VOLUME 28 · NUMBER 20 · JULY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Emerging Targeted Therapies for Breast Cancer

Ricardo H. Alvarez, Vicente Valero, and Gabriel N. Hortobagyi

See accompanying articles on page 3248 and 3256

From The University of Texas M. D. Anderson Cancer Center.

Submitted August 5, 2009; accepted March 4, 2010; published online ahead of print at www.jco.org on June 7, 2010.

Supported by the Nelly B. Connally Breast Cancer Fund.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Ricardo H. Alvarez, MD, The University of Texas M. D. Anderson Cancer Center, Department of Breast Medical Oncology, 1155 Herman P. Pressler, CPB5.3458, Houston, TX 77030-3721; e-mail: ralvarez@mdanderson.org.

0732-183X/10/2820-3366/$20.00

DOI: 10.1200/JCO.2009.25.4011

ABSTRACT

Increased understanding of the molecular events involved in cancer development has led to the identification of a large number of novel targets and, in parallel, to the development of multiple approaches to anticancer therapy. Targeted therapy focuses on specific molecules in the malignant cell signal transduction machinery, including crucial molecules involved in cell invasion, metastasis, apoptosis, cell-cycle control, and tumor-related angiogenesis. In breast cancer, two new targeted agents have recently been approved: lapatinib, directed against the human epidermal growth factor receptor 2 (HER2); and bevacizumab, directed against vascular endothelial growth factor (VEGF). Multiple other targeted agents are under evaluation in clinical trials, including inhibitors of the epidermal growth factor receptor (EGFR), dual EGFR and HER2 inhibitors, other VEGF or VEGF-receptor inhibitors, and agents that alter crucial signaling pathways, such as RAS/MEK/ERK; phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin; insulin-like growth factor/insulin-like growth factor receptor; poly (ADP-ribose) polymerase 1; and others. In this review, we present the most promising studies of these new targeted therapies and novel combinations of targeted therapies with traditional cytotoxic agents.

J Clin Oncol 28:3366-3379. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Although numerous systemic agents are available to treat metastatic breast cancer (MBC), most tumors eventually become unresponsive to systemic therapy. In recent years, several targeted agents have become available that have improved the outcomes of patients with solid tumors. One of these agents, trastuzumab (Herceptin; Genentech, South San Francisco, CA), a monoclonal antibody against the human epidermal growth factor receptor 2 (HER2), has proven effective in the treatment of women with HER2-positive breast cancer.[1-4] Other targeted agents are also showing promise in breast cancer treatment. Two—lapatinib (Tykerb; GlaxoSmithKline, Research Triangle Park, NC), a selective, reversible dual inhibitor of the epidermal growth factor receptor (EGFR; HER1) and HER2, and bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF)—have recently been approved by the US Food and Drug Administration for patients with certain types of breast cancer.[5,6] However, most targeted agents that have shown promise against breast cancer are still in preclinical or early clinical testing. Here, we review the most current information regarding the emerging targeted therapies for breast cancer. We excluded trastuzumab from this review, because its role in breast cancer is well established.

EPIDERMAL GROWTH FACTOR RECEPTOR FAMILY

EGFR is a transmembrane growth factor receptor tyrosine kinase (TK) frequently expressed in epithelial tumors. In breast cancer, EGFR plays a major role in promoting cell proliferation and malignant growth (Fig 1).[7] EGFR and HER2 are frequently overexpressed in breast cancer, and such overexpression is associated with aggressive clinical behavior and poor clinical outcome.[8-11] In addition, EGFR overexpression was found in half of triple-receptor–negative (TRN) breast tumors but in only approximately 15% of unselected tumors.[12]

Pure EGFR Inhibitors: Gefitinib and Erlotinib

Gefitinib (Iressa; AstraZeneca, Macclesfield, Chesire, United Kingdom) is a small molecule that reversibly inhibits EGFR TK autophosphorylation and inhibits downstream signaling.[13,14] In a phase I, dose-escalation study in 88 patients with multiple solid tumors, the dose-limiting toxicities (DLTs) at 1,000 mg/d were grade 3 diarrhea and grade 3 somnolence.[15] The most frequent drug-related adverse effects were acne-like rash and diarrhea.

Multiple phase II studies of single-agent gefitinib and gefitinib plus chemotherapy or hormonal therapy

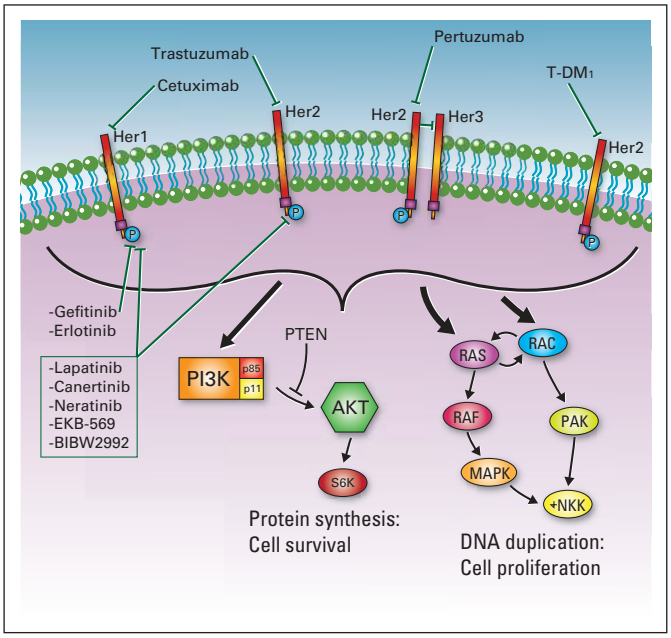

Fig 1. Epidermal growth factor receptor (EGFR) family. The EGFR family is composed of four homologous receptors: ERBB1 (EGFR/HER1), ERBB2 (HER2/*neu*), ERBB3 (HER3), and ERBB4 (HER4). The three receptors are implicated in the development of cancer; the role of ERBB4 is less clear. Six different ligands, known as EGF-like ligands, bind to EGFR. After ligand binding, the ERBB receptor becomes activated by dimerization between two identical receptors (ie, homodimerization) or between different receptors of the same family (ie, heterodimerization). Dimerization leads to phosphorylation of several intracellular catalytic substrates, including members of the Ras/Raf/mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol-3-kinase (PI3K)/Akt/PTEN family, and other important signaling pathways that regulate apoptosis, protein synthesis, and cellular proliferation. The morphology of the extracellular domain of four EGFRs is almost identical; however, they vary considerably in the functional activity. For instance, ERBB3 lacks inherent kinase function but can heterodimerize with other ERBB receptors. Indeed, the ERBB2-ERBB3 dimer, which is considered the most active ERBB signaling dimer, is fundamental for ERBB2-mediated signaling in tumors with ERBB2 amplification.

for breast cancer have been completed (Appendix Table A1, online only). Single-agent gefitinib showed minimal clinical benefit (CB). Although the studies of combination therapy were not randomized, gefitinib did not significantly improve overall response rate and time to treatment failure on a chemotherapy regimen.

More recently, an exploratory analysis of two randomized, phase II trials comparing anastrozole or tamoxifen plus gefitinib versus anastrozole or tamoxifen plus placebo was published.[16] In both trials, endocrine-therapy–naïve patients had longer progression-free survival (PFS) with hormonal therapy plus gefitinib.

Erlotinib (Tarceva; OSI Pharmaceuticals, Melville, NY) is a small molecule that reversibly inhibits the EGFR TK and prevents receptor autophosphorylation.[17] Preclinical studies have demonstrated that both erlotinib and gefitinib inhibit breast cancer proliferation in vitro, and the greatest effects are in HER2-positive cell lines.[14]

In a clinical trial of erlotinib monotherapy in patients with MBC, the main adverse effects were acneiform rash, diarrhea, and asthenia.[18] One of 69 patients had a partial response (PR). Several trials of erlotinib in combination with drugs known to be active in breast cancer were recently conducted. In a dose-escalation study of erlotinib plus capecitabine and docetaxel in patients with MBC, the overall response rate was 67%; two patients had a complete response, and 12 had a PR.[19] The regimen was generally well tolerated; manageable skin and gastrointestinal problems were the most common treatment-related adverse effects. Several other preliminary studies of erlotinib combined with docetaxel,[20] vinorelbine plus capecitabine,[21] and bevacizumab[22] have been reported.

On the basis of data from a preclinical mouse xenograft model, patients with stages I to IIIA invasive breast cancer were treated with erlotinib 150 mg/d orally for 6 to 14 days until the day before surgery.[23] Ki67 expression was reduced in estrogen-receptor–positive tumors but not in tumors that overexpressed HER2 or were TRN.

TRASTUZUMAB-DM1

Trastuzumab-DM1 is the first antibody-drug conjugate that is based on trastuzumab. Trastuzumab-DM1 consists of trastuzumab linked to an antimicrotubule drug, maytansine (also known as DM1). Trastuzumab-DM1 showed activity in a xenograft model of HER2-positive, trastuzumab-resistant tumors.[24] A phase I study of trastuzumab-DM1 in heavily pretreated patients with HER2-overexpressing MBC showed clinical activity, with thrombocytopenia as the DLT, at a dosage of 4.8 mg/kg every 3 weeks. The recommended dosage for phase II studies was 3.6 mg/kg every 3 weeks.[25] In a recent preliminary report of a phase II study of trastuzumab-DM1 in 112 patients with HER2-overexpressing MBC in whom treatment with trastuzumab, lapatinib, or both had failed to show promising activity, the independent review panel confirmed an overall response rate of 25% (28 patients) and a CB rate of 34% (38 patients).[26]

Two phase III studies of trastuzumab-DM1 are ongoing. One study tests the activity of trastuzumab-DM1 versus standard therapy with lapatinib-capecitabine as second-line therapy for patients with HER2-positive MBC. The other study tests docetaxel plus trastuzumab versus single-agent trastuzumab-DM1 as first-line therapy for HER2-positive MBC.

EGFR INHIBITORS PLUS AGENTS TARGETING OTHER PATHWAYS

Inhibition of EGFR/HER1 phosphorylation by anti-EGFR agents does not always correlate with antitumor effects. This suggests that tumor proliferation may be controlled by alternate growth factors in the presence of EGFR inhibitors and that the antitumor activity of anti-EGFR agents may be improved by combining them with therapies targeting other signal transduction pathways.[27] However, several studies in patients with breast cancer who were treated with these compounds as single agents showed disappointing results.[28]

Dual EGFR and HER2 Inhibitors

Interest in the role of EGFR in HER2-amplified tumors was renewed with the advent of dual TK inhibitors (TKIs) that interact with several EGFR members. Of these, lapatinib (Tykerb) is the agent that has been studied most extensively (Table 1). Other dual EGFR-HER2 inhibitors studied for breast cancer include cetuximab, canertinib, neratinib, and pertuzumab (Table 2).

Table 1. Phase II and III Trials of Lapatinib for Treatment of Breast Cancer

Study and Author	No. of Patients	Type of Study	Patient Population	Lapatinib Dose (mg/d)	Combination Therapy	Response (%) PR	CR	CB	Patient Outcome
Lapatinib single agent									
Blackwell et al[29]	78	Phase II	HER2 positive and Tz refractory	1,250-1,500	—	5.1	0	9	All patients had KPS > 70%. Efficacy outcomes: TTP was 15.3 weeks, and PFS was 15.3 weeks (range, 9.7 to 16.3 weeks). AE: skin rash (47%), diarrhea (46%), and nausea (31%)
Burstein et al[30]	229	Phase II	A, T, and Cap refratory	1,500					
Arm A	140				HER2 positive and Tz refractory	4	0		76% of patients had received four or more lines of therapy. HER2-positive patients: response rate was 4.3% and 1.4% by investigator and independent assessment, respectively.
Arm B	89				HER2 negative	0	0		No response rate observed in HER2 negative. Independent review assessment of median TTP and PFS were similar in HER2 positive and HER2 negative (9.1 weeks and 7.6 weeks, respectively). AE: diarrhea (54%), skin rash (30%), nausea (24%)
Gomez et al[31]	138	Phase II	HER2 positive; first-line treatment	1,500 once daily *v* 500 twice daily	—	24	0	31	Median TTP was 7.9 weeks (1,500 mg once a day, 7.9 weeks; 500 mg twice daily, 7.9 weeks), and median duration of response was 28.4 weeks (1,500 mg once a daily, 27.6 weeks; 500 mg twice daily, 29 weeks). AE: diarrhea, rash, pruritus, and nausea. No significant difference in efficacy between dosing schedules.
Lapatinib in combination with chemotherapy, hormone therapy, and targeted therapy									
Geyer et al[5]	324	Randomized, phase III	HER2 positive and A, T, and Cap refractory						The median TTP for L + Cap *v* Cap were 8.4 months and 4.4 months (HR, 0.49; 95% CI, 0.34 to 0.71; $P < .001$), respectively. The median PFS for L+ Cap *v* Cap were 8.4 and 4.1 months (HR, 0.47; 95% CI, 0.33 to 0.67; $P < .001$). Most common AEs were gastrointestinal toxicity: diarrhea, 60% *v* 39%; nausea, 44% *v* 42%; and vomiting, 26% *v* 24% for L + Cap compared with Cap alone, respectively. AE: grade 4 toxicity diarrhea in two patients (1%) in the L + Cap arm.
Arm A	163			1,250	Cap 2,000 mg/d for 14 days	35	1	44	
Arm B	161				cap 2,500 mg/d for 14 days	23	0	29	

(continued on following page)

Table 1. Phase II and III Trials of Lapatinib for Treatment of Breast Cancer (continued)

Study and Author	No. of Patients	Type of Study	Patient Population	Lapatinib Dose (mg/d)	Combination Therapy	Response (%)			Patient Outcome
						PR	CR	CB	
Di Leo et al[32]	579	Randomized, phase III	HER2 negative or HER2 UT						There were no significant differences in TTP, EFS, or OS between treatment arms, although differences in ORR were noted. In 86 patients (15%) with HER2-positive, treatment with P + L resulted in statistically significant improvements in TTP, EFS, ORR, and CB compared with P + Pl.
Arm A				1,500	P 175 mg/m^2 every 3 weeks	30	5	40.5	
Arm B				Pl	P 175 mg/m^2 every 3 weeks	23	2	32	
Johnston et al[33]	1,286	Randomized, phase III	Hormone receptor positive, HER2 negative; or hormone receptor positive, HER2 positive	Arm A:	Let 2.5 mg daily	NA	NA	NA	Hormone receptor positive/ HER2 negative: no significant treatment benefit on PFS (HR, 0.90; 95% CI, 0.77 to 1.05; $P = .188$).
Arm A				1,500	Let 2.5 mg daily	NA	NA	NA	Subgroup analysis of patients who had HER2 negative and lower expression of ER (H-score < 160) had significant improvement in median PFS (13.6 months *v* 6.6 months; HR, 0.65; 95% CI, 0.47 to 0.9; $P < .005$) when are treated with L + Let.[34]
Arm B				Pl					Overall, 219 of 1,286 patients were hormone receptor positive/HER2 positive. The PFS was 8.2 *v* 3 months for L + Let *v* Let alone (HR, 0.71; $P = .019$). Significant improvement in CB rate (29% to 48%; $P = .003$) for the combination arm.
O'Shaughnessy et al[35]	296	Randomized, phase III	HER2 positive					13.2	The primary and secondary end points were PFS and CB rate at 24 weeks. The combination of L and Tz demonstrated synergy and improved the median PFS: 12 *v* 8.4 weeks (HR, 0.73; 95% CI, 0.6 to 1; $P = .008$); CB rate, 25% *v* 13% (HR, 2.1; 95% CI, 1.1 to 4.2; $P = .01$) compared with L as a single agent, respectively. There were no significant differences in ORR or OS.
Arm A			A, T, Cap, and Tz refractory	1,500	—				
Arm B				1,000	Tz: 2 mg/kg weekly after 4 mg/kg loading dose			25.2	

Abbreviations: PR, partial response; CR, complete response; CB, clinical benefit; HER2, human epidermal growth factor receptor 2; Tz, trastuzumab; KPS, Karnofsky performance status; TTP, time to tumor progression; PFS, progression-free survival; AE, adverse event; A, anthracyclines; T, taxanes; Cap, capecitabine; L, lapatinib; HR, hazard ratio; UT, untested; EFS, event-free survival; OS, overall survival; ORR, overall response rate; P, paclitaxel; Pl, placebo; Let, letrozole; NA, not available; ER, estrogen receptor.

Table 2. Dual EGFR and HER2 Inhibitors

Agent	Drug Class	Mechanism of Action	Study Comments
Cetuximab (Erbitux)	mAb	Binds to the extracellular domain of EGFR[36]	A phase I, dose-escalation study of cetuximab and P in patients with MBC showed that two of six patients in the second cohort (cetuximab 100 mg/m^2) developed DLT effects, in the form of grade 3 rash. Ten patients were evaluable for response; two experienced SD, and eight experienced PD.[37] Preliminary results were reported from a randomized trial in which patients with TRN MBC refractory to one to three lines of chemotherapy were randomly assigned to CP plus cetuximab *v* cetuximab alone.[38] Cetuximab alone was well tolerated and had an RR of 6%. This arm was closed for insufficient activity, and the cetuximab-plus-CP arm had 18% RR and 27% CB. A preliminary report in patients with MBC treated with irinotecan plus CP *v* the same regimen plus cetuximab showed that cetuximab did not improve antitumor activity, PFS, or OS but increased toxicity.[39] However, on subset analysis, the addition of cetuximab increased the overall RR associated with irinotecan plus CP in TRN breast cancer.
Canertinib	TKI	Irreversible inhibitor of all EGFR family	Preclinical activity was documented in mouse xenografts model, including breast cancer.[40,41] A phase I study in heavily pretreated patients on canertinib, including patients with breast cancer, showed MTD doses of 225 mg three times a week and 250 mg with a 7-day on, 7-day off schedule.[42] In phase I and phase II studies, the most common adverse effects were gastrointestinal toxicity and rash.[43,44] Compared with oral delivery, intravenous delivery produced fewer gastrointestinal adverse events and increased bioavailability three-fold.[45] A phase I study of canertinib plus docetaxel in patients with advanced solid tumors[46] resulted in a recommended phase II dose of canertinib 50 mg/d plus docetaxel 75 mg/m^2.
Neratinib	TKI	Irreversible inhibitor of EGFR and HER2[47]	In a phase I/II study in MBC patients who were HER2 positive and who experienced progression on Tz therapy, 45 patients were treated with neratinib 160 mg or 240 mg daily plus Tz.[48] Among 33 evaluable patients, the objective RR was 27% (95% CI, 13% to 46%), and median PFS was 19 weeks (95% CI, 15 to 32 weeks). In a phase II study, patients with stage IIIB to IV, HER2-positive MBC were assigned to arm A (n = 65) if they had received Tz and to arm B (n = 66) if they had not received Tz or another HER2-targeting drug, and patients received neratinib 240 mg daily.[49] The primary end point, median PFS, was 23 weeks (95% CI, 16 to 39 weeks) for arm A and 40 weeks (95% CI, 32 to 55 weeks) for arm B. RR for arms A and B were 26% and 56%, respectively, and CB rates were 36% and 68%, respectively. One fourth of the patients required dose reductions; grade 3 diarrhea was seen in five patients (19%).
Pertuzumab (Omnitarg; Genentech)	mAb	Bind different HER2 epitope of the HER2 than Tz, blocking heterodimerization of HER2 with EGFR and *ErbB3*[50]	In HER2-positive breast cancer cell lines, Tz plus pertuzumab increased apoptosis and cell growth arrest compared with Tz alone.[51] A two-stage, phase II study of pertuzumab plus Tz in patients with previously treated (including with adjuvant Tz), HER2-positive MBC showed that, of 66 patients evaluable for response, five experienced CR, 11 had PR, and 17 had SD for approximately 6 months.[52] Thirty-three (50%) of 66 patients had CB. There were no clinical cardiac events and no occurrences of decrease in LVEF greater than 10%. Patients are currently being enrolled on a phase III study of pertuzumab plus Tz as first-line treatment for HER2-positive MBC (CLEOPATRA study).

Abbreviations: mAb, monoclonal antibody; EGFR, epidermal growth factor receptor; P, paclitaxel; MBC, metastatic breast cancer; DLT, dose-limiting toxicity; SD, stable disease; PD, progressive disease; TRN, triple-receptor negative; CP, carboplatin; RR, response rate; CB, clinical benefit; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; HER2, human epidermal growth factor receptor 2; Tz, trastuzumab; CR, complete response; PR, partial response; LVEF, left ventricular ejection fraction; CLEOPATRA, Clinical Evaluation of Pertuzumab and Trastuzumab.

LAPATINIB

Lapatinib is a selective, reversible, dual EGFR-HER2 inhibitor. Lapatinib has a slower rate of dissociation from EGFR than erlotinib and gefitinib, which results in prolonged target-site downregulation.[53]

Lapatinib plus capecitabine was approved by the US Food and Drug Administration on March 13, 2007, for the treatment of patients with advanced or HER2-overexpressing MBC previously treated with an anthracycline, a taxane, and trastuzumab.[5] In a phase I study of lapatinib in heavily pretreated patients with EGFR- and HER2-positive MBC, no DLT was found[54]; the most common adverse effects were diarrhea and rash, and there were no grade 4 toxic effects. Four of 59 evaluable patients with trastuzumab-resistant disease, including two with inflammatory breast cancer, had a PR, and all of these patients had high expression of activated phosphorylated HER2. Phase II trials of single-agent lapatinib have shown modest CB rates in patients with HER2-positive breast cancer (Table 1).

LAPATINIB PLUS CAPECITABINE

The pivotal trial that led to regulatory approval of lapatinib showed that lapatinib plus capecitabine increased PFS compared with capecitabine alone in patients with locally advanced or metastatic HER2-positive breast cancer not controlled by previous treatment with

anthracyclines, taxanes, and trastuzumab.[5] The study was closed prematurely, because the first interim analysis showed that the addition of lapatinib was associated with a 51% reduction in the risk of disease progression. The median times to progression for patients treated with lapatinib plus capecitabine and for patients treated with capecitabine plus placebo were 8.4 months and 4.4 months, respectively (hazard ratio, 0.49; 95% CI, 0.34 to 0.71; $P < .001$; Appendix Fig A1, online only). Eleven patients in the capecitabine group had progressive CNS metastasis compared with four in the combination-therapy group ($P = .10$). One third of women with HER2-positive MBC who receive trastuzumab develop CNS metastasis.[55] Small molecules, such as lapatinib, can cross the blood-brain barrier. In a recent phase II study of patients with HER2-positive breast cancer and brain metastasis, rates of objective response, defined as $\geq 50\%$ reduction in the volume of the brain lesion(s), were 6% for patients treated with lapatinib and 20% for patients treated with lapatinib and capecitabine; furthermore, 21% of the patients treated with lapatinib alone and 40% of the patients treated with combination therapy experienced at least a 20% volumetric reduction in their CNS lesion(s).[56]

Concerns have been voiced about the potential cardiotoxicity of lapatinib, but a recent pooled analysis of 3,689 lapatinib-treated patients revealed low rates of cardiac toxic effects. These effects were mostly asymptomatic decreases in left cardiac ejection fraction.[57]

Preclinical studies showed a synergistic interaction between lapatinib and trastuzumab in HER2-overexpressing breast cancer cell lines and tumor xenografts.[58] Preliminary results of a randomized, phase III trial of lapatinib with or without trastuzumab in patients with heavily pretreated HER2-positive MBC demonstrated synergy and improved median PFS with combination therapy.[35] Ongoing are a large trial of lapatinib plus trastuzumab as adjuvant therapy (the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization [ALTTO] trial) and a small trial of lapatinib plus trastuzumab as primary systemic therapy (the Neo-ALTTO trial) in patients with HER2-positive, early-stage breast cancer.

LAPATINIB PLUS HORMONAL AGENTS

Evidence is accumulating that signaling interplay between the estrogen receptor, HER2, EGFR, and insulin-like growth factor (IGF) 1 receptor plays a role in the acquired resistance to hormonal therapies.[59,60] In a preclinical model, lapatinib restored tamoxifen sensitivity in hormone-receptor–positive, tamoxifen-resistant breast cancer.[61] Several studies investigating lapatinib plus hormonal agents are planned.

In the EGF30008 trial, a phase III study of letrozole with or without lapatinib in postmenopausal patients with hormone-receptor–positive, HER2-positive MBC, the combination therapy resulted in a 29% reduction in the risk of disease progression ($P = .019$), and the median PFS improved from 3.0 to 8.2 months.[33] Ongoing is a large, European, phase II study of letrozole with or without lapatinib as neoadjuvant therapy in patients with hormone-sensitive, HER2-negative, operable breast cancer (the LET-LOB study).[62] Lapatinib is also active in patients with newly diagnosed inflammatory breast cancer, both alone and with paclitaxel.[63]

PERTUZUMAB

The discovery of the crucial role of ERBB3 in mediating signaling with different dimers and blocking ERBB2-dependent signaling through the phosphatidylinositol-3-kinase (PI3K) –Akt pathways provides an excellent opportunity for the development of TKIs with specific activity against ERBB3.[64] Because ERBB3 lacks intrinsic kinase activity, though, the generation of specific HER3-directed TKIs is challenging. Pertuzumab is an ERBB2 antibody that inhibits ERBB3 signaling by blocking ligand-induced HER2-to-HER3 heterodimerization. Preclinical observation in several breast cancer cell lines suggested that interfering with the ERBB3 component may be more relevant than inhibition of EGFR in HER2-amplified breast cancer cell lines.[65] In patients with ovarian cancer, high levels of ERBB3 correlated with shorter overall survival than *ERBB2* overexpression.[66]

NERATINIB

Recent preliminary data showed impressive antitumor activity in patients with trastuzumab-pretreated, *HER2*-amplified breast cancer after treatment with neratinib, a highly selective irreversible inhibitor of EGFR and ERBB2. Mature data are awaited, and more studies are underway.

NEW-GENERATION ANTI-HER2 TYROSINE KINASES

A new generation of anti–HER2 TKs is being developed. Among these new agents are EKB-569 and BIBW 2992, which are currently being studied in clinical trials.[67,68] The bispecific (ertumaxomab)[69] and trispecific antibodies that target ERBB2 are also under investigation.

The therapeutic armamentarium against the EGFR family, especially HER2-positive disease, has grown in the past decade. Results from the clinical trials highlight the potential of combination anti-HER2 therapies that might be superior to single-agent strategies. For instance, combination of both anti-HER2 therapies–lapatinib and trastuzumab–in patients in whom trastuzumab failed is superior to lapatinib alone.[35] Coexpression of both estrogen receptor and HER2 are reported in approximately 50% of patients with breast cancer; preclinical data suggest that *HER2* overexpression confers intrinsic resistance to hormonal therapy. However, new clinical evidence reveals that the combination of anti-HER2 and hormonal therapy could be considered the treatment of choice at this time.[33,70]

VEGF INHIBITORS

Angiogenesis plays an essential role in breast cancer development, invasion, and metastasis.[71] Agents that block the VEGF pathway have been shown to effectively inhibit tumor angiogenesis and growth in preclinical tumor models (Fig 2; Appendix Fig A2, online only). Studies in early-stage breast cancer show that elevated VEGF expression is associated with decreased relapse-free survival and overall survival in patients with both lymph-node–positive and lymph-node–negative disease.[73,74] Several drugs that target VEGF ligands or receptors have now emerged into the clinic (Appendix Table A2, onlineonly).

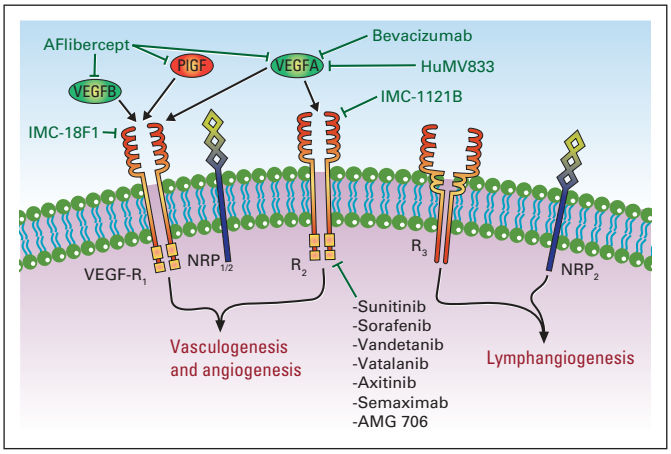

Fig 2. Vascular endothelial growth factor (VEGF) family. The VEGF family comprises seven secreted glycoproteins: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factors (PlGFs) −1 and −2. Free VEGF members exert effects by binding a variety of cell-surface receptors, including VEGF receptor 1 (a 180-kDa transmembrane protein also called fms-like tyrosine kinase-1 or Flt-1), and VEGF receptor 2 (a 200-kDa transmembrane protein also called kinase insert domain-containing receptor, or KDR). A third structurally related tyrosine kinase receptor is the 180-kDa VEGFR-3, which is expressed broadly on endothelial cells during early embryogenesis but which becomes restrictive to endothelial cells of adult lymphatic tissues and is necessary for adult lymphangiogenesis. Two additional VEGF receptors, neuropilin 1 (NRP-1) and neuropilin 2 (NRP-2), have also been recently implicated in VEGF-mediated vascularization and lymphangiogenesis.[72]

Bevacizumab

On February 22, 2008, the US Food and Drug Administration approved bevacizumab (Avastin; Genentech) plus paclitaxel as first-line therapy in patients with MBC. An early phase I/II, dose-escalation trial of single-agent bevacizumab in 75 patients with MBC showed a response rate of 6.7%.[75] Hypertension was the most common adverse effect, and it occurred in 22% of patients. Headache associated with vomiting was seen in four patients at a dose of 20 mg/kg and was considered the DLT.

The trial that resulted in US Food and Drug Administration approval of bevacizumab for breast cancer was the Eastern Cooperative Oncology Group trial ECOG 2100, in which 680 patients with previously untreated locally recurrent breast cancer or MBC received paclitaxel 90 mg/m^2 on days 1, 8, and 15 with or without bevacizumab 10 mg/kg on days 1 and 15 in 4-week cycles until progression occurred.[6] Most patients (96%) had HER2-negative disease. The primary end point, median PFS, was significantly better with combination therapy (11.8 *v* 5.9 months; hazard ratio, 0.60; 95% CI, 0.43 to 0.62; $P \leq .001$). The PFS benefit observed with bevacizumab was independent of patient age, number of metastatic sites, previous adjuvant taxane use, disease-free interval after adjuvant therapy, and hormone receptor status. The overall response rate was also better with combination therapy, at 36.9% with combination therapy versus 21.2% without ($P < .001$). Bevacizumab was not associated with an increased risk of death; however, an audit of the trial by a group of experts revealed several occurrences of small bowel perforation that had not been attributed to bevacizumab.

The US Food and Drug Administration decision to grant accelerated approval of bevacizumab plus paclitaxel on the basis of the observed PFS benefit generated much debate. Overall survival is universally accepted as the most reliable cancer end point, but PFS is not recognized by many investigators as an important surrogate end point in patients with MBC. However, demonstrating in a clinical trial that a drug improves overall survival requires larger numbers of patients and a prolonged period of time. Since the US Food and Drug Administration approval of bevacizumab for MBC, several other anticancer drugs have been approved by using PFS as a primary end point.

Several phase III studies of bevacizumab combined with different chemotherapy agents have been reported (Table 3). Mature data from four studies[6,77,80,81] demonstrated an improvement in PFS when bevacizumab was added to chemotherapy. Bevacizumab as neoadjuvant therapy is under investigation in a large study by the National Surgical Adjuvant Breast and Bowel Project (NSABP-B40), and bevacizumab as maintenance therapy in patients with TRN breast cancer is being investigated in the Bevacizumab Adjuvant Therapy in Triple-Negative Breast Cancer (BEATRICE) trial. There are two large, ongoing, randomized, phase III trials of bevacizumab as adjuvant therapy: ECOG 5103, which compares chemotherapy versus chemotherapy plus bevacizumab, and the Bevacizumab and Trastuzumab Adjuvant Therapy in HER2-Positive Breast Cancer (BETH) trial, which compares chemotherapy with docetaxel, carboplatin, and trastuzumab with or without bevacizumab for HER2-amplified breast cancer.

Aflibercept

Aflibercept is a soluble decoy receptor protein that consists of a fusion of the second immunoglobulin domain of the VEGF receptor-1 (VEGFR-1) and the third immunoglobulin domain of the human VEGFR-2 with the constant region of human immunoglobulin G_1.[78] Aflibercept recognizes the entire VEGF family that binds to VEGFR-1 and VEGFR-2, including placental growth factor, and possesses higher affinity for VEGF than bevacizumab in vitro. Aflibercept potently inhibited tumor growth, metastasis formation, and ascites formation in several murine tumor models.[79]

A phase II trial of aflibercept 4 mg/kg every 21 days in patients with MBC who had received fewer than two regimens for MBC was stopped early, after the first stage was completed with 21 patients, as there were no objective responses, and because the median PFS was 2.4 months.[82]

MONOCLONAL ANTIBODIES TARGETING PORTIONS OF VEGFR

Several monoclonal antibodies, including HuMV833, IMC-1121B, and IMC-18F1, have been designed to target selected portions of VEGFR.[83-85] These agents are under investigation in clinical trials.

MULTIKINASE INHIBITORS THAT INHIBIT VEGFRS

Sunitinib

Sunitinib malate (Sutent; Pfizer, New York, NY) is an oral TKI that targets several receptor TKs, including VEGFR-1, VEGFR-2, and VEGFR-3; platelet-derived growth factor receptor-α (PDGFR-α) and PDGFR-β; c-Kit; and colony-stimulating factor-1 receptor.[86] In a phase I study in which patients with solid tumors received sunitinib 15 to 59 mg/m^2, six of 28 patients had a PR.[87] The most common adverse effects were fatigue, hypertension, and skin manifestations. In a phase II trial in 64 patients with MBC previously treated with anthracyclines and taxanes who received sunitinib at a starting dose of 50 mg once daily for 4 weeks of a 6-week cycle, seven patients (11%) had a PR,

Table 3. Phase III Trials of Bevacizumab in Breast Cancer

Trial	No. of Patients	Patient Population	Bevacizumab Dose	Combination Therapy	End Point	Benefit in Anti-VEGF Therapy	Study Primary Results
AVF2119[76]	462	PT MBC	15 mg/kg every 3 weeks	Cap 2,500 mg/m^2/d from day 1 to day 14	PFS	No	Bev and Cap significantly increased the ORR compared with Cap as a single agent (9.1% *v* 19.8%; $P = .001$), but not PFS (4.2 *v* 4.0 months; HR, 0.98). No significant differences were found in the incidence of diarrhea, hand-foot syndrome, and serious bleeding episodes between treatment groups.
ECOG 2100[6]	722	FL MBC	10 mg/kg every 2 weeks	P 90 mg/m^2 on days 1, 8, and 15	PFS	Yes	Bev and P significantly prolonged PFS compared with P alone (median, 11.8 *v* 5.9 months; HR for progression, 0.60; $P = < .001$) and increased ORR (36.9% *v* 21.2%). No differences in OS between the two groups (median 26.7 *v* 25.5 months; HR, 0.88; $P = .16$). AE: grade 3 or 4 hypertension (14.8% *v* 0%; $P < .001$), proteinuria (3.6% *v* 0%; $P < .001$), headache (2.2% *v* 0%; $P = .008$), and cerebrovascular ischemia (1.9% *v* 0%; $P = .02$) were more common in patients receiving the combination treatment.
AVADO[80]	736	FL MBC	7.5 mg/kg every 3 weeks or 15 mg/kg every 3 weeks	D 100 mg/m^2 every 3 weeks	PFS	Yes	In unstratified analysis, patients receiving Bev had significantly longer PFS compared with the D monotherapy group (Bev at 7.5 mg/kg: median PFS, 8.7 *v* 8.0 months; HR, 0.79; $P = .0318$; Bev at 15 mg/kg: median PFS, 8.8 *v* 8.0 months; HR, 0.72; $P = .0099$). ORR improved with the addition of Bev. Bev 7.5 mg/kg, 55% *v* 44% ($P = .0295$); Bev 15 mg/kg 63% *v* 44% ($P < .001$) The study was not powered to find differences in OS.
RIBBON1[81]	1,237*	FL MBC	15 mg/kg every 3 weeks	Cap, taxanes (Nab-Pac and D), anthracycline	PFS	Yes	The median follow up was 15.6 months in the Cap cohort and 19.2 months in the taxanes and anthracycline cohort. The addition of Bev to Cap, taxanes, or anthracycline-based chemotherapy resulted in statistically significant improvement in PFS.
MO19391[77]	2,027*	HER2 negative MBC or HER2 positive if previous Tz	10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks	Taxane-based chem-otherapy	Safety	Yes	Median follow up was 7.4 months; approximately 75% of patients received taxanes, and 25% were treated with non-taxane regimens (Cap and VNR). Safety and efficacy of Bev plus D or P was similar to results of ECOG2100 and AVADO.

Abbreviations: VEGF, vascular endothelial growth factor; PT, pretreated; MBC, metastatic breast cancer; Cap, capecitabine; PFS, progression-free survival; Bev, bevacizumab; ORR, overall response rate; HR, hazard ratio; ECOG2100, Eastern Cooperative Oncology Group trial 2100; FL, first line; P, paclitaxel; OS, overall survival; AE, adverse event; AVADO, Avastin and Docetaxel; D, docetaxel; RIBBON1, Regimens in Bevacizumab for Breast Cancer; Nab-Pac, Nab-paclitaxel; HER2, human epidermal growth factor receptor 2; Tz, trastuzumab; VNR, vinorelbine.

*Currently enrolling patients.

and three patients had stable disease for more than 6 months, for an overall CB rate of 16%.[88] Objective responses occurred in three of 20 patients with TRN tumors and in three of 12 patients with HER2-positive tumors. Grade 3 fatigue and hand-foot syndrome occurred in 14% and 9% of patients, respectively; one third of patients experienced grade 3 neutropenia. In a phase II, randomized study, 46 patients with HER2-negative MBC were randomly assigned to receive paclitaxel 90 mg/m^2 weekly and bevacizumab 10 mg/kg every 2 weeks with or without sunitinib 25 mg daily for 21 days as first-line chemotherapy.[89] Sunitinib was associated with high rates of dose modification and treatment discontinuation because of toxic effects—including neutropenia, febrile neutropenia, and fatigue—that led to closure of the study.

Sunitinib also was studied in combination with metronomic dosing of cyclophosphamide and methotrexate in patients with MBC.[90] Fifteen patients were treated in three sunitinib dose cohorts: 12.5 mg/d, 25 mg/d, and 37.5 mg/d. Three patients developed grade 3 neutropenia, and five developed mucositis. One patient had a PR at

week 14, and one patient had stable disease for 47 weeks. Enrollment continues.

Sorafenib

Studies of sorafenib (Nexavar; Bayer/Onyx Pharmaceuticals, West Haven, CT) have mainly focused on optimizing dosing to maximize activity against Ras.[91] In preclinical studies, daily sorafenib significantly inhibited tumor growth and microvessel density in an MDA-MB-231 breast cancer xenograft model.[92] A phase I study showed a favorable toxicity profile of sorafenib 400 mg twice daily in patients with advanced solid tumors.[93]

In a two-stage, phase II study of sorafenib 300 mg twice daily in patients with MBC refractory to anthracyclines and taxanes, the median number of cycles was 2, and dose reductions were necessary because of dermatitis/skin rash (n = 3), hand-foot syndrome (n = 2), and hypertension (n = 1).[94] One of 20 patients eligible for efficacy evaluation had a PR that lasted 3.6 months. The study was closed after the first stage because of lack of sufficient response.

Vandetanib

Vandetanib (Zactima; AstraZeneca) is a potent inhibitor of kinase insert domain-containing receptor (VEGFR-2), VEGFR-3, and EGFR/HER1.[95] A phase I dose-finding study established a dose of 300 mg daily.[96] A phase II study in 46 patients with MBC refractory to anthracyclines and taxanes showed no objective responses.[97] The authors hypothesized that the lack of activity could be related to inadequate blood concentration of vandetanib. Most patients achieved a plasma concentration greater than the 50% inhibitory concentration; however, adverse effects commonly seen with VEGF inhibitors (eg, hypertension, headache, thrombosis) and EGF inhibitors (eg, severe rash) were not seen.

Vatalanib

Vatalanib is an oral inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 and of other related kinases.[98] A phase I study in patients with advanced solid tumors established that the maximum-tolerated dose was 750 mg twice daily, whereas the biologically active dose was greater than 1,000 mg twice daily.[99] The Hoosier Oncology Group recently finished accruing patients for a phase I/II study of vatalanib plus trastuzumab in patients with newly diagnosed, HER2-overexpressing MBC.[100]

Axitinib

Axitinib is a potent small-molecule TKI of all known VEGFRs, PDGFR-β, and c-Kit.[101] The initial phase I study in patients with solid tumors showed a 10% PR rate.[102] Fewer than 10% of the patients experienced grade 3 or 4 toxic effects; hypertension was the most common adverse effect and was reported in 22 patients (61%), 11 of whom had grade 3 or 4 hypertension. The incidence and severity of hypertension were dose related. Other DLTs observed were stomatitis (6%) and hemoptysis (3%).

In 2007, preliminary findings were reported from a phase II multicenter, randomized, double-blind, placebo-controlled trial of docetaxel (80 mg/m^2 every 3 weeks) alone or with axitinib (5 mg twice daily) in 168 patients with chemotherapy-naive MBC.[103] The overall response rate was 40% with docetaxel plus axitinib and was 23% with docetaxel plus placebo (P = .038); the median time to treatment failure was 9 months with docetaxel plus axitinib and was 6.3 months for docetaxel plus placebo (P = .012). Grades 3 and 4 adverse effects were more common with axitinib: febrile neutropenia (16% *v* 7%), fatigue (13% *v* 5%), stomatitis (13% *v* 2%), diarrhea (11% *v* 0%), and hypertension (5% *v* 2%).

RAS/MEK/ERK PATHWAY INHIBITORS

The Ras superfamily of GTPases act as crucial regulatory switches coordinating a variety of biologic functions. These proteins are classified in five families: Ras, Rho, Rab, Sar1/Arf, and Ran.[104] Although fewer than 5% of breast cancers have *ras* mutations, hyperactivation of the Ras protein in breast cancer has been described.[105] Overexpression of Rho was associated with locoregional and distant metastasis of breast cancer[106] and also inflammatory breast cancer.[107]

Tipifarnib (Zarnestra; Johnson & Johnson, New Brunswick, NJ), a farneseyltransferase inhibitor, inhibited the growth of MCF-7 breast cancer cell xenografts in a dose-dependent manner.[108] In a phase I trial, single-agent tipifarnib was administered at doses up to 1,300 mg twice daily for 5 days every 2 weeks without significant toxicity.[109] The authors recommended that the tipifarnib dose for phase II trials be 500 mg twice daily for 5 consecutive days followed by 9 days of rest.

In a phase II study of tipifarnib in patients with hormone-sensitive MBC who experienced progression during second-line hormonal therapy, 10% of patients had a PR, and 25% had CB.[110] The main adverse effects were neutropenia, thrombocytopenia, and neurotoxic effects. In another study, tipifarnib was combined with dose-dense doxorubicin and cyclophosphamide as neoadjuvant therapy for patients with locally advanced breast cancer; after four cycles, patients underwent surgery.[111] Five of 32 patients had at least 50% farnesyltransferase inhibition in the primary tumor, as revealed by serial biopsies during treatment, and seven of 21 patients had a pathologic complete response. These data are interesting, because pathologic complete response occurred in patients with estrogen-receptor–positive tumors.

In a randomized, phase II study in 120 patients with MBC who experienced antiestrogen therapy failure, addition of tipifarnib to letrozole did not improve the objective response rate.[112] However, in another phase II study in patients with no prior therapy for MBC, tipifarnib combined with fulvestrant resulted in a CB rate of 51.6%.[113]

PI3K/AKT/ MAMMALIAN TARGET OF RAPAMYCIN PATHWAY INHIBITORS

The PI3K signaling pathway is crucial to many aspects of key cellular functions, including growth, proliferation, survival, angiogenesis, and motility.[114] Recent studies indicate that, in patients with cancer, amplification, mutation, and translocation that result in activation are more common in the PI3K/AKT/ mammalian target of rapamycin (mTOR) pathway than in any other pathway.[115] Activating mutation of PI3K has been described in approximately 40% of primary breast tumors, which suggests the importance of PI3K in breast cancer tumorigenesis.[116] Three mTOR antagonists are being studied for breast cancer treatment[117]: everolimus, a mammalian target of rapamycin inhibitor with better oral availability than sirolimus; temsirolimus, a water-soluble ester of sirolimus; and deforolimus (AP23573), a non-rapamycin analog prodrug that has been tested in phase I and II

clinical trials and that shows promising results in several tumor types, including sarcoma. All three agents have shown activity against breast cancer in preclinical studies.[118,119] Phase I studies of everolimus[120] and temsirolimus[121] showed good adverse effect profiles.

Everolimus

Everolimus (Cetican; Novartis Pharma AG, Basel, Switzerland) was developed in an attempt to improve the pharmacokinetic characteristics of sirolimus, particularly to increase oral bioavailability. In a phase II, randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with operable estrogen-receptor–positive breast cancer,[122] everolimus plus letrozole was associated with a significantly higher clinical response rate (68% *v* 59%; $P = .0616$).

Temsirolimus

Temsirolimus (Torisel; Wyeth, Philadelphia, PA) is a water-soluble ester of sirolimus with antitumor activity in preclinical breast cancer models.[119] In a phase I study in patients with advanced malignancies treated with weekly intravenous temsirolimus (7.5 to 220 mg/m^2), the DLT was thrombocytopenia.[121]

In a phase II study in previously treated patients with locally advanced breast cancer or MBC treated with weekly intravenous temsirolimus (75 mg or 250 mg), 13.8% of patients had CB. The most common adverse effects were mucositis, maculopapular rash, and nausea.[123] Preliminary results of a large, phase II study of temsirolimus plus letrozole or letrozole alone showed similar rates of CB for the two approaches (82% and 83% for continuous and intermittent temsirolimus, respectively, and 79% for letrozole alone)[124] but suggested that PFS might be longer for combination therapy.[125]

In a phase III study, more than 1,200 postmenopausal patients with estrogen-receptor–positive MBC suitable for first-line therapy were randomly assigned to letrozole with or without temsirolimus.[126] The trial was terminated early after interim analysis demonstrated a lack of additional benefit with the combination therapy. Studies of temsirolimus in combination with other drugs are ongoing.

INSULIN-LIKE GROWTH FACTOR INHIBITORS

The IGF system involves a complex regulatory network composed of two receptors, two ligands, and IGF-binding proteins. Several monoclonal antibodies (CP-751,856, AMG 479, and IMC-A12)[127-129] are in early clinical development in the treatment of breast cancer.

POLY (ADP-RIBOSE) POLYMERASE 1 INHIBITORS

Poly (ADP-ribose) polymerase 1 (PARP-1) is a critical enzyme in cell proliferation and DNA repair. Multiple PARP-1 inhibitors have been tested preclinically as potentiators of chemotherapy and radiotherapy.[130] A preliminary analysis of a randomized, phase II study of gemcitabine plus carboplatin with or without the PARP-1 inhibitor BSI-201 in patients with TRN MBC showed a higher objective response rate and longer PFS and overall survival with BSI-201[131] (Fig 3; Appendix Fig A3, online only).

Olaparib (AZD2281) is a novel PARP inhibitor with significant activity in patients with breast, ovarian, and prostate cancer with

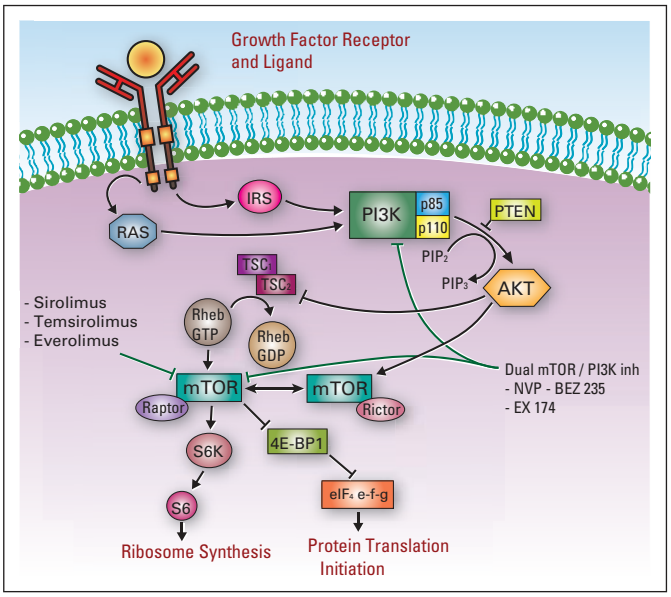

Fig 3. The mammalian target of rapamycin (mTOR) signaling network. mTOR is a highly conserved pathway that regulates cell proliferation and metabolism in response to environmental factors. The growth factor receptor is linked with mTOR signaling via the phosphatidylinositol-3-kinase (PI3K)/Akt family. *PTEN* plays an important role in this pathway; loss of *PTEN* function through mutation, deletion, or epigenetic silencing results in increased activation of Akt and mTOR. The mTOR proteins regulate activities of the translational regulators 4E-BP1 and p70S6 kinase (S6K). mTOR antagonists have been developed to inhibit mTORC1 (raptor).

BRCA1 or *BRCA2* mutation.[132] A phase I study showed that 12 of 19 patients had CB, and nine patients had PR by Response Evaluation Criteria in Solid Tumors (RECIST). A preliminary report of a single-arm, phase II study in patients with *BRCA*-deficient breast cancer treated with olaparib was recently published.[133] Nine of 24 patients who received 400 mg daily of olaparib had PR by RECIST; 19% of patients experienced grade 3 or 4 toxic effects, including fatigue (11%), nausea (2%), and vomiting (5.5%). Several phase II studies of other PARP inhibitors (ie, ABT-888, AGO14699, and MK4827) are underway.

FUTURE DIRECTIONS

The past decade has also been one of dramatic changes in breast cancer treatment, including increasing use of targeted therapy. However, despite great enthusiasm for targeted therapy, these agents have exhibited only anecdotal or modest activity when used as single agents in unselected patients. In addition, selection of patients for targeted therapy remains a challenge, because we lack reliable biomarkers to predict activity for most of the targeted agents.

The development of new drugs in oncology faces multiple challenges in this new molecular era. The final major contribution to the transformation of breast cancer treatment has been not a technical or pharmacologic revolution but rather a transformation in the way we think about the disease and its treatment. Continued application of old paradigms of drug evaluation (on the basis of response rates and toxicity) to new targeted therapies may be inappropriate, because neither tumor response nor toxicity is a useful surrogate for dose selection or efficacy. We need a better understanding of the molecular

biology of signaling pathways, and we need to discover new biomarkers that we can use to select the optimal dose of targeted agents for phase II clinical studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Gabriel N. Hortobagyi, Novartis (U), Bristol-Myers Squibb (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Gabriel N. Hortobagyi, Novartis **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Ricardo H. Alvarez
Financial support: Gabriel N. Hortobagyi
Administrative support: Vicente Valero, Gabriel N. Hortobagyi
Collection and assembly of data: Ricardo H. Alvarez, Gabriel N. Hortobagyi
Data analysis and interpretation: Ricardo H. Alvarez, Vicente Valero, Gabriel N. Hortobagyi
Manuscript writing: Ricardo H. Alvarez
Final approval of manuscript: Ricardo H. Alvarez, Vicente Valero, Gabriel N. Hortobagyi

REFERENCES

1. 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 344:783-792, 2001

2. Vogel CL, Cobleigh MA, Tripathy D, et al: Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 20:719-726, 2002

3. Cobleigh MA, Vogel CL, Tripathy D, et al: Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 17:2639-2648, 1999

4. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673-1684, 2005

5. Geyer CE, Foster J, Lindquist D, et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 356:2733-2743, 2006

6. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357:2666-2676, 2007

7. Yarden Y, Sliwkowski MX: Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2:127-137, 2001

8. Harris AL, Nicholson S, Sainsbury JR, et al: Epidermal growth factor receptors in breast cancer: Association with early relapse and death, poor response to hormones and interaction with neu. J Steroid Biochem 34:123-131, 1989

9. Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177-182, 1987

10. Klijn JG, Berns PM, Schmitz PI, et al: The clinical significance of epidermal growth factor receptor (EGF-R) in human breast cancer: A review on 5232 patients. Endocr Rev 13:3-17, 1992

11. Fox SB, Smith K, Hollyer J, et al: The epidermal growth factor receptor as a prognostic marker: Results of 370 patients and review for 3009 patients. Breast Cancer Res Treat 29:41-49, 1994

12. Nielsen TO, Hsu FD, Jensen K, et al: Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res 10:5367-5374, 2004

13. Baselga J: Targeting the epidermal growth factor receptor: A clinical reality. J Clin Oncol 19:41s–44s, 2001 (suppl)

14. Anido J, Matar P, Albanell J, et al: ZD1839, a specific epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, induces the formation of inactive EGFR/HER2 and EGFR/HER3 heterodimers and prevents heregulin signaling in HER2-overexpressing breast cancer cells. Clin Cancer Res 9:1274-1283, 2003

15. Baselga J, Rischin D, Ranson M, et al: Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol 20:4292-4302, 2002

16. Cristofanilli M, Schiff R, Valero V, et al: Exploratory subset analysis according to prior endocrine treatment of two randomized phase II trials comparing gefitinib with placebo in combination with tamoxifen or anastrozole in hormone receptor-positive metastatic breast cancer. J Clin Oncol 27:15s, 2009 (suppl; abstr 1014)

17. Pollack VA, Savage DM, Baker DA, et al: Inhibition of epidermal growth factor receptor-associated tyrosine phosphorylation in human carcinomas with CP-358,774: Dynamics of receptor inhibition in situ and antitumor effects in athymic mice. J Pharmacol Exp Ther 291:739-748, 1999

18. Dickler MN, Cobleigh MA, Miller KD, et al: Efficacy and safety of erlotinib in patients with locally advanced or metastatic breast cancer. Breast Cancer Res Treat 115:115-121, 2009

19. Twelves C, Trigo JM, Jones R, et al: Erlotinib in combination with capecitabine and docetaxel in patients with metastatic breast cancer: A dose-escalation study. Eur J Cancer 44:419-426, 2008

20. Kaur H, Silverman P, Singh D, et al: Toxicity and outcome data in a phase II study of weekly docetaxel in combination with erlotinib in recurrent and/or metastatic breast cancer. J Clin Oncol 24:18s, 2006 (suppl; abstr 10623)

21. Venturini M, Catzeddu T, Del Mastro L, et al: Erlotinib given sequentially to capecitabine and vinorelbine as first-line chemotherapy in metastatic breast cancer patients: A dose finding study. J Clin Oncol 22:14s, 2004 (suppl; abstr 834)

22. Dickler M: Phase II trial of erlotinib (OSI-774), and epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor, and bevacizumab, a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF), in patients with metastatic breast cancer. J Clin Oncol 22:14s, 2004 (suppl; abstr 2001)

23. Guix M, Granja Nde M, Meszoely I, et al: Short preoperative treatment with erlotinib inhibits tumor cell proliferation in hormone receptor-positive breast cancer. J Clin Oncol 26:897-906, 2008

24. Lewis Phillips GD, Li G, Dugger DL, et al: Targeting HER2- positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 68:9280-9290, 2008

25. Modi S, Beeram M, Krop IE, et al: A phase I study of trastuzumab-DM1, a first-in-class HER2-antibody drug conjugate, in patients with advanced HER2+ breast cancer. J Clin Oncol 26:48s, 2008 (suppl; abstract 1028)

26. Vogel CL, Burris HA, Limentani S, et al: A phase II study of trastuzumab-DM1, a HER2 antibody conjugate, in patients with HER2 metastatic breast cancer: Final results. J Clin Oncol 27:15s, 2009 (suppl; abstr 1017)

27. Jones HE, Goddard L, Gee JM, et al: Insulin-like growth factor-I receptor signalling and acquired resistance to gefitinib (ZD1839; Iressa) in human breast and prostate cancer. Endocr Relat Cancer 11:793-814, 2004

28. Baselga J, Arteaga CL: Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. J Clin Oncol 28:2445-2459, 2005

29. Blackwell KL, Pegram MD, Tan-Chiu E, et al: Single-agent lapatinib for HER2-overerexpression advanced or metastatic breast cancer that progressed on first- or second-line trastuzumab-containing regimens. Ann Oncol 20:1026-1031, 2009

30. Burstein H, Storniolo AN, Franco S, et al: A phase II, open-label, multicenter study of lapatinib in two cohorts of patients with advanced or metastatic breast cancer who have progressed while receiving trastuzumab-containing regimens. Ann Oncol 19:1068-1074, 2008

31. Gomez HL, Doval DC, Chavez MA, et al: Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. J Clin Oncol 26:2999-3005, 2008

32. Di Leo A, Gomez HL, Aziz Z, et al: Phase III, double-blind, randomized study comparing lapatinib

plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. J Clin Oncol 26:5544-5552, 2008

33. Johnston S, Pippen J Jr, Pivot X, et al: Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 27:5538-5546, 2009

34. Finn RS, Press MF, Dering J, et al: Estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and epidermal growth factor receptor expression and benefit from lapatinib in a randomized trial of paclitaxel with lapatinib or placebo as first-line treatment in HER2-negative or unknown metastatic breast cancer. J Clin Oncol 27:3908-3915, 2009

35. O'Shaughnessy J, Blackwell KL, Burstein H, et al: A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy. J Clin Oncol 26:44s, 2008 (suppl; abstr 1015)

36. Goldstein NI, Prewett M, Zuklys K, et al: Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. Clin Cancer Res 1:1311-1318, 1995

37. Modi S, D'Andrea G, Norton L, et al: A phase I study of cetuximab/paclitaxel in patients with advance-stage breast cancer. Clin Breast Cancer 7:270-277, 2006

38. Carey LA, Mayer E, Marcom PK, et al: TBCRC 001: EGFR inhibition with cetuximab in metastatic triple negative (basal-like) breast cancer. Breast Cancer Res Treat 106:S32, 2007 (Abstr 307)

39. O'Shaughnessy J, Weckstein DJ, Vukelja SJ, et al: Preliminary results of a randomized phase II study of weekly irinotecan/carboplatin with or without cetuximab in patients with metastatic breast cancer. Breast Cancer Res Treat 106:S32, 2007 (abstr 308)

40. Slichenmyer WJ, Elliott WL, Fry DW: CI-1033, a pan-erbB tyrosine kinase inhibitor. Semin Oncol 28:80-85, 2001 (suppl 16)

41. Allen LF, Lenehan PF, Eiseman IA, et al: Potential benefits of the irreversible pan-erbB inhibitor, CI-1033, in the treatment of breast cancer. Semin Oncol 29:11-21, 2002 (3 suppl 11)

42. Calvo E, Tolcher AW, Hammond LA, et al: Administration of CI-1033, an irreversible pan-erbB tyrosine kinase inhibitor, is feasible of a 7-day on, 7-day off Schedule: A phase I pharmacokinetic and food effect study. Clin Cancer Res 10:7112-7120, 2004

43. Campos S, Hamid O, Seiden MV, et al: Multicenter, randomized phase II trial of oral CI-1033 for previously treated advanced ovarian cancer. J Clin Oncol 23:5597-5604, 2005

44. Nemunaitis J, Eiseman I, Cunningham C, et al: Phase I clinical and pharmacokinetics evaluation of oral CI-1033 in patients with refractory cancer. Clin Cancer Res 11:3846-3853, 2005

45. Simon GR, Garret CR, Olson SC, et al: Increased bioavailability of intravenous versus oral CI-1033, a pan erbB tyrosine kinase inhibitor: Results of a phase I pharmacokinetic study. Clin Cancer Res 12:4645-4651, 2006

46. Garland LL, Hidalgo M, Mendelson DS, et al: A phase I clinical and pharmacokinetic study of oral CI-1033 in combination with docetaxel in patients with advanced solid tumors. Clin Cancer Res 12: 4274-4282, 2006

47. Tsou HR, Overbeek-Klupers EG, Hallett WA, et al: Optimization of 6, 7-disubstituted-4-(arylamino)quinoline-3-carbonitriles as orally active, irreversible inhibitors of human epidermal growth factor receptor-2 kinase activity. J Med Chem 48: 1107-1131, 2005

48. Swaby R, Blackwell K, Jiang Z, et al: Neratinib in combination with trastuzumab for the treatment of advanced breast cancer: A phase I/II study. J Clin Oncol 27:15s, 2009 (suppl; abstract 1004)

49. Burstein HJ, Sun Y, Tan AR, et al: Neratinib (HKI-272), an irreversible pan erbB receptor tyrosine kinase inhibitor: Phase 2 results in patients with an advanced HER2-positive breast cancer. Breast Cancer Res Treat 102:2008 (suppl; abstr 37)

50. Cho HS, Mason K, Ramyar KX, et al: Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab. Nature 421:756-760, 2003

51. Nahta R, Hung MC, Esteva FJ: The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. Cancer Res 64:2343-2346, 2004

52. Gelmon KA, Fumoleau P, Verma S, et al: Results of a phase II trial of trastuzumab and pertuzumab in patients with HER2-positive metastatic breast cancer who had progressed during trastuzumab therapy. J Clin Oncol 26:47s, 2008 (suppl; abstr 1026)

53. Wood ER, Truesdale AT, McDonald OB, et al: A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): Relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells. Cancer Res 64:6652-6659, 2004

54. Burris HA 3rd, Hurwitz HI, Dees EC, et al: Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. J Clin Oncol 23:5305-5313, 2005

55. Clayton AJ, Danson S, Jolly S, et al: Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer 91:639-643, 2004

56. Lin NU, Diéras V, Paul D, et al: Multicenter phase II study of lapatinib in patients with brain metastases form HER2-positive breast cancer. Clin Cancer Res 15:1452-1459, 2009

57. Perez EA, Koehler M, Byrne J, et al: Cardiac safety of lapatinib: Pooled analysis of 3,689 patients enrolled in clinical trials. Mayo Clinic Proc 83:679-686, 2008

58. Konecny GE, Pegram MD, Venkatesan N, et al: Activity of the dual kinase inhibitor lapatinib (GW572016) against HER2-overexpressing and trastuzumab-treated breast cancer cells. Cancer Res 66:1630-1639, 2006

59. Jones HE, Gee JM, Hutcheson IR, et al: Growth factor receptor interplay and resistance in cancer. Endocr Relat Cancer 13:S45-S51, 2006

60. Nichoson RI, Hutcheson IR, Knowlden JM, et al: Non endocrine pathways and endocrine resistance: Observations with antiestrogens and signal transduction inhibitors in combination. Clin Cancer Res 10:346S-354S, 2004

61. Chu I, Blackwell K, Chen S, et al: The dual ErbB1/ErbB2 inhibitor, lapatinib (GW572016), cooperates with tamoxifen to inhibit both cell proliferation- and estrogen-dependent gene expression in antiestrogen-resistant breast cancer. Cancer Res 65:18-25, 2005

62. Frassoldati A, Guarneri V, Piacentini F, et al: Letrozole versus letrozole plus lapatinib (GW572016) in hormone-sensitive, HER2-negative operable breast cancer: A double-blind, randomized, phase II study with biomarker evaluation (EGF109077-LAP107692/LETLOB). Clin Breast Cancer 8:97-100, 2008

63. Cristofanilli M, Boussen H, Ben Ayed F, et al: A phase II combination study of lapatinib and paclitaxel as neoadjuvant therapy in patients with newly diagnosed inflammatory breast cancer. Breast Cancer Res Treat 100:S5, 2006 (suppl; abstr 1)

64. Baselga J, Swain SM: Novel anticancer targets: Revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer 9:463-475, 2009

65. Lee-Hoeflich ST, Crocker L, Yao E, et al: A central role for HER3 in HER2-amplified breast cancer: Implications for targeted therapy. Cancer Res 68:5878-5887, 2009

66. Tanner B, Hasenclever D, Stern K, et al: ErbB-3 predicts survival in ovarian cancer. J Clin Oncol 24:4317-4323, 2006

67. Erlichman C, Hidalgo M, Boni JP, et al: Phase I study of EKB-569, an irreversible inhibitor of the epidermal growth factor receptor, in patients with advanced solid tumors. J Clin Oncol 24:2252-2260, 2006

68. Mom C, Eskens F, Gietema J, et al: Phase I study with BIBW 2992 an irreversible dual tyrosine kinase inhibitor of epidermal growth factor receptor 1 (EGFR) and 2 (HER2) in a 2 week on 2 week off schedule. J Clin Oncol 24:18s, 2006 (suppl; abstr 3025)

69. Kiewe P, Hansmuller S, Kahlert S, et al: Phase I trial of the trifunctional anti-HER2 anti-CD3 antibody ertumaxomab in metastatic breast cancer. Clin Cancer Res 12:3085-3091, 2006

70. Kaufman B, Mackey JR, Clemens MR, et al: Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positieve, hormone receptor-positive metastatic breast cancer: Results from the randomized phase III TAnDEM study. J Clin Oncol 27:5529-5537, 2009

71. Folkman J: What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 82:4-6, 1990

72. Ellis LM, Hicklin DJ: VEGF-targeted therapy: Mechanism of anti-tumor antivity. Nat Rev Cancer 8:579-591, 2008

73. Relf M, LeJeune S, Scott PA, et al: Expression of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor beta-1, platelet-derived endothelial cell growth factor, placental growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis. Cancer Res 57:963-969, 1997

74. 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 10:1706-1716, 2004

75. Cobleigh MA, Langmuir VK, Sledge GW, et al: A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol 30:117-124, 2003 (suppl 16)

76. Miller KD, Chap LI, Holmes FA, et al: Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 23:792-799, 2005

77. Pierga J, Pritchard KI, Thomssen C, et al: Safety and efficacy of first-line bevacizumab plus chemotherapy for locally recurrent or metastatic breast cancer: Analysis of MO19391 according to chemotherapy. J Clin Oncol 27:15s, 2009 (suppl; abstr 1033)

78. Lau SC, Rosa DD, Jayson G: Technology evaluation: VEGF Trap (cancer), Regeneron/sanofi-aventis. Curr Opin Mol Ther 7:493-501, 2005

79. Holash J, Davis S, Papadopoulos N, et al: VEGF-Trap: A VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A 99:11393-11398, 2002

80. Miles D, Chan A, Romieu G, et al: Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (AVADO). J Clin Oncol 26:43s, 2008 (suppl; abstr LBA1011)

81. Robert NJ, Dieras J, Glaspy J, et al: RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer. J Clin Oncol 27:42s, 2009 (suppl; abstr 1005)

82. Hobday TJ, Rowland A, Dueck D, et al: N0537: A North Central Cancer Treatment Group (NCCTG) phase II trial of VEGF Trap in patients with metastatatic breast cancer previously treated with an anthracycline and/or taxane. Breast Cancer Res Treat 100:167s, 2008 (suppl; abstr 164)

83. Jayson GC, Mulatero C, Ranson M, et al: Phase I investigation of recombinant anti-human vascular endothelial growth factor antibody in patients with advanced cancer. Eur J Cancer 41:555-563, 2005

84. Camidge DR, Eckhardt SG, Diab S, et al: A phase I dose-escalation study of weekly IMC-1121B, a fully human anti-vascular endothelial growth factor receptor 2 IgG1 monoclonal antibody, in patients with advanced cancer. J Clin Oncol 24:18s, 2006 (suppl; abstr 3032)

85. Krishnamurthi SS, LoRusso PM, Goncalves PH, et al: Phase I study of weekly anti-vascular endothelial growth factor receptor-1 (VEGFR-1) monoclonal antibody IMC-18F1 in patients with advanced solid malignancies. J Clin Oncol 26:637s, 2008 (suppl; abstr 14630)

86. Mendel DB, Laird AD, Xin X, et al: In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: Determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 9:327-337, 2003

87. Faivre S, Delbaldo C, Vera K, et al: Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitargeted tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 24:25-35, 2006

88. Burstein HJ, Elias AD, Rugo HS, et al: Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and taxane. J Clin Oncol 26:1810-1816, 2008

89. Mayer E, Kozloff M, Qamar R, et al: SABRE-B: A randomized phase II trial evaluating the safety and efficacy of combining sunitinib with paclitaxel and bevacizumab as first-line treatment for HER2-negative metastatic breast cancer—Final results. Breast Cancer Res Treat 102, 2008 (suppl; abstr 3126)

90. Rugo HS, Lyandres J, Melisko M, et al: Phase I study of sunitinib in combination with metronomic dosing of cyclophosphamide and methotrexate in patient with metastatic breast cancer. Breast Cancer Symposium 102, 2008 (suppl; abstr 165)

91. Adnane L, Trail PA, Taylor I, et al: Sorafenib (BAY 43-90006, Nexavar), a dual-action inhibitor that targets RAF/MEK/ERK pathway in tumor cells and tyrosine kinases VEGFR/PDGFR in tumor vasculature Methods Enzymol 407:597-612, 2005

92. Strumberg D, Clark JW, Awada A, et al: Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: A review of four phase I trials in patients with advanced refractory solid tumors. Oncologist 12:426-437, 2007

93. Strumberg D, Richly H, Hilger RA, et al: Phase I clinical and pharmacokinetic study of the novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. J Clin Oncol 23:965-972, 2005

94. Moreno-Aspitia A, Morton RF, Hillman DW, et al: Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. J Clin Oncol 27:11-15, 2009

95. Wedge SR, Ogilvie DJ, Dukes M, et al: ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res 62:4645-4655, 2002

96. Holden SN, Eckhardt SG, Basser R, et al: Clinical evaluation of ZD6474, and orally active inhibitor of VEGF and EGF receptor signaling, in patients with solid, malignant tumors. Ann Oncol 16:1391-1397, 2005

97. Miller KD, Trigo JM, Wheeler C, et al: A multicenter phase II trial of ZD6474, a vascular endothelial growth factor receptor-2 and epidermal growth factor receptor tyrosine kinase inhibitor, in patients with previously treated metastatic breast cancer. Clin Cancer Res 11:3369-3376, 2005

98. Wood JM, Bold G, Buchdunger E, et al: PTK787/ZK222584, a novel potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration. Cancer Res 60:2178-2189, 2000

99. Thomas AL, Morgan B, Horsfield MA, et al: Phase I study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of PTK787/ZK222584 administered twice daily in patients with advanced cancer. J Clin Oncol 23:4162-4171, 2005

100. PTK787 plus trastuzumab for HER2 overexpressing metastatic breast cancer. http://clinicaltrials.gov/ct2/show/NCT00216047

101. Choueiri TK: Axitinib, a novel anti-angiogenic drug with promising activity in various solid tumors. Curr Opin Investig Drugs 9:658-671, 2008

102. Rugo HS, Herbst RS, Liu G, et al: Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: Pharmacokinetic and clinical results. J Clin Oncol 23:5474-5483, 2005

103. Rugo HS, Stopeck A, Joy AA, et al: A randomized, double-blind phase II study of the oral tyrosine kinase inhibitor Axitinib in combination with docetaxel compared to docetaxel plus placebo in metastatic breast cancer. J Clin Oncol 25:18s, 2007 (suppl; abstr 1003)

104. Takai Y, Sasaki T, Matozaki T: Small GTP-binding proteins. Physiol Rev 81:153-208, 2001

105. O'Regan RM, Khuri FR: Farnesyl transferase inhibitors: The next targeted therapies for breast cancer? Endocr Relat Cancer 11:191-205, 2004

106. Kleer CG, van Golen KL, Zhang Y, et al: Characterization of RhoC expression in benign and malignant breast disease: A potential new marker for small breast carcinomas with metastatic ability. Am J Pathol 160:579-584, 2002

107. van Golen KL, Davies S, Wu ZF, et al: A novel putative low-affinity insulin-like growth factor factor-binding protein, LIBC (Lost in inflammatory breast cancer), and RhoC GTPase correlate with the inflammatory breast cancer phenotype. Clin Cancer Res 5:2511-2519, 1999

108. End DW, Smets G, Todd AV, et al: Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. Cancer Res 61:131-137, 2001

109. Zujewski J, Horak ID, Bol CJ, et al: Phase I and pharmacokinetic study of farnesyl protein transferase inhibitor R115777 in advanced cancer. J Clin Oncol 18:927-941, 2000

110. Johnston SR, Hickish T, Ellis P, et al: Phase II study of the efficacy and tolerability of two dosing regimens of the farnesyl transferase inhibitor, R115777, in advanced cancer. J Clin Oncol 21:2492-2499, 2003

111. Sparano JA, Moulder S, Kazi A, et al: Targeted inhibition of farnesyltransferase in locally advanced breast cancer: A phase I and II trial of tipifarnib plus dose-dense doxorubicin and cyclophosphamide. J Clin Oncol 24:3013-3018, 2006

112. Johnston SR, Semiglazov VF, Manikhas GM, et al: A phase II, randomized, blinded study of the farnesyltransferase inhibitor tipifarnib combined with letrozole in the treatment of advanced breast cancer after antiestrogen therapy. Breast Cancer Res Treat 110:327-335, 2208

113. Li T, Christos PJ, Sparano JA, et al: Phase II trial of the farnesyltransferase inhibitor tipifarnib plus fulvestrant in hormone receptor-positive metastatic breast cancer: New York Cancer Consortium Trial P6205. Ann Oncol 20:642-647, 2009

114. Cheng JQ, Lindsley CW, Cheng GZ, et al: The Akt/PKB pathway: Molecular target for cancer drug discovery. Oncogene 24:7482-7492, 2005

115. Hennessy BT, Smith DL, Ram PT, et al: Exploiting the PI3K/AKT pathway for cancer drug discovery. Nat Rev Drug Discov 4:988-1004, 2005

116. Isakoff SJ, Engelman JA, Irie HY, et al: Breast cancer associated PI3KCA mutations are oncogenic in mammary epithelial cells. Cancer Res 65:10992-11000, 2006

117. Meric-Bernstam F, Gonzalez-Angulo AM: Targeting the mTOR signaling network for cancer therapy. J Clin Oncol 27:2278-2287, 2009

118. Lane HA, Wood JM, McSheehy PM, et al: MTOR inhibitor RAD001 (Everolimus) has antiangiogenic/vascular properties distinct from a VEGFR tyrosine kinase inhibitor. Clin Cancer Res 15:1612-1622, 2009

119. Yu K, Toral-Barza L, Discafani C, et al: MTOR, a novel target in breast cancer: The effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer. Endocr Relat Cancer 8:249-258, 2001

120. Tabernero J, Rojo F, Calvo E, et al: Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: A phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol 26:1603-1610, 2008

121. Raymond E, Alexandre J, Faivre S, et al: Safety and pharmacokinetics of escalated doses of weekly intravenous infusion of CCI-779, a novel mTOR inhibitor, in patients with cancer. J Clin Oncol 22:2336-2347, 2004

122. Baselga J, Semiglazov V, van Dam P, et al: Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J Clin Oncol 27:2630-2637, 2009

123. Chan S, Scheulen ME, Johnston S, et al: Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients

with locally advanced or metastatic breast cancer. J Clin Oncol 23:5314-5322, 2006

124. Baselga J, Fumoleau P, Gil M, et al: Phase II, 3-arm study of CCI-779 in combination with letrozole in postmenopausal women with locally advanced or metastatic breast cancer: Preliminary results. J Clin Oncol 22:14s, 2004 (suppl; abstr 544)

125. Carpenter JT, Roche H, Campone M, et al: Randomized 3-arm, phase II study of temsirolimus in combination with letrozole in postmenopausal women with locally advanced or metastatic breast cancer. J Clin Oncol 23:16s, 2005 (suppl; abstr 564)

126. Chow LSY, Jassem J, Baselga J, et al: Phase III study of temsirolimus with letrozole or letrozole alone in postmenopausal women with locally advanced or metastatic breast cancer. Breast Cancer Res Treat 97, 2006 (suppl; abstr 6091)

127. Haluska P, Shaw HM, Batzel GN, et al: Phase I dose escalation study of the antiinsulin-like growth factor-I receptor monoclonal antibody CP-751,871 in patients with refractory solid tumors. Clin Cancer Res 13:5834-5840, 2007

128. Tolcher AW, Rothenberg ML, Rodon J, et al: A phase I pharmacokinetic and pharmacodynamic study of AMG 479, a fully human monoclonal antibody against insulin-like growth factor type 1 receptor (IGF-1R), in advanced solid tumors. J Clin Oncol 25:18s, 2007 (suppl; abstr 3002)

129. Higano CS, Yu Y, Whiting SH, et al: A phase I, first in man study of weekly IMC-A12, a fully human insulin like growth factor-I receptor IgG1 monoclonal antibody, in patients with advanced solid tumors. J Clin Oncol 25:18s, 2007 (suppl; abstr 3505)

130. Plummer ER: Inhibition of Poly(ADP-ribose) polymerase in cancer. Current Opin Pharmacol 6:364-368, 2006

131. O'Shaughnessy J, Osborne C, Pippen J, et al: Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin in patients with metastatic triple negative cancer: Results of a randomized phase II trial. J Clin Oncol 27:18s, 2009 (suppl; abstr 3)

132. Fong PC, Boss DS, Yap TA, et al: Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 361:123-134, 2009

133. Tutt A, Robson M, Garber JE, et al: Phase II trial of the oral PARP inhibitor Olaparib in BRCA-deficient advanced breast cancer. J Clin Oncol 27: 18s, 2009 (CRA501)

