Advances in breast cancer research have led to the development of investigational agents that demonstrate efficacy against new targets, including vascular endothelial growth factor. Likewise, new human epidermal growth factor receptor 2 antagonists are being investigated and new formulations of cytotoxic agents are being developed to improve the targeted efficacy of these agents. However, important outstanding questions remain in the management of breast cancer in terms of biomarkers for therapeutic response and the acceptable benefit-to-risk profiles of new therapies. (Adv Stud Med. 2007;7(16):517-522)

Advances in research will change the future standard of care for the treatment of breast cancer. Vascular endothelial growth factor (VEGF) has been identified as an important target that may translate into future therapies, microtubule-targeted therapies are under investigation, and new human epidermal growth factor receptor 2 (HER2) antagonists are on the horizon. Research is also looking into maximizing clinical benefits by targeting multiple pathways and reformulating cytotoxic regimens. This article will review the current state of breast cancer research and the advances that will most likely impact patient management in the future.

ANTI-VEGF THERAPY

The VEGF pathway is now an accepted therapeutic target in many solid tumors. Activity with anti-VEGF therapy has been demonstrated in colorectal cancer, renal cell cancer, non–small-cell lung cancer (NSCLC), ovarian cancer, and breast cancer. Anti-VEGF therapy with bevacizumab in combination with chemotherapy is now an approved first-line therapy for patients with metastatic colorectal cancer and NSCLC.1,2 Sunitinib, a VEGF receptor tyrosine kinase inhibitor (TKI), is now considered first-line therapy for metastatic renal cell cancer after encouraging data in clinical trials.3 In addition, a phase III study of bevacizumab in breast cancer has shown efficacy. The introduction of these data to the literature have validated the concept that angiogenesis is an important therapeutic target in the management of cancer.

The anti-VEGF class of agents is comprised of drugs that target different aspects of the VEGF pathway. Bevacizumab is a monoclonal antibody that targets the VEGF pathway by binding to the VEGF ligand. Small-molecule TKIs that bind to the intracellular tyrosine kinase include sunitinib and sorafenib.

The E2100 trial was conducted by the Eastern Cooperative Oncology Group (ECOG) and investigated the use of paclitaxel with or without bevacizumab in metastatic breast cancer. Eligible enrollees were receiving chemotherapy as a first-line treatment for metastatic breast cancer, and many had received previous adjuvant therapy. Patients were randomized in an open-label design to receive weekly paclitaxel alone at 90 mg/m² (3...
weeks on, 1 week off) or with the addition of bevacizumab at 10 mg/kg intravenous every other week. Data have been reported in 722 enrollees, revealing a significant benefit in terms of progression-free survival with the addition of bevacizumab versus paclitaxel alone (11.4 months vs 6.11 months, \( P < .0001 \); Figure 1).\(^4\) Response rates were also significantly improved with the addition of bevacizumab (29.9% vs 13.8%, \( P < .0001 \)).\(^4\) Although an overall survival benefit was not demonstrated (28.4 months vs 25.2 months, \( P = .12 \)),\(^4\) these data are highly compelling in light of other data reported in metastatic disease. However, the lack of observed survival benefit may have prevented the approval of bevacizumab in metastatic breast cancer at the present time, pending additional data.

The use of bevacizumab in the adjuvant setting is currently under investigation in a series of pilot studies. These pilot studies are being conducted to characterize the cardiac safety of bevacizumab. Concerns exist with adding targeted agents, such as bevacizumab, to chemotherapy regimens that contain doxorubicin, after cardiac toxicity was observed with the addition of trastuzumab to doxorubicin-based chemotherapy. If proven safe, a randomized phase III ECOG-led study will evaluate the efficacy of bevacizumab when added to an anthracycline- and taxane-based regimen as part of adjuvant therapy.

Additional studies in animal models have investigated the role of estrogen in modulating angiogenesis. In one study, estradiol was shown to stimulate VEGF expression in the rat endometrium, and VEGF is now considered to be an important mediator for these angiogenic properties observed with estrogen.\(^5\) Although hormonal therapy is effective in women with hormone receptor-positive disease, patients still relapse and experience disease recurrence. Researchers have hypothesized that VEGF-mediated angiogenesis plays a role in the development of resistance to hormonal therapy. Of note, the National Cancer Institute's Cancer and Leukemia Group B (CALGB) will be conducting a randomized trial (study 40503) that will compare outcomes in patients with metastatic breast cancer receiving first-line endocrine therapy with or without the addition of bevacizumab.

**NOVEL ANTI-HER2 AGENTS**

The epidermal growth factor receptor (EGFR) pathway has also been investigated extensively for its role in breast cancer, as demonstrated with the successful use of the HER2-antagonist trastuzumab in patients with HER2-positive breast cancer. Although HER1-targeted agents, such as gefitinib and erlotinib, have not been able to demonstrate success in breast cancer as single agents in unselected populations of patients, trials with these agents in combination with chemotherapy are ongoing in patients with estrogen receptor (ER)-, progesterone receptor-, and HER2-negative breast cancer ("triple-negative" disease).

Meanwhile, lapatinib, a small-molecule TKI agent that targets HER1 and HER2, has demonstrated a benefit in breast cancer.\(^6\) In a study of lapatinib therapy in patients who had not received trastuzumab, a response rate of 25% to 30% was observed.\(^7\) Another study that compared capecitabine with or without lapatinib in HER2-positive patients who experienced disease progression on trastuzumab therapy reported a significant doubling in the time-to-disease progression (36.9 months vs 19.7 months, \( P < .0001 \)).\(^6,9\) Importantly, fewer patients receiving lapatinib with capecitabine experienced a relapse in central nervous system (CNS) metastases, which could be due to the fact that small-molecule lapatinib is better able to penetrate the CNS.\(^9\)

Lapatinib has also been investigated in a population of unselected (HER2-positive and HER2-negative) patients with stage III and IV breast cancer. Patients received paclitaxel alone or paclitaxel with the addition

![Figure 1. PFS with Paclitaxel Alone vs Bevacizumab Plus Paclitaxel as First-line Therapy for Locally Recurrent or Metastatic Breast Cancer](https://example.com/figure1.png)
of lapatinib. Although a significant benefit with the addition of lapatinib in terms of time-to-disease progression was observed in HER2-positive patients \((P = .011)\), no significant benefit was observed in those with HER2-negative disease \((P = .747\); Figure 2\).\(^\text{10}\)

Additional lapatinib studies are planned to investigate the role of this agent in HER2-positive breast cancer. In the neoadjuvant setting, the CALGB has planned a trial that will compare chemotherapy plus trastuzumab alone, chemotherapy plus lapatinib alone, or chemotherapy plus the combination. Concomitant paclitaxel will be the chemotherapy administered in the neoadjuvant regimen, and an anthracycline-based regimen will be administered as an adjuvant therapy after surgery.

Another novel target, HSP90, has also been identified that may provide benefit in HER2-positive disease. The HSP90 target is a chaperone protein that is required for the maturation and stabilization of certain proteins, and is particularly important in post-translational modification. HER2 and Akt (protein kinase B) have been found to be client molecules of this chaperone protein. An investigational HSP90 inhibitor, 17-AAG, has shown the ability to selectively target HER2 in a xenograph model of HER2-positive breast cancer and has also been shown to provide a benefit in patients who progressed with trastuzumab therapy.\(^\text{11}\)

Presently, a phase II trial evaluating trastuzumab plus 17-AAG is ongoing for patients with HER2-positive metastatic breast cancer, to investigate the combination of 2 agents targeting the HER2 pathway.

**CAN WE INCREASE ACTIVITY BY TARGETING MULTIPLE PATHWAYS?**

It is also important to consider the possibility of increasing therapeutic response by targeting multiple disease-related pathways, including HER2, VEGF, EGFR, and ER targets. In one phase II trial of combination trastuzumab and bevacizumab therapy, investigators reported a response rate of 54.1%.\(^\text{12}\) Although only 1 case of transient asymptomatic decline in left ventricular ejection fraction (LVEF) was initially reported, 1 patient subsequently developed congestive heart failure.\(^\text{12}\) It should be emphasized that these patients had not received previous trastuzumab therapy, and a randomized, controlled trial would be needed to differentiate the effects of trastuzumab and bevacizumab in breast cancer management. Furthermore, the effects of this combination on LVEF should be better characterized before proceeding with large-scale trials. Combinations, such as bevacizumab and lapatinib, are also under way and may have lower potential for cardiotoxicity.

**NEW FORMULATIONS OF CONVENTIONAL CYTOTOXIC CHEMOTHERAPY**

New formulations of conventional cytotoxic agents are also under development to achieve improved efficacy and safety profiles. Nanoparticle albumin-bound (nab)-paclitaxel has been developed in an effort to use albumin to improve the water-solubility of paclitaxel and assist in transporting the agent through surface receptors in tumor cells. In a phase III trial that compared every-3-week schedules of nab-paclitaxel and paclitaxel, nab-paclitaxel resulted in significant improvements in overall response rate (33% vs 19%, \(P = .001\)) and time to progression (23 weeks vs 16.9 weeks, \(P = .006\)) compared with paclitaxel. However, whereas paclitaxel demonstrated a significantly higher rate of neutropenia \((P <.001)\), nab-paclitaxel was associated with a significantly higher rate of neuropathy \((P <.001)\),\(^\text{13}\) thus there is likely an important trade-off in terms of the adverse effect profile with nab-paclitaxel. A randomized phase II trial compared every-3-week nab-paclitaxel to weekly (days 1, 8, and 15, every 28 days) nab-paclitaxel and every-3-week
docetaxel, and reported that weekly nab-paclitaxel at a dose of 150 mg/m² resulted in a significantly higher response rate than docetaxel ($P = .003$), and was also more effective than every-3-week nab-paclitaxel and weekly dose of 100 mg/m² nab-paclitaxel.14

These initial data show that novel chemotherapy formulations, such as nab-paclitaxel, may improve outcomes in breast cancer, but additional data are needed to characterize the efficacy and safety profiles of these agents.

**NOVEL MICROTUBULE-TARGETING AGENTS**

Microtubules are required for the formulation and function of the mitotic spindle in cell division, and have been investigated as a therapeutic target in breast cancer. Both taxanes and vinca alkaloids target microtubules. Although taxanes have a stabilizing effect, vinca alkaloids destabilize the microtubule. A variety of epothilones, which are stabilizing agents, are now under development as microtubule-targeted therapy in cancer (Table).15-17 A trial of the microtubule inhibitor ixabepilone plus capecitabine versus capecitabine alone in 752 patients with metastatic breast cancer found that the addition of ixabepilone improved progression-free survival (5.8 months vs 4.2 months, $P = .0003$), but there was a trade-off in terms of toxicity. Those receiving ixabepilone experienced higher rates of multiple adverse effects, including leukopenia ($P < .0001$), anemia ($P = .005$), neutropenia ($P < .0001$), thrombocytopenia ($P = .011$), and febrile neutropenia ($P = .001$).18

Ixabepilone was recently approved for use in patients with metastatic or locally advanced breast cancer, either in combination with capecitabine in those who have not responded to an anthracycline or taxane, or as monotherapy in patients who have not responded to an anthracycline, a taxane, or capecitabine therapy.

**CONCLUSIONS**

Although new approaches to breast cancer management are on the horizon, many important questions still remain. Reproducible and reliable biomarkers are still needed to predict therapeutic response and guide therapy. Rational combination regimens need to be explored, and clinicians need to decide if the potential for added toxicity with combination strategies, especially with the use of cytotoxic agents, is worth an incremental benefit. Mechanisms of resistance to therapy should be addressed to improve the ability to predict therapeutic response. Finally, the comparative efficacy of different dosing schedules also needs to be explored in greater detail.

**DISCUSSION**

*Dr Ellis:* I would like to raise some important issues with bevacizumab. We are observing marked benefits in terms of relapse-free survival without seeing appreciable overall survival benefits, therefore, we have

<table>
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<th>Agent (manufacturer)</th>
<th>Epothilone Analog</th>
<th>Development Phase</th>
<th>Clinical Toxicities</th>
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<tr>
<td>Ixabepilone (Bristol-Myers Squibb)</td>
<td>Aza-epothilone B</td>
<td>Approved October 2007</td>
<td>Hypersensitivity reactions, neutropenia, and neuropathy</td>
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<td>Epo-906/patupilone (Novartis)</td>
<td>Epothilone B (natural product)</td>
<td>III</td>
<td>Diarrhea</td>
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<td>ZK-EPO (Schering AG/Berlex)</td>
<td>Epothilone B (fully synthetic)</td>
<td>II</td>
<td>Neuropathy, nausea, and ataxia</td>
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<td>KOS-862 (Roche)</td>
<td>Epothilone D (desoxyepothilone B)</td>
<td>II</td>
<td>Neuropathy, impaired gait, and cognitive/perceptual abnormalities</td>
</tr>
<tr>
<td>BMS-310705 (Bristol-Myers Squibb)</td>
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<td>I / II</td>
<td>Hypersensitivity reactions, pancytopenia, neuropathy, and arthralgia/myalgia</td>
</tr>
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to ask ourselves what this means biologically. Perhaps there are compensatory effects on angiogenesis induced by bevacizumab that cause a surge of tumor growth when the drug is stopped.

**Dr Dickler:** Do you really think that the drug acts differently in breast cancer than in other solid tumors? We have seen promising overall survival benefits with bevacizumab in other solid tumors, such as colorectal and lung cancer.

**Dr Stearns:** We sometimes do see a mixed response to therapy and wonder if certain breast cancers with a specific biology respond accordingly based on the underlying angiogenic process.

**Dr Blackwell:** I agree and have observed this mixed response to therapy. Perhaps we need to understand the biology of the disease to a greater extent and re-stage our patients more frequently, maybe every 4 weeks in the context of a trial, to help understand this phenomenon.

In terms of the future of breast cancer therapy, there are some exciting HER-targeted agents that look beyond HER2. Drugs that perhaps target the whole family, especially in an irreversible way, are the most exciting. Vaccine therapy against HER2 is also of interest, as well as upcoming antiangiogenic agents and new chemotherapy strategies that improve blood-brain barrier penetration. New hormonal therapy strategies would be welcome, including ER-targeted agents, but I do not see as many of these on the horizon. It would also be extremely clinically valuable if the role of progesterone receptor as a predictive factor was clarified.

**Dr Partridge:** I think that Dr Blackwell touched on most of the important research. It is important to emphasize that as we expand and improve our therapeutic options, long-term survivorship and the recognition of breast cancer as a chronic disease are going to come to the forefront.

**Dr Wolff:** The most important issue with the advent of all these new options is to identify the right patients for the right drugs. Ensuring that patients have access to reliable, reproducible ER testing is critical at this point.

**Dr Isaae:** Accurate testing for ER and HER2 markers is important, allowing us to reliably tailor therapy. There are still many unknowns in making the best use of the drugs that we do have, and how to sequence therapy.

**Dr Griffith:** From a nursing perspective, we need to have better measures to balance potential toxicity and efficacy, especially with longer periods of survivorship.

**Dr Wolff:** In general, we need better tools to track the impact of various toxicities. Although overall survival has become the most important outcome in the clinical trial setting, we may want to look at drugs that offer improved survival as well as an improved toxicity profile.

**Dr Ellis:** We still need to emphasize prevention efforts. Hormonal therapy has a great potential to be used in prevention, but we still do not know how to identify the best candidates for therapy. Also, we still need to work towards a cure for patients with metastatic breast cancer. The trials with bevacizumab underscore the potential challenges in achieving this goal. The ongoing genome atlas project for breast cancer holds a great degree of promise in documenting genetic abnormalities and their potential as new therapeutic targets.

**Dr Wolff:** I have seen many patients receiving tamoxifen experience a relapse after the drug is discontinued, and we may witness the same type of situation in patients receiving some of these new therapies, including trastuzumab. With a better understanding of the biology of breast cancer, we may be able to direct these patients to appropriate trials that target specific pathways and present an opportunity to protect the patient against disease recurrence.

**Dr Stearns:** I think that the ultimate goal is to provide the right first-line treatment while minimizing the potential for adverse effects. We have seen small initial advances in this direction, and current trials suggest that additional advances are possible.

### REFERENCES


12. Pegram M, Chan D, Dichmann RA, et al. Phase II combined biological therapy targeting the HER2 proto-oncogene and the vascular endothelial growth factor using trastuzumab (T) and bevacizumab (B) as first line treatment of HER2-amplified breast cancer. Presented at: 29th Annual San Antonio Breast Cancer Symposium; December 14-17, 2006; San Antonio, TX. Abstract 301.


