	Abnormality	Incidence (%)	Function	Involvement with PI3K/Akt and Raf/MEK/ERK signalling
Oncogenes				
ErbB2 [8,9,11,12]	Overexpression	25–30	185 KDa transmembrane tyrosine kinase	Upstream activator of both pathways
PI3K [13]	Mutation causing overactivation	26	Kinase	Pivotal member of PI3K/Akt signal pathway
Akt [14]	Overactivation	~30	Serine/threonine kinase	Pivotal member of PI3K/Akt signal pathway
Cyclin D1 [14,15]	Overexpression Amplification	60–70 15–20	Cell-cycle mediator	Activated by Akt/PI3K
Cyclin E [15]	Overexpression	30	Cell-cycle mediator	Activated by Akt/PI3K
c-myc [16]	Overexpression Amplification	Up to 70% ~20%	Transcription factor	Activated by signalling through both pathways
Tumour suppressors				
PTEN [13,14,17]	Loss of function	4–16	Phosphatase that negatively regulates Akt	Downregulates Akt activity
p53 [18]	Mutation causing inactivation	40–50	Negative regulator of cell cycle	May negatively regulate signalling through Akt
BRCA-1 [19]	Mutation	~5	Regulates DNA transcription and repairs DNA damage	ND
BRCA-2 [20]	Mutation leading to truncated protein	8	Repairs DNA damage	ND
Rb [18]	Mutation causing inactivation	30–40		ND

Akt = Ak transforming factor; ERK = extracellular signal regulated kinase; MEK = mitogen activated protein kinase; ND = not determined; PI3K = phosphatidylinositol-3-kinase.

genes or the activation of oncogenes are implicated in the aetiology of breast cancer. These genes are summarized in Table 1; a full description of them is available elsewhere. [10] Many of these disease-associated genes either directly participate in signalling through the PI3K/Akt and Raf/MEK/ERK pathways or are regulators of these pathways. As such, it is conceivable that any of these genes could serve as a viable therapeutic target. The challenge lies in identifying which is the most appropriate target for therapeutic intervention.

2. Oncogene addiction: an opportunity for design of targeted agents?

Paradoxically, despite the involvement of several activated oncogenes and loss of function of several tumour suppressor genes in the aetiology of cancer, the growth of many solid tumours appears to be highly dependent on just one oncogene (Figure 1). This phenomenon was first identified and referred to as 'oncogene addiction' by Weinstein in 2002. [21]

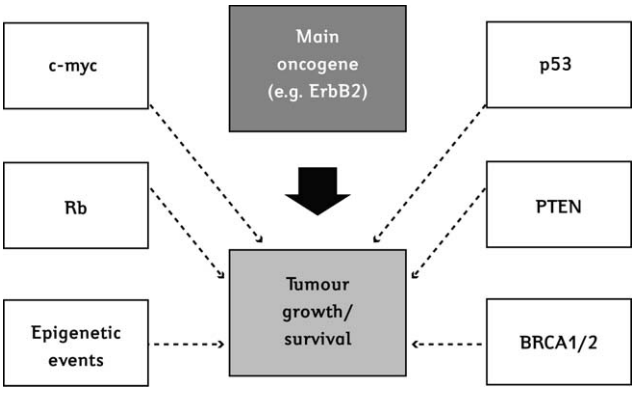

Fig. 1 – ErbB2-positive breast cancer is an example of oncogene addiction where just one of several disease-causing mutations appears to drive tumorigenesis. [21,22]

Oncogene addiction has been demonstrated in preclinical studies in several tumour types, including ErbB2-positive breast cancer. [22] For example, in one *in vitro* study, downregulation of ErbB2 gene expression using a specific antisense oligonucleotide was shown to inhibit

DNA synthesis and reduce the proliferation of breast cancer cells by up to 60%; no such inhibition was observed in breast cancer cells that did not overexpress ErbB2. [23] Similarly, in a mouse model of doxycycline-induced ErbB2 overexpression, doxycycline administration resulted in spontaneous growth and metastasis of ErbB2-overexpressing tumours while withdrawal of doxycycline led to ErbB2 downregulation and complete regression of primary tumours and lung metastases. [24]

Oncogene addiction has profound implications for the future development of targeted agents for the treatment of not only breast cancer, but also other tumour types. Specifically, this phenomenon could be exploited in the design of targeted agents tailored to suppress the activity of a single oncogene, thereby markedly inhibiting tumour growth. [21,22] Furthermore, proof of principle may already exist in the clinical setting, as oncogene addiction could explain the pronounced success of several targeted agents that have entered the clinic over the past decade for the management of difficult-to-treat malignancies. [22] One such example is the targeted agent imatinib, which quickly became the gold standard for the treatment of chronic myeloid leukaemia, a haematological malignancy dependent upon the Bcr-Abl oncogene. [25–27] Similarly, oncogene addiction to ErbB2 may explain the clinical success of the targeted agent trastuzumab in the treatment of ErbB2-overexpressing breast tumours. [22,28–31] The advent of trastuzumab-containing regimens resulted in significant survival benefits in patients with ErbB2-positive disease in the adjuvant setting. [30]

3. Improving targeted treatment of ErbB2-positive breast cancer

Despite showing clinical promise, there remain significant challenges in the treatment of ErbB2-positive breast cancer with currently available ErbB2-targeted therapy (specifically trastuzumab), particularly in the metastatic setting; this is explored in more detail in the accompanying articles in this supplement. The validation of novel targets for rational drug design is, therefore, needed (i.e., addicted oncogene; causative mutation; key driver), and it is critical to determine whether the putative target can be identified in a consistent, practical and cost-effective manner. It is also important to ensure that novel targeted agents are selective for malignant cells versus healthy cells, in order to maximize clinical benefit while minimizing the risk of adverse side effects that can often lead to poor treatment tolerance and/or treatment withdrawal.

A further obstacle to be overcome for the improved targeted treatment of breast cancer with signal transduction inhibitors is 'redundancy'. Redundancy between signalling pathways is implicated in tumour escape mechanisms and response to treatment in several tumour types. For example, cross-talk between the oestrogen receptor and ErbB2 receptor signalling pathways is implicated in tamoxifen resistance in breast cancer. [32,33] There is also redundancy within the ErbB receptor signalling system, where intracellular and cellular effect are determined by the constituents of the dimers formed between ErbB family members (homodimers or heterodimers – generally involving ErB2). Overexpression of heterodimers and redundancy in the intracellular signalling pathways they activate has been implicated in non-response or loss of response to trastuzumab and to ErbB1 inhibitors in preclinical breast cancer studies. [34]

Combinations of targeted agents, each specific for a target on a distinct signal 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. Since ErbB1, ErbB2 and the vascular endothelial growth factor receptor (VEGFR) all share Raf/MEK/ERK as a downstream signalling pathway, and since there is cross-talk between this pathway and the PI3K/Akt survival pathway, the evaluation of combinations of targeted agents that inhibit all three pathways could conceivably show promise in the treatment of ErbB2-positive breast cancer. Hence, a future challenge for solid tumours, including 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 another targeted agent and/or with a standard chemotherapy. Predicting and managing toxicities with such novel combinations and treatment sequences will also be important. One such example could be the known efficacy of the combination of trastuzumab plus anthracycline in metastatic ErbB2-positive breast cancer, which carries an attendant raised risk of cardiovascular adverse events [29,35,36] that is of sufficient concern for this combination not to be recommended in current treatment guidelines. [37,38] As discussed in the final review in this supplement, such trials are either planned or already ongoing.

The evaluation of novel targeted agents for the treatment of any malignancy also poses special challenges to laboratory and clinical scientists. These include the creation of appropriate models to effectively assess the effect of the agent on its putative target (monitoring target inhibition), the validation of new surrogate endpoints, and the use of effective clinical trial designs incorporating the most appropriate endpoints to enable an accurate assessment of clinical outcome.

4. Overview of targeted agents: focus on ErbB2-positive breast cancer pipeline

A number of novel targeted agents are currently in development, or approved, for the treatment of several difficult-to-treat solid tumour types (Table 2). In terms of the treatment of ErbB2-positive breast cancer, of these

Table 2 – Promising targeted agents currently approved or in development for the treatment of cancer[a]

General target	Specific target	Agent or approach
Signal transduction	Growth factor receptors	
	ErbB1 (EGFR)	**Erlotinib, gefitinib**
	ErbB2 (HER2)	**Trastuzumab, pertuzumab**
	ErbB1 and ErbB2	**Lapatinib**
	Bcr-Abl	Imatinib
	Ras	Farnesyl transferase inhibitors
	Raf	Antisense oligonucleotides
Angiogenesis and metastasis	VEGFR	**Sunitinib, pazopanib**
	VEGF	**Bevacizumab**
	Matrix metalloproteinases	AE-941
	Integrins	Humanized LM609 mAb
Tumour suppressor gene	p53	Gene therapy
	p16	Gene therapy
Cell cycle control	Cyclin dependent kinases	Flavopiridol
	mTOR	Temsirolimus (CCI779), everolimus

[a] Drugs in bold are approved or in development for ErbB2-positive breast cancer.
EGFR = epidermal growth factor receptor; mAb = monoclonal antibody; mTOR = mammalian target of rapamycin; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.

targeted agents, trastuzumab is already approved for the treatment of ErbB2-positive metastatic and early breast cancer.[39] Several other molecules are in the development pipeline for the treatment of ErbB2-positive breast cancer, the most advanced of which is the small-molecule dual-targeted inhibitor lapatinib, which potently and reversibly inhibits the receptor tyrosine kinase activity of ErbB1 and ErbB2.[40–43] The evidence to date suggests that ErbB1 is not a clinically relevant target in breast cancer, and that the clinical activity of lapatinib is due to its inhibitory activity against ErbB2.[44] This is not surprising since ErbB2-positive breast cancer has been shown to be an example of 'oncogene addiction', where tumour growth is primarily driven by a single oncogene (i.e., ErbB2 overexpression), as described earlier in this article.[21,22]

Further evidence for the lack of relevance of ErbB1 as a therapeutic target in breast cancer is provided by the disappointing results of a Phase II study of the ErbB1 inhibitor gefitinib in the treatment of patients with advanced breast cancer who had not been heavily pretreated; although some patients in this study did achieve stable disease, no complete or partial responses were observed.[45] Similarly, in a retrospective subgroup analysis of a Phase III study evaluating first-line therapy with lapatinib plus paclitaxel versus paclitaxel alone in patients with metastatic breast cancer unselected for ErbB2-positivity, overexpression of ErbB1 did not predict for clinical benefit with lapatinib.[46]

However, in other tumour types, such as head and neck, bladder and lung cancer, ErbB1 may be a relevant therapeutic target. For example, both lapatinib and the ErbB1 inhibitor cetuximab have shown promising data in patients with squamous cell carcinoma of the head and neck.[47,48] Similarly, lapatinib monotherapy has shown activity in locally advanced or metastatic transitional cell carcinoma of the urothelial tract,[49] and the ErbB1 inhibitors gefitinib and erlotinib have both demonstrated efficacy in advanced or metastatic non-small cell lung cancer, as first-line therapy or second-line to chemotherapy, respectively.[50,51]

Aside from lapatinib, novel monoclonal antibodies, such as pertuzumab, and inhibitors of angiogenesis are among those agents in development for ErbB2-positive breast cancer, which are discussed in the following review in this supplement. Other targeted agents that could show future promise in the treatment of breast cancer, but are currently in development in other tumour types, include those which target the PI3K/PTEN/Akt/mTOR pathway.[52]

The articles in this supplement explore the issues and latest advances relating to the treatment of ErbB2-positive breast cancer and summarize a satellite symposium which took place at The European Cancer Conference (ECCO) 14, held in Barcelona on September 24, 2007, entitled *New insight, new outlook: evolving options and future challenges for targeted therapies in ErbB2 (HER2)-positive breast cancer*. Specifically, the articles in this supplement cover three important topics: the unmet needs and current challenges that need to be overcome to improve clinical outcomes in patients with ErbB2-positive breast cancer receiving targeted therapies; recent advances with novel targeted agents in development for ErbB2-positive breast cancer that may ultimately represent

improved first-line options and/or offer hope to those patients who do not respond to, or who fail on, trastuzumab-based regimens; and future options for improved targeted therapy of early and metastatic ErbB2-positive breast cancer. Particular focus will be placed on the current and ongoing preclinical and clinical development of lapatinib throughout this supplement, as this is the most advanced of the targeted agents in the pipeline (and already approved in the United States and Europe) for the treatment of ErbB2-positive breast cancer.

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References

1. Yarden Y, Baselga J, Miles D. Molecular approach to breast cancer treatment. *Semin Oncol* 2004; 31(5 Suppl 10):6–13.
2. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol* 2001;2(2): 127–37.
3. Normanno N, De Luca A, Maiello MR, et al. The MEK/MAPK pathway is involved in the resistance of breast cancer cells to the EGFR tyrosine kinase inhibitor gefitinib. *J Cell Physiol* 2006;207(2):420–7.
4. Salh B, Marotta A, Matthewson C, et al. Investigation of the Mek–MAP kinase–Rsk pathway in human breast cancer. *Anticancer Res* 1999;19(1B):731–40.
5. Tokunaga E, Kimura Y, Mashino K, et al. Activation of PI3K/Akt signaling and hormone resistance in breast cancer. *Breast Cancer* 2006;13(2):137–44.
6. Zhou H, Kim YS, Peletier A, McCall W, Earp HS, Sartor CI. Effects of the EGFR/HER2 kinase inhibitor GW572016 on EGFR- and HER2-overexpressing breast cancer cell line proliferation, radiosensitization, and resistance. *Int J Radiat Oncol Biol Phys* 2004;58(2):344–52.
7. Giuliani R, Durbecq V, Di Leo A, et al. Phosphorylated HER-2 tyrosine kinase and Her-2/neu gene amplification as predictive factors of response to trastuzumab in patients with HER-2 overexpressing metastatic breast cancer (MBC). *Eur J Cancer* 2007;43(4):725–35.
8. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235(4785):177–82.
9. 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.
10. Osborne C, Wilson P, Tripathy D. Oncogenes and tumor suppressor genes in breast cancer: potential diagnostic and therapeutic applications. *Oncologist* 2004;9(4):361–77.
11. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;244(4905):707–12.
12. Pegram MD, Konecny G, Slamon DJ. The molecular and cellular biology of HER2/neu gene amplification/overexpression and the clinical development of herceptin (trastuzumab) therapy for breast cancer. *Cancer Treat Res* 2000;103:57–75.
13. Saal LH, Holm K, Maurer M, et al. PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. *Cancer Res* 2005;65(7):2554–9.
14. Bose S, Chandran S, Mirocha JM, Bose N. The Akt pathway in human breast cancer: a tissue-array-based analysis. *Mod Pathol* 2006;19(2):238–45.
15. Steeg PS, Zhou Q. Cyclins and breast cancer. *Breast Cancer Res Treat* 1998;52(1–3):17–28.
16. Nass SJ, Dickson RB. Defining a role for c-Myc in breast tumorigenesis. *Breast Cancer Res Treat* 1997;44(1):1–22.
17. Panigrahi AR, Pinder SE, Chan SY, Paish EC, Robertson JF, Ellis IO. The role of PTEN and its signalling pathways, including AKT, in breast cancer; an assessment of relationships with other prognostic factors and with outcome. *J Pathol* 2004;204(1):93–100.
18. Andersen TI, Gaustad A, Ottestad L, et al. Genetic alterations of the tumour suppressor gene regions 3p, 11p, 13q, 17p, and 17q in human breast carcinomas. *Genes Chromosomes Cancer* 1992;4(2):113–21.
19. Ford D, Easton DF, Peto J. Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. *Am J Hum Genet* 1995;57(6):1457–62.
20. Thorlacius S, Sigurdsson S, Bjarnadottir H, et al. Study of a single BRCA2 mutation with high carrier frequency in a small population. *Am J Hum Genet* 1997;60(5):1079–84.
21. Weinstein IB. Cancer. Addiction to oncogenes – the Achilles heal of cancer. *Science* 2002;297(5578):63–4.
22. Weinstein IB, Joe AK. Mechanisms of disease: Oncogene addiction – a rationale for molecular targeting in cancer therapy. *Nat Clin Pract Oncol* 2006;3(8):448–57.
23. Colomer R, Lupu R, Bacus SS, Gelmann EP. erbB-2 antisense oligonucleotides inhibit the proliferation of breast carcinoma cells with erbB-2 oncogene amplification. *Br J Cancer* 1994;70(5):819–25.
24. Moody SE, Sarkisian CJ, Hahn KT, et al. Conditional activation of Neu in the mammary epithelium of transgenic mice results in reversible pulmonary metastasis. *Cancer Cell* 2002;2(6):451–61.
25. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006;355(23):2408–17.

26. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002;346(9):645–52.
27. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348(11):994–1004.
28. 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.
29. Slamon D, Eiermann W, Robert N, et al. Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: second interim efficacy analysis. Oral presentation at the San Antonio Breast Cancer Symposium 2006 available at: http://www.bcirg.org/NR/rdonlyres/eqkdodg2dy7t557o7s6uvj7ytpe6gcfg5gmh2ely6hnhh5pjlabz3nd6jddlnao7qoikej3edohsijyiisfvp367uuc/BCIRG006+2nd+Interim+Analysis.pdf.
30. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007;369(9555):29–36.
31. 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.
32. Pietras RJ. Biologic basis of sequential and combination therapies for hormone-responsive breast cancer. *Oncologist* 2006;11(7):704–17.
33. Shou J, Massarweh S, Osborne CK, et al. Mechanisms of tamoxifen resistance: increased estrogen receptor–HER2/neu cross-talk in ER/HER2-positive breast cancer. *J Natl Cancer Inst* 2004;96(12):926–35.
34. Hsieh AC, Moasser MM. Targeting HER proteins in cancer therapy and the role of the non-target HER3. *Br J Cancer* 2007;97(4):453–7.
35. Perez EA, Suman VJ, Davidson NE, et al. Interim cardiac safety analysis of NCCTG N9831 Intergroup adjuvant trastuzumab trial. *J Clin Oncol ASCO Annual Meeting Proceedings* 2005;23(Suppl 16): Abstract #556.
36. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005;23(31):7811–9.
37. NCCN Practice Guidelines in Oncology – breast cancer v.2.2007. Available at: http://nccn.org/professionals/physician_gls/PDF/breast.pdf
38. Recurrent metastatic breast cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2007;18(Suppl 2):ii9–11.
39. Plosker GL, Keam SJ. Trastuzumab: a review of its use in the management of HER2-positive metastatic and early-stage breast cancer. *Drugs* 2006;66(4):449–75.
40. Di Leo A, Gomez H, Aziz Z, et al. Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: A phase III randomized, double-blind study of 580 patients. *J Clin Oncol ASCO Annual Meeting Proceedings* 2007;25(18S): Abstract #1011. Presentation available at: http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=47&abstractID=35691.
41. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355(26):2733–43.
42. Rusnak DW, Affleck K, Cockerill SG, et al. The characterization of novel, dual ErbB-2/EGFR, tyrosine kinase inhibitors: potential therapy for cancer. *Cancer Res* 2001;61(19):7196–203.
43. 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.
44. Spector NL, Xia W, Burris H, 3rd, 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.
45. Francis P, Green M, Gebski V, et al. Gefitinib has a low clinical benefit rate in advanced breast cancer patients. *Breast Cancer Res Treat* 2005;94(Suppl 1): Abstract #4080.
46. Finn RS, Press MF, Dering J, et al. Biomarker analysis of lapatinib with paclitaxel versus paclitaxel as first-line treatment in 580 patients with metastatic breast cancer *Eur J Cancer Suppl* 2007;5(4):212 (Abstract O#2097).
47. Harrington KJ, Bourhis J, Nutting CM, et al. A phase I, open-label study of lapatinib plus chemoradiation in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). *J Clin Oncol ASCO Annual Meeting Proceedings* 2006;24(18S): Abstract #5533.
48. Vermorken J, Mesia R, Vega V, et al. Cetuximab extends survival of patients with recurrent or metastatic SCCHN when added to first line platinum based therapy – Results of a randomized phase III (Extreme) study. *J Clin Oncol ASCO Annual Meeting Proceedings* 2007;25 (18S): Abstract #6091.
49. Wülfing C, Machiels JPH, Richel DJ, et al. EGF20003: A single arm, multicentre, open-label phase II study of orally administered lapatinib (GW572016) as single-agent, second-line treatment of patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract. Final analysis. *Ann Oncol* 2004;15(Suppl 3): Abstract #416O.
50. Johnson JR, Cohen M, Sridhara R, et al. Approval summary for erlotinib for treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. *Clin Cancer Res* 2005;11(18):6414–21.
51. Reck M, Buchholz E, Romer KS, Krutzfeldt K, Gatzemeier U, Manegold C. Gefitinib monotherapy in chemotherapy-naive patients with inoperable stage III/IV non-small-cell lung cancer. *Clin Lung Cancer* 2006;7(6):406–11.
52. Noh WC, Kim YH, Kim MS, et al. Activation of the mTOR signaling pathway in breast cancer and its correlation with the clinicopathologic variables. *Breast Cancer Res Treat* 2007 Sep 6; Epub ahead of print.