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Current Treatment Options for Metastatic Breast Cancer: What Now?

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Abstract: Approximately 30% of patients with breast cancer will develop metastatic breast disease. Metastatic breast cancer is considered an incurable disease, with complete remission rarely achieved after treatment. The goal of treatment for metastatic breast cancer patients is to increase overall survival time and delay disease progression while ameliorating symptoms and improving or maintaining quality of life. Single-agent therapeutic regimens are appropriate for most metastatic breast cancer patients. Patients with the luminal A subtype of breast cancer, which is more indolent in nature and tends to be more sensitive to treatment in general, often respond well to single-agent therapy. Several chemotherapy regimens are recommended for the treatment of metastatic breast cancer. Compared with single-agent regimens, these combination regimens often produce a greater improvement in the rate of objective response as well as a prolongation of progression-free survival. There is little evidence, however, of improvement in overall survival. Combination chemotherapy regimens are often associated with a greater degree of toxicity depending on schedules and doses used. The use of bevacizumab in metastatic breast cancer is currently a topic of controversy. It is hoped that forthcoming trial data will enable the identification of a group of patients, based on tumor biology, who could benefit from bevacizumab-based therapy.

Introduction to Metastatic Breast Cancer

Hope S. Rugo, MD

Metastatic breast cancer is a more treatable disease than ever before. However, despite advancements in patient management, this advanced form of breast cancer is essentially universally fatal—nearly every woman who either presents with or develops metastases will eventually die from the disease. Mortality is generally due to complications associated with organ tumor infiltration.

Epidemiology

In 2010, it was estimated that 207,090 women would be diagnosed with breast cancer.¹ In general, most breast cancer patients present with earlier-stage disease. Approximately 60% of patients are diagnosed with a localized breast tumor, and 33% are diagnosed when the tumor has spread to regional lymph nodes.² Thanks to current improvements in surgery and adjuvant therapy, the majority of women who are diagnosed and treated for early-stage breast cancer will remain disease-free. Unfortunately, even with the many therapeutic advances currently implemented in clinical practice for early-stage disease, approximately 30% of patients will subsequently develop metastatic breast cancer.³ These patients tend to be younger and tend to present with more locally advanced disease, although recurrence can occur at any age. Approximately one-quarter of patients with lymph node–negative breast cancer and one-half with lymph node–positive breast cancer will ultimately develop distant, recurrent disease.⁴ Further, a small proportion of patients remain undiagnosed until they develop widespread disease—approximately 5% of women are not diagnosed until they have already developed metastatic breast cancer.²

Prognosis

Many of the therapeutic advances made in the treatment of metastatic breast cancer can be attributed to an improved understanding of the underlying biology of the disease, particularly better knowledge of the different subtypes of breast tumors. For example, observance of the genetic mutations present in metastatic breast cancer (mutations identified from de novo disease and maintained through disease progression, as well as mutations acquired over the course of progression) has provided a better definition of the specific breast cancer subtypes. Biologic differences in breast tumors can have important implications for the course of the disease. Slow-growing breast cancers tend to recur late, and they are more resistant to chemotherapy but sensitive to hormone therapy. Rapidly proliferating tumors tend to recur early and will metastasize more frequently to visceral organs. Increased understanding of these characteristics plays an important role in guiding treatment decisions, including selection of single versus combination agent regimens and the use of targeted biologic agents.

One important and intriguing area of research in metastatic breast cancer is mechanisms of disease resistance. For example, patients who present with early-stage breast cancer and then experience disease recurrence have some tumor cell resistance to standard therapy that was either present at the time of diagnosis or acquired over time. Many of the goals of ongoing preclinical and clinical investigations involve understanding the mechanisms of this resistance and then trying to reverse the effect. Ultimately, the goal would be to use these treatments in the earlier disease setting in order to prevent recurrence and progression to metastatic breast cancer.

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Metastatic breast cancer is considered an incurable disease, with complete remission rarely achieved after treatment. Once a patient has developed this advanced-stage of disease, the median survival is approximately 24 months, although significant variations exist with longer survival in hormone-sensitive disease, and shorter survival in primary chemotherapy resistance. Thus, the goal of treatment for metastatic breast cancer patients is to increase patient overall survival time and delay disease progression while ameliorating symptoms and improving or maintaining overall quality of life. This monograph will focus on important areas in the current management of metastatic breast cancer, focusing on the use of both single agents and combination therapies. We will conclude with a discussion regarding new directions for treatment of metastatic disease.

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Single-Agent Therapy in Metastatic Breast Cancer

Joyce A. O'Shaughnessy, MD

In general, most metastatic breast cancer patients are well-served with the use of single-agent therapeutic regimens. Patients with the luminal A subtype of breast cancer, which is more indolent in nature and tends to be more sensitive to treatment in general, will often respond well to single-agent therapy. This section will examine the data supporting single agents and discuss how bone-targeting agents can be used to prevent skeletal-related events.

Single-Agent Endocrine Therapies

For patients with hormone receptor-positive disease (either estrogen receptor [ER] or progesterone receptor [PR]), endocrine therapies are some of the most critical agents for treatment. In general, these agents are administered as single-drug regimens. However, there is some evidence to support combined endocrine regimens, at least in premenopausal patients. In a meta-analysis of 4 randomized clinical trials by Klijn and colleagues,¹ which included a combined total of 506 premenopausal women with advanced breast cancer, a significant benefit in overall survival (OS) was shown with the combination of tamoxifen plus a luteinizing hormone-releasing hormone (LHRH) agonist versus an LHRH agonist alone (hazard ratio [HR], 0.78, stratified log-rank test $P=.02$). Similarly, a benefit in progression-free survival (PFS) was also reported (HR, 0.70, stratified log-

rank test $P=.0003$), as was an improved rate of response (odds ratio: 0.67, stratified Mantel-Haenszel test $P=.03$). Outside of this analysis, there are no prospective, randomized data to conclusively support combination endocrine therapy; thus, single-agent endocrine therapy is considered the standard of care.

Aromatase inhibitors are the most effective endocrine therapy for patients with ER/PR-positive metastatic breast cancer. Robertson and colleagues recently reported important long-term, follow-up data from the FIRST (Fulvestrant First-Line Study) trial, a multicenter, randomized, open-label, phase II study comparing the efficacy and safety of the ER antagonist fulvestrant with anastrozole.² A total of 205 postmenopausal women with previously untreated hormone receptor-positive locally advanced or metastatic breast cancer were randomized to receive either fulvestrant or anastrozole, which were administered until disease progression or any other event that required treatment discontinuation. Patients who had previously received endocrine therapy for advanced disease were not included in the study. In the initial report,² similar rates of clinical benefit (72.5% vs 67.0%, odds ratio: 1.30, 95% confidence interval [CI], 0.72–2.38; $P=.386$) and objective response (36.0% vs 35.5%) were demonstrated for fulvestrant and anastrozole, respectively. In that initial analysis, the median time to progression (TTP) was found to be significantly prolonged among fulvestrant-treated patients

compared with anastrozole-treated patients (not reached vs 12.5 months; HR, 0.63; 95% CI, 0.39–1.00; $P=.0496$). In the updated analysis, a much larger proportion of patients had progressed.³ The median TTP was significantly prolonged in the fulvestrant arm compared with the anastrozole arm (23.4 vs 13.1 months; HR, 0.66; 95% CI, 0.47–0.92; $P=.01$). Importantly, this benefit in TTP was observed across all prespecified patient subgroups, including age (<65 vs ≥ 65 years), receptor status (ER/PR-positive vs ER-positive or PR-positive), visceral involvement (yes vs no), use of prior chemotherapy (yes vs no), or evidence of measurable disease (yes vs no). Further, patients in both treatment groups responded similarly to subsequent endocrine therapy. These data justify the first-line use of fulvestrant over aromatase inhibitors and have the potential to change practice.

Chia and colleagues demonstrated that fulvestrant was equivalent to exemestane in the setting of disease progression following treatment with a nonsteroidal aromatase inhibitor. The EFECT (Evaluation of Faslodex versus Exemestane Clinical Trial) trial was a double-blind, placebo-controlled, multicenter, phase III trial that randomized 693 patients with hormone receptor–positive advanced breast cancer to treatment with either fulvestrant or exemestane.⁴ All patients were postmenopausal and had experienced disease progression or recurrence after treatment with a nonsteroidal aromatase inhibitor; approximately 60% of patients had received at least 2 prior endocrine therapies. In both treatment groups, the median TTP was 3.7 months (HR, 0.963, 95% CI, 0.819–1.133; $P=.6531$). In addition, the overall response rate and clinical benefit rate were comparable between the treatment groups (overall response rate of 7.4% with fulvestrant vs 6.7% with exemestane; $P=.736$ and clinical benefit rate of 32.2% with fulvestrant vs 31.5% with exemestane; $P=.853$). Both agents were equally well tolerated, with no significant difference in the frequency of adverse events. A subanalysis subsequently reported that both agents were also similarly active in patients with or without visceral metastases.⁵

Antiandrogen agents are another important component of endocrine therapy for metastatic breast cancer, especially as they have the potential to circumvent androgen receptor–mediated resistance to ER blockade. Fluoxymesterone has been associated with a great deal of clinical benefit, particularly among patients with ER-positive metastatic breast cancer that has a characteristically indolent and long natural history. Ethinyl estradiol is a very effective endocrine therapy to use in the late-line setting, often offering excellent symptom palliation for patients.

Single-Agent Taxanes

Taxanes are considered the standard of care in metastatic breast cancer.⁶ Clinical studies suggest that taxanes are the most active single agents in the frontline treatment of these patients.^{7–9}

In a controlled, multicenter, open-label phase III trial by Jones and colleagues, patients were randomized to receive docetaxel 100 mg/m² (n=225) or paclitaxel 175 mg/m² (n=224) on day 1, every 21 days until tumor progression, unacceptable toxicity, or withdrawal of consent.¹⁰ Median OS was 15.4 months in the docetaxel arm versus 12.7 months in the paclitaxel arm (HR, 1.41; 95% CI, 1.15–1.73; $P=.03$). The median TTP was also longer in the docetaxel arm compared with the paclitaxel arm (5.7 months vs 3.6 months, respectively; HR, 1.64; 95% CI, 1.33–2.02; $P<.0001$). The overall response rate was 32% in the docetaxel arm and 25% in the paclitaxel arm ($P=.10$).

Seidman and colleagues in the phase III, randomized Cancer and Leukemia Group B trial 9840 compared continuous dosing of weekly paclitaxel (100 mg/m² reduced to 80 mg/m²) to the then-standard every-3-week dosing schedule (175 mg/m²) in patients with 1 or no prior chemotherapy treatments for advanced disease.¹¹ Weekly dosing improved response rate (42% vs 29%; unadjusted odds ratio, 1.75; $P=.0004$), TTP (median, 9 vs 5 months; adjusted HR, 1.43; $P<.0001$), and survival (median, 24 vs 12 months; adjusted HR, 1.28; $P=.0092$), but was associated with an increase in grade 3 neuropathy (24% vs 12%; $P=.0003$). Based on these data, weekly dosing of paclitaxel at 80–90 mg/m² has become a standard therapy for both advanced and early stage disease, most commonly given with a 1-week break every 3 weeks to reduce cumulative toxicity.

In 2009, Gradishar and associates reported results from a randomized, phase II trial evaluating nab-paclitaxel and docetaxel as first-line treatment of metastatic breast cancer (N=302), in which weekly nab-paclitaxel (150 mg/m²) demonstrated significantly longer PFS than docetaxel (100 mg/m² every 3 weeks).¹² In this study, nab-paclitaxel was administered at 3 different doses: 300 mg/m² every 3 weeks, 100 mg/m² weekly, and 150 mg/m² weekly. According to investigator assessment, PFS was 14.6 months in the 150 mg/m² weekly nab-paclitaxel arm compared with 7.8 months in the docetaxel arm ($P=.012$). Independent radiologist assessment found PFS to be 12.9 months with 150 mg/m² weekly nab-paclitaxel and 7.5 months with docetaxel ($P=.0065$). Overall response, as assessed by independent review, was 49% in the 150 mg/m² weekly nab-paclitaxel arm, 45% in the 100 mg/m² weekly nab-paclitaxel arm, and 35% in the docetaxel arm. (These differences were not statistically significant.)

At the 2011 American Society of Clinical Oncology (ASCO) Breast Cancer Symposium, Gradishar and coworkers reported updated results from this study.¹³ Overall survival was 33.8 months in the 150 mg/m² weekly nab-paclitaxel arm (n=74) and 26.6 months in the docetaxel arm (HR, 0.688; n=74). PFS was 14.6 months in the 150 mg/m² weekly nab-paclitaxel arm and 7.8 months in the docetaxel arm (HR, 0.568; $P=.012$). Among patients in the 150 mg/m² weekly nab-paclitaxel arm, the overall response rate was 74%, as compared with 39% in the docetaxel arm ($P<.001$). Patients receiving docetaxel were more likely to

experience grade 3/4 neutropenia and grade 3/4 fatigue than patients receiving nab-paclitaxel (at any dose). Grade 3 neuropathy was most frequent among patients who received 150 mg/m² nab-paclitaxel. The median time to improvement in neuropathy ranged from 20–22 days among patients who received nab-paclitaxel, compared with 41 days among patients who received docetaxel.

An earlier, randomized phase III trial showed that nab-paclitaxel (260 mg/m² intravenously, without premedication) was associated with significantly higher response rates compared with standard paclitaxel (175 mg/m², intravenously with premedication) in patients with metastatic breast cancer.¹⁴ The response rate was 33% in patients receiving nab-paclitaxel (n=229) and 19% in patients receiving standard paclitaxel (n=225; *P*=.001). The nab-paclitaxel patients also experienced a longer time to tumor progression than the standard paclitaxel patients (23.0 weeks vs 16.9 weeks, respectively; HR, 0.75; *P*=.006). The incidence of grade 4 neutropenia was significantly lower in the nab-paclitaxel arm compared with the standard paclitaxel arm (9% vs 22%, respectively; *P*<.001). The incidence of febrile neutropenia was similar in both arms. Nab-paclitaxel patients were more likely to experience grade 3 sensory neuropathy than the standard paclitaxel patients (10% vs 2%, respectively; *P*<.001); this neuropathy responded rapidly to management.

Capecitabine

Several clinical trials have evaluated capecitabine as a single agent for metastatic breast cancer. Two open-label, randomized, phase II trials demonstrated that capecitabine was active in both the first- and second-line treatment settings for metastatic breast cancer.

In a trial by O'Reilly and colleagues, 43 patients with anthracycline-resistant metastatic breast cancer were randomized to receive either capecitabine or paclitaxel.¹⁵ The response rates were 36% and 26% in the capecitabine and paclitaxel arms, respectively. Both the median TTP (3.0 vs 3.1 months) and median OS (7.6 vs 9.4 months) were comparable between the treatment groups.

In a trial by O'Shaughnessy and colleagues, 95 patients with advanced or metastatic breast cancer received either capecitabine or cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).¹⁶ Patients were 55 years or older and had not received prior cytotoxic chemotherapy for their disease. In the capecitabine arm, 30% of patients achieved an overall response (including 5% complete responses); this rate was nearly twice that seen in the CMF arm (16%, with no complete responses). The median TTP was prolonged with capecitabine as compared with CMF (4.1 vs 3.0 months, respectively), but median OS was similar between the 2 arms (19.6 vs 17.2 months, respectively). Capecitabine was associated with fewer cases of alopecia and myelosuppression, but with a higher rate of diarrhea and hand-foot syndrome.

Eribulin Mesylate

Eribulin mesylate, a nontaxane inhibitor of microtubule dynamics, was investigated in the EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin) study, an international, multicenter, open-label, randomized, phase III clinical trial.¹⁷ In this study, 762 patients with locally recurrent or metastatic breast cancer were randomized to either single-agent eribulin or another treatment of their physician's choice (96% of the patients in this arm received single-agent chemotherapy—most commonly, vinorelbine, gemcitabine, or capecitabine; 4% received hormonal therapy; and no patients received a biologic agent). All patients had received between 2–5 prior chemotherapy regimens (median of 4 prior chemotherapy regimens), which included an anthracycline and a taxane (unless contraindicated). Upon randomization, patients were stratified according to geographic location, prior capecitabine exposure, and HER2 status.

Median OS was significantly improved among patients who received eribulin compared with patients who received a treatment of physician's choice (13.1 vs 10.6 months, respectively; HR, 0.81; 95% CI, 0.66–0.99; *P*=.041); this was a clinically meaningful increase of 23% for eribulin-treated patients. In an exploratory subset analysis of OS, eribulin-treated patients were favored compared with treatment of physician's choice across all stratification factors except for patients from region 2 (including Eastern Europe, Russia, and Turkey). In an independent review, no significant difference was observed in median PFS between the eribulin arm and the treatment of physician's choice arm (3.7 vs 2.2 months, respectively; HR, 0.87; 95% CI, 0.71–1.05; *P*=.137). However, the difference in PFS as assessed by study investigators was statistically significant (HR, 0.76; 95% CI, 0.64–0.90; *P*=.002), most likely due to the smaller number of patients who were censored. An objective response was reported in more patients in the eribulin arm compared with the control arm (12% vs 5%; *P*=.002); 3 of the responses in the eribulin arm were complete responses.

A subgroup analysis of the EMBRACE study was also recently reported.¹⁸ Although eribulin demonstrated benefit across patient subgroups as compared with treatment of physician's choice, most of the differences were not statistically significant. Among hormone receptor-positive patients, eribulin conferred a 17% decreased risk of death (HR, 0.83; 95% CI, 0.64–1.06); in hormone receptor-negative patients, eribulin-treated patients had a 34% decreased risk of death (HR, 0.66; 95% CI, 0.45–0.99). Among HER2-positive and HER2-negative patients, the decrease in risk of death associated with eribulin treatment was 24% (HR, 0.76; 95% CI, 0.47–1.24) and 19% (HR, 0.81; 95% CI, 0.64–1.02), respectively.

Which Patients Should Receive Single-Agent Therapy?

The tempo of disease progression and the patient's symptoms largely dictate the ability to use single-agent treatment regimens. Combination regimens will often be used in patients with a heavy tumor burden and very symptomatic disease, who often have evidence of end organ compromise. Typically, these patients have the luminal B subtype of breast cancer, which is associated with a more aggressive natural history, a higher tumor burden, and more extensive and symptomatic metastases. Additionally, patients with triple-negative metastatic breast cancer also often require combination regimens. However, for many patients, especially those with hormone receptor-positive disease, sequential single agents are an important strategy to control disease progression without the need for significantly aggressive treatment. These patients often have the luminal A subtype of breast cancer, which is more indolent in nature and tends to be more sensitive to treatment in general.

Bone-Targeting Agents

For patients with metastatic bone disease, bone-targeting agents such as the bisphosphonates zoledronic acid and pamidronate, as well as the monoclonal antibody denosumab, have been used to prevent skeletal-related events. In general, these agents are administered with bone-supporting therapies such as calcium citrate and vitamin D, in addition to chemotherapy or endocrine therapy, to women with metastatic disease who have an expected survival time of at least 3 months.¹⁹ Data from randomized clinical trials supporting the use of these agents in metastatic breast cancer show that treatment is associated with a reduced incidence of skeletal-related events.

Several studies first established pamidronate to be effective in the prevention of skeletal-related events for patients with metastatic breast cancer. The Protocol 19 Aredia Breast Cancer Study Group conducted 2 prospective, multicenter, randomized, double-blind, placebo-controlled trials including women with breast cancer who had at least 1 lytic bone lesion and were receiving either cytotoxic chemotherapy or hormonal therapy. All patients were randomized to receive either a pamidronate or placebo infusion every 3–4 weeks. In a pooled analysis of all 751 evaluable patients,²⁰ the rate of skeletal morbidity was significantly reduced in the pamidronate group compared with the placebo group (2.4 vs 3.7; $P < .001$). Compared with pamidronate-treated patients, a significantly greater proportion of placebo-treated patients experienced skeletal complications (51% vs 64%; $P < .001$). These studies also demonstrated a significantly prolonged median time to first skeletal complication among pamidronate-treated patients compared with placebo-treated patients (12.7 vs 7.0 months; $P < .001$).

Subsequent clinical trial evidence has suggested that in patients with breast cancer that has metastasized to the bone, zoledronic acid may be superior to pamidronate for prevention of skeletal-related morbidity. In a phase III, double-blind trial that compared zoledronic acid to pamidronate, both given as an infusion every 3–4 weeks for 12 months, zoledronic acid significantly decreased the incidence and need for radiation therapy to bone.²¹ Although a similar proportion of skeletal-related events was reported in both treatment arms, the rate of skeletal morbidity was slightly lower among patients treated with zoledronic acid. More definitive data were reported in a randomized phase III trial of 1,130 patients with metastatic breast cancer and bone metastases (either osteolytic, osteoblastic, or mixed lesions) who were treated with either zoledronic acid or pamidronate.²² In this study, the proportion of patients with a skeletal-related event was lower in the zoledronic acid arm compared with the pamidronate arm (48% vs 58%), although this difference did not reach statistical significance. Further, this trend was only apparent among those patients with at least 1 osteolytic lesion; among the overall population, the proportion of patients experiencing a skeletal-related event was more comparable (43% vs 45%, respectively). However, the median time to first skeletal-related event was significantly prolonged among patients treated with zoledronic acid compared with pamidronate (310 vs 174 days; $P = .013$). Overall, a multiple event analysis determined that in terms of the risk of developing a skeletal-related event, a significant benefit was achieved with zoledronic acid in both the osteolytic subset of patients (30%; $P = .010$) as well as in the overall population (20%; $P = .037$).

More recently, denosumab, a monoclonal antibody directed against the receptor activator of nuclear factor κ B (RANK) ligand, was found to be superior to zoledronic acid for delaying and preventing skeletal-related events in patients with metastatic breast cancer. In a randomized, double-blind study of 2,046 metastatic breast cancer patients with bone metastases,²³ denosumab was superior to zoledronic acid in delaying time to first on-study skeletal-related event (HR, 0.82; 95% CI, 0.71–0.95; $P = .01$ for superiority). Denosumab was also superior to zoledronic acid for delaying time to first and subsequent on-study skeletal-related events (rate ratio: 0.77; 95% CI, 0.66–0.89; $P = .001$).

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Combination Therapy in Metastatic Breast Cancer

Edith A. Perez, MD

Several chemotherapy regimens are recommended for the treatment of metastatic breast cancer. Compared with single-agent regimens, these combination regimens often produce a greater improvement in the rate of objective response as well as a prolongation of progression-free survival (PFS); there is little evidence, however, of improvement in overall survival (OS), although there is no trial that has been able to totally address this issue. Further, combination regimens are often associated with a greater degree of toxicity depending on schedules and doses used.

A number of combination regimens are recommended for the treatment of metastatic breast cancer.¹ Although these regimens are considered to be fairly equivalent, the National Comprehensive Cancer Network (NCCN) panel categorizes them as either preferred or

other. In this section, newer studies of novel and investigative combination strategies are discussed.

Combination Chemotherapy

Two phase III clinical trials have evaluated the epothilone ixabepilone in metastatic breast cancer. In the pivotal international CA163-046 study, 752 metastatic breast cancer patients with anthracycline-pretreated/resistant disease and taxane-resistant disease were randomized to receive either ixabepilone plus capecitabine or capecitabine alone.² Compared with single-agent capecitabine, patients treated with the combination of ixabepilone plus capecitabine experienced significantly prolonged median PFS (4.2 vs 5.8 months, respectively), and a 25% reduction in the estimated risk of disease pro-

gression (HR, 0.75; 95% CI, 0.64–0.88; $P=.0003$). Twice as many patients in the combination arm also achieved an objective response (14% in the single-agent arm vs 35% in the combination arm; $P<.0001$). A secondary endpoint from this trial, OS, was also analyzed. Although a trend towards improved median OS was observed in the combination arm compared with single-agent capecitabine, this difference was not significant (12.9 vs 11.1 months, HR, 0.9; 95% CI, 0.77–1.05; $P=.19$).

In a second phase III study, 1,221 metastatic breast cancer patients who were previously treated with an anthracycline and a taxane were randomized to treatment with either ixabepilone plus capecitabine or single-agent capecitabine.³ The primary endpoint of this study was OS. No significant difference in median OS was demonstrated between the 2 treatment groups (16.4 months in the combination arm vs 15.6 months in the single-agent arm, HR, 0.9, 95% CI, 0.78–1.03; $P=.1162$) within the overall population. However, when the analysis was adjusted for performance status and other prognostic factors, patients treated with the combination achieved a significantly superior OS compared to patients treated with single-agent capecitabine (HR, 0.85; 95% CI, 0.75–0.98; $P=.0231$). This trial also confirmed results seen in the CA163-046 phase III trial,² demonstrating that patients treated with ixabepilone plus capecitabine achieved significantly prolonged median PFS (6.2 vs 4.2 months; HR, 0.79; $P=.0005$) and a significantly higher rate of objective response (43% vs 29%; $P<.0001$).

A pooled analysis that focused on patients with reduced performance status from this phase III trial and another one was recently published.⁴ The analysis found that those patients with a reduced performance status (Karnofsky performance status [KPS] 70–80) who were treated with the ixabepilone plus capecitabine combination achieved significant improvements in median OS compared with those who were treated with single-agent capecitabine (12.3 vs 9.5 months, respectively; HR, 0.75; $P=.0015$). Conversely, there was no significant difference in median OS between the 2 treatment groups among patients with a high (KPS 90–100) performance status (16.7 months in the combination arm vs 16.2 months in the single-agent arm, HR, 0.98; $P=.8111$). However, significant improvements in both median PFS and objective response rates were achieved regardless of performance status. For low-performance status patients, the median PFS was 4.6 months in the combination arm versus 3.1 months in the single-agent arm (HR, 0.76; $P=.0021$). For high-performance status patients, the median PFS was 6.0 in the combination arm versus 4.4 months in the single-agent arm (HR, 0.58; $P=.0009$). The objective response rates in low-performance status patients were 35% in the combination arm versus 19% in the single-agent arm. Among high-performance status patients, the objective response rates were 45% in the combination arm

versus 28% in the single-agent arm. The ixabepilone plus capecitabine combination may be particularly attractive in the setting of triple-negative disease when compared with capecitabine alone.⁵ In this retrospective analysis, response and time to progression were clearly superior in the patients with triple-negative disease who received the combination instead of the single agents.

Dual HER2 Inhibition

Blackwell and colleagues tested the efficacy and safety of combining the 2 HER2 inhibitors lapatinib and trastuzumab in patients with HER2-positive metastatic breast cancer.⁶ All patients (N=296) had experienced progression on prior trastuzumab-containing regimens (median of 3 prior trastuzumab-containing regimens) and were randomized to receive either lapatinib alone or lapatinib in combination with trastuzumab. Patients receiving the combination therapy achieved significantly prolonged PFS compared with the lapatinib-only group (HR, 0.73; 95% CI, 0.57–0.93; $P=.008$). Additional significant benefits were also achieved for the rate of clinical benefit (24.7% in the combination arm vs 12.4% in the single-agent arm; $P=.01$); there was no significant difference in the rate of objective response between the 2 groups (10.3% vs 6.9%, respectively; $P=.46$). Although there was a trend toward improvement in OS with the combination therapy, the effect did not reach statistical significance (HR, 0.75, 95% CI, 0.53–1.07; $P=.106$). Patients in the combination arm were significantly more likely to experience diarrhea ($P=.03$). The data are consistent with results in the neoadjuvant setting, demonstrating a higher pathologic complete response with dual HER2 blockade strategies.

Novel Combinations With Endocrine Therapy

The TAMRAD (Tamoxifen and RAD001) trial, a randomized, controlled, phase II trial, randomized 111 patients with HER2-negative, hormone receptor-positive metastatic breast cancer to treatment with either tamoxifen alone or tamoxifen plus the mammalian target of rapamycin (mTOR) inhibitor everolimus.⁷ All patients had prior exposure to aromatase inhibitor therapy, and they were stratified according to the presence of primary versus secondary hormone resistance. The investigators reported that the rate of clinical benefit was significantly improved with the combination of everolimus plus tamoxifen compared with tamoxifen alone (61.1% vs 42.1%, respectively; $P=.045$ in an exploratory analysis). This trend in higher clinical benefit rate was evident across all patient subgroups analyzed, including those with or without visceral metastasis, those who had or had not received previous adjuvant tamoxifen, those who had or had not received prior metastatic chemotherapy, and those who were or were not hormone resistant. Interest-

ingly, those patients with secondary hormone resistance achieved a greater magnitude of clinical benefit. Patients receiving everolimus plus tamoxifen had an increased median time to progression (TTP) and median OS compared to patients receiving tamoxifen alone. TTP was 8.6 months in the combination group versus 4.5 months in the single-agent group (HR, 0.53, 95% CI, 0.35–0.81; $P=.0026$). Median OS was not reached in the combination group and was 24 months in the single-agent group (HR, 0.32; 95% CI, 0.15–0.68; $P=.0019$). Results of the 724-patient BOLERO-2 trial were released in September 2011, reporting a significant improvement in centrally reviewed PFS for patients receiving exemestane plus everolimus (10.6 months), compared to exemestane alone (4.1 months), after disease progression on a nonsteroidal aromatase inhibitor ($P<.01$).⁸

Clinical Trials for Metastatic Breast Cancer

The strategy underlying both basic and translational clinical research in the context of metastatic breast cancer is to optimize patients' lives. A great deal of energy has been expended in the recent past to identify a suitable surrogate marker for the elusive concept of improving quality of life. This search has led to the utilization of a variety of endpoints in both the phase II and phase III clinical trial settings. For some investigators and patients, what really matters is whether an improvement in OS can be demonstrated. For others, the finding of PFS may be most important. Even response rate is considered by some to be a measurable assessment of improvement.

There is some controversy related to which, if any, of these endpoints (OS, PFS, or response rate) should be the appropriate marker to assess when determining if a particular therapy should be incorporated into clinical practice. The general consensus is that many surrogate endpoints are important, and they all should be considered as an aggregate in order to change standards of clinical practice. However, it will remain important for physicians, patients, and regulatory agencies to continue working towards a "best definition" for clinical benefit in metastatic breast cancer. For phase III trials especially, studies are often developed based on a consensus of the best endpoint to utilize in that particular setting.

At the conclusion of a phase II or a phase III clinical trial, what is increasingly done is to assess these study endpoints (OS, PFS, and/or response rate) in the context of the overall tolerability of therapy. This approach is used to help determine whether a new agent or regimen has led to an improved life for the patient.

As we look at data from clinical trials, even if we determine that OS should be the primary endpoint for a decision to change standards of practice, it is important to realize that breast cancer is a very heterogeneous disease. Thus, even in the context of a controlled clinical trial that demonstrates a significant improvement in median OS,

there may be a substantial number of patients who do not derive any benefit. Conversely, even if a clinical trial fails to demonstrate a significant improvement in median OS in the experimental arm versus the control arm, it may still include patients who achieved improved OS.

One potentially interesting clinical endpoint to consider in future clinical trials is PFS, as defined according to a consensus of physicians, patients, and regulatory agencies. This idea raises the question of the most useful definition of PFS: Should it be defined as a relative improvement (ie, improvement of 15%, 25%, or 40% in the experimental arm vs the control arm) or as an improvement in the number of months (ie, improvement of at least 5 months)? There also may be other surrogate endpoints that may eventually be shown to correlate with patient outcomes, and it will be important to incorporate these endpoints into future clinical studies. Examples of these endpoints, which are currently in the investigational setting, include circulating tumor cells and molecular imaging.

Which Patients Should Receive Combination Therapy?

All of these issues are important to consider in the discussion of whether we should utilize single agents or combination therapy approaches for management of metastatic breast cancer patients. It is clear from multiple clinical studies that many combination therapies improve PFS, and some even improve OS, compared with single-agent therapy. However, it has yet to be determined in a prospective, randomized study whether single-agent therapy or combination regimens result in improved OS. Although current guidelines recommend either sequential single agents or combination therapy as the preferred chemotherapy strategy for metastatic breast cancer, they do not suggest that combination therapy is superior to the use of sequential single agents.¹

Based on the totality of data now available, it is becoming increasingly apparent that the optimum management of metastatic breast cancer in the future will have to rely on combination strategies that take advantage of the diverse molecular abnormalities that occur in these tumors. Although a single-agent strategy can be effective, it does not result in cures for all patients. Certainly, the combination strategies that we have so far have not led to cures in all patients either, but at least by detailing the molecular variability in breast cancer, we will be able to develop better combination strategies that will ultimately improve patient outcomes. A concise example is the use of concurrent chemotherapy or anti-estrogen therapy with anti-HER2 treatments, and the use of pertuzumab plus trastuzumab in combination with chemotherapy, based on the CLEOPATRA (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated Her2-Positive Metastatic Breast Cancer) trial, but much more work is ongoing.

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Clinical Implications of the Latest Data on Bevacizumab

Hope S. Rugo, MD

The targeting of tumor-related angiogenesis has been an important goal in antineoplastic therapy. This strategy was first initiated after promising preclinical observations, many in tumorigenic animal models, which suggested that new tumor blood vessel growth was promoted by factors within the tumor itself, and that this angiogenesis was associated with survival, progression, and metastasis of the tumor.

Targeting VEGF in Cancer

One of the primary molecules involved in angiogenesis that has been studied in the context of cancer is the vascular endothelial growth factor (VEGF). Many tumors (including breast cancers) have been found to overexpress VEGF,¹⁻³ and in fact VEGF overexpression is correlated with poor prognosis in breast cancer.^{4,5} In normal physiology, VEGF exerts its proangiogenic actions through binding to receptors located on the surface of endothelial cells.¹ Binding and subsequent activation of the VEGF receptor-mediated pathway has many consequences, including regulation of cell migration, proliferation, and survival; increase of vascular permeability; and regulation of hemodynamics. These activities are also regulated by VEGF in the context of the tumor, with the added role of inducing new blood vessel formation and penetration into the tumor leading to increased blood supply.

VEGF-mediated angiogenesis is an important component of tumor growth in both early and late stages of cancer

development.⁶ Expression of VEGF is a key factor in the “angiogenic switch” that occurs in avascular premalignant tumors, causing them to become vascularized and leading to subsequent tumor growth and promotion of vascular invasion. Later, as the tumor spreads, micrometastases are seeded at distant organs and undergo a similar angiogenic switch in order to initiate their own angiogenesis and tumor growth.⁷⁻⁸

A number of therapies have been developed that are designed to inhibit the actions of the VEGF-initiated pathway because of its importance in cancer survival, progression, and metastasis. These therapies include soluble decoy receptors (VEGF trap), small molecule inhibitors of the intracellular tyrosine kinase enzymatic portion of the VEGF receptor, and monoclonal antibodies directed against VEGF. The monoclonal antibody bevacizumab has been the most promising VEGF-targeted therapy. Based on positive results in clinical trials, bevacizumab was first approved by the US Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer⁹ and subsequently gained approval for use in other solid tumor malignancies, including non-small cell lung cancer, glioblastoma, and metastatic kidney cancer. The accelerated approval of bevacizumab for the treatment of metastatic breast cancer was recently called into question by the FDA, and the initial steps to remove this indication have begun.¹⁰ However, in light of this controversy, it is important to consider the original evidence supporting the use of bevacizumab in metastatic breast cancer, especially when interpreting results of more recent clinical trials leading to this controversy.

Throughout the clinical development of bevacizumab in metastatic breast cancer, it has become increasingly evident that the most effective use of anti-angiogenic therapy is likely to be in treating patients with a clearly defined tumor biology, or a specific patient population. In addition to early phase I and II data that suggested objective response rates approaching 10% in metastatic breast cancer patients previously treated with bevacizumab monotherapy,¹¹ data from several phase III clinical trials have now been reported.

Clinical Studies of Bevacizumab in Breast Cancer

The first phase III trial testing the efficacy of bevacizumab in metastatic breast cancer randomized 462 patients with chemotherapy-resistant disease to receive capecitabine with or without bevacizumab. The addition of bevacizumab resulted in an improvement in response rate (19.8% vs 9.1%; $P=.001$), but no difference in PFS (4.86 vs 4.17 months; HR, 0.98), which was the primary endpoint.¹² It was thought that perhaps the failure to show a benefit in PFS was due to the extent of prior treatment and resistance to therapy in this patient population, a question that could be answered by the highly anticipated results of E2100.

ECOG (Eastern Cooperative Oncology Group) E2100 was a pivotal open-label, randomized, phase III trial that tested the efficacy and safety of bevacizumab combined with paclitaxel as initial therapy for metastatic breast cancer.¹³ A total of 722 patients were randomized to receive either single-agent paclitaxel or paclitaxel combined with bevacizumab. Significantly, median PFS was prolonged in the combination arm compared with the single-agent arm (11.8 vs 5.9 months, respectively, HR, 0.60; $P<.001$), and the rate of objective response was also increased (36.9% vs 21.2%, respectively; $P<.001$). However, median overall survival (OS)—a secondary study endpoint—was not significantly different (26.7 vs 25.2 months, HR, 0.88; $P=.16$). Patients in the combination-therapy arm experienced significantly more grade 3/4 toxicities consistent with known bevacizumab effects, including hypertension (14.8% vs 0%; $P<.001$), proteinuria (3.6% vs 0%; $P<.001$), headache (2.2% vs 0%; $P=.008$), and cerebrovascular ischemia (1.9% vs 0%; $P=.02$).

Despite the lack of OS benefit, ECOG E2100 was used as a basis for the FDA accelerated approval of bevacizumab to treat metastatic breast cancer. However, interpretation of this trial was not without controversy; the most critical comments concerned the lack of external monitoring of this cooperative group-led trial. An FDA-mandated external review of the data supported the study's findings, but found missing data in a subset of patients. Further phase III trials were simultaneously conducted to verify and extend this dataset.

The AVADO (Avastin And Docetaxel) study was a randomized, double-blind, placebo-controlled, phase III

study that evaluated the combination of bevacizumab with docetaxel as initial therapy for HER2-negative metastatic breast cancer.¹⁴ In this 3-arm trial, 736 patients were randomized to receive docetaxel combined with either placebo or 1 of 2 bevacizumab doses (7.5 mg/kg or 15 mg/kg). In a stratified analysis, both bevacizumab doses combined with docetaxel achieved a significantly prolonged median PFS compared with docetaxel plus placebo. The magnitude of benefit was larger with the higher dose (9.0 months in the low-dose arm, 10.0 months in the high-dose arm, and 8.1 months in the placebo arms; HR, 0.80; $P=.045$ for the low-dose arm vs the placebo arm; HR, 0.67; $P<.001$ for the high-dose arm vs the placebo arm). The design of this trial included a specified number of doses of docetaxel and bevacizumab followed by bevacizumab alone to avoid cumulative toxicity; median progression occurred after discontinuation of chemotherapy. Again, although response rates were also increased with the bevacizumab plus docetaxel combinations compared with placebo plus docetaxel (55% for the low-dose arm, 64% for the high-dose arm, and 46% for the placebo arms; $P=.07$ for the low dose vs placebo; $P<.001$ for the high dose vs placebo), a significant improvement in OS was not observed. The toxicity profile of docetaxel was not significantly affected by the addition of bevacizumab.

The results of RIBBON-1 (Regimens in Bevacizumab for Breast Oncology), a double-blind, randomized, phase III trial, were recently published.¹⁵ In this study, bevacizumab was combined with several standard chemotherapy regimens and compared with these chemotherapy regimens alone as first-line therapy for patients with HER2-negative metastatic breast cancer. A total of 1,237 patients were randomized to receive chemotherapy alone (plus placebo) or chemotherapy plus bevacizumab; optional chemotherapy regimens included single-agent capecitabine, or taxane-based or anthracycline-based chemotherapy combinations. For data analysis, the investigators divided the patients into 2 independently powered cohorts, defined by the choice of chemotherapy: cohort 1 consisted of patients treated with capecitabine, and cohort 2 consisted of patients treated with taxane-based or anthracycline-based chemotherapy. In both cohorts, the median PFS was significantly prolonged with the addition of bevacizumab compared with the addition of placebo (cohort 1: 8.6 vs 5.7 months; HR, 0.69; 95% CI, 0.56–0.84; log-rank $P<.001$; cohort 2: 9.2 vs 8.0 months; HR, 0.64; 95% CI, 0.52–0.80; log-rank $P<.001$). Again, no significant improvements in OS were reported.

RIBBON-2 was a similarly designed phase III trial, which was identical to RIBBON-1 except that the addition of bevacizumab to chemotherapy was evaluated in the second-line treatment setting for metastatic breast cancer.¹⁶ Among 684 patients, the median PFS was significantly prolonged in the chemotherapy-plus-bevacizumab group compared with the placebo-plus-bevacizumab group (7.2 vs 5.1 months, HR, 0.775; $P=.0072$). No benefit in OS was reported.

Results from the ATHENA (Avastin Therapy for Advanced Breast Cancer) study were recently published.¹⁷ This large, multinational, open-label trial investigated bevacizumab plus taxane-based chemotherapy for the first-line treatment of locally recurrent or metastatic breast cancer. This study was thought to be more representative of general oncology practice than the previous randomized clinical trials. A total of 2,251 patients with HER2-negative disease were treated with bevacizumab plus taxane-based (or other nonanthracycline) chemotherapy. The median time to progression (TTP) in this study was 9.5 months (95% CI, 9.1–9.9).

Implications of the FDA Decision on Bevacizumab

In December 2010, the FDA announced that it had initiated a process to remove the metastatic breast cancer indication for bevacizumab. A first-of-its-kind public hearing was then conducted in June of 2011, with an independent review committee. Although the benefits in PFS and response observed in the ECOG E2100 trial were quite striking, the FDA consensus was that the PFS benefit in the subsequent phase III trials was not substantial enough to warrant continued approval of bevacizumab. This decision may have been somewhat influenced by the expense of bevacizumab. The increased toxicities reported with bevacizumab treatment in other malignancies as well as in breast cancer were also likely a consideration.

It is important to remember that the results of the bevacizumab phase III trials in metastatic breast cancer were positive, and they all reached their endpoint of PFS. What is really under consideration currently is the relative value of this PFS benefit. To date, many groups have continued to support the use of bevacizumab in the metastatic breast cancer setting, including the European Medicines Agency (in combination with paclitaxel only) and guidelines from the National Comprehensive Cancer Network (preferred in combination with paclitaxel).^{10,18}

Which Patients Will Benefit?

Based on the subset analyses that have been conducted to date, it is difficult to distinguish a specific subset of metastatic breast cancer patients that is likely to benefit more from bevacizumab therapy. It is possible that studies accounting for hormone receptor expression or HER2 expression are not adequate to define a subgroup of patients that will benefit. The ongoing ECOG 5103 adjuvant bevacizumab clinical trial, which has recently completed accrual, is aimed to more carefully evaluate this question. It is hoped that the trial will enable the identification of a group of patients, based on tumor biology, who could possibly benefit from bevacizumab-based therapy. A number of other trials are evaluating

the benefit of adding bevacizumab to chemotherapy in specific biologic tumor subsets, such as triple-negative disease, in the adjuvant or neoadjuvant setting.

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Discussion: Current Treatment Options for Metastatic Breast Cancer

Hope S. Rugo, MD, Joyce A. O'Shaughnessy, MD, and Edith A. Perez, MD

Hope S. Rugo, MD I am curious as to what the other 2 experts think of the current controversy surrounding bevacizumab use in metastatic breast cancer.

Joyce A. O'Shaughnessy, MD There is no question to me that bevacizumab offers a proportion of our patients a dramatic clinical benefit. It has a more moderate benefit in another segment of the patient population, and very little or no benefit in about one-third of patients. In general, it appears that those patients with the most aggressive disease derive the most benefit from bevacizumab treatment, and patients with the most indolent disease derive the least benefit. We as physicians have improved our ability over time to discern which patients are most likely to be harmed by bevacizumab therapy. A similar learning curve exists regarding those metastatic breast cancer patients whose tumor biology is most likely to be susceptible to bevacizumab therapy. Identification of these patients is not a trivial goal. It is much easier to identify patients likely to benefit from treatments such as endocrine therapies and trastuzumab or lapatinib, but in those cases we have the aid of hormone receptor expression and HER2 expression.

In my current practice, I try to first identify those patients who will most likely not benefit from bevacizumab therapy, and avoid it in these individuals. I do use bevacizumab as first-line treatment for triple-negative metastatic breast cancer; these patients have few alternatives to cytotoxic chemotherapy regimens. I also think that bevacizumab is useful in patients with particularly aggressive estrogen receptor–positive disease, characterized by very short disease-free intervals. Finally, I think that bevacizumab has a role in the treatment of patients with chemotherapy-resistant metastatic breast cancer. Although the benefit here may be short, it is greater than what would be achieved with chemotherapy alone.

Edith A. Perez, MD Interestingly, I think that the entire controversy regarding the use of bevacizumab to treat women with metastatic breast cancer has brought many important issues of drug development to light, including those surrounding translational research, clinical trial research, and accelerated approval of new agents by the FDA. In some ways, it is good that this debate is occurring, as I think it will guide future drug development and clinical trial design. Further, while the accelerated FDA approval process is an important mechanism to allow patients to benefit from a particularly promising agent, bevacizumab provides an excellent example of the importance of conducting follow-up trials to confirm efficacy and safety.

The scientific rationale for targeting angiogenesis in cancer is very strong and supported by robust preclinical data, and so it has been somewhat surprising to me that the results with anti-angiogenesis treatment in the clinical setting have been less than striking. It is becoming obvious that the interpretation of the bevacizumab clinical trials, all of which showed improvements in PFS but not OS, suggests that in the setting of metastatic breast cancer, relative improvement in PFS may not be a satisfactory threshold for drug approval, although this is still debatable.

Another important issue in the debate surrounding bevacizumab is cost versus benefit of therapy. Although regulatory agencies do not currently incorporate a cost-benefit analysis into approval decisions, there is no question that many physicians and health care professionals have begun to value relative (and statistically significant) improvements in PFS and OS in the context of therapeutic cost.

Hope S. Rugo, MD You have both brought up many good points regarding where we are currently with bevacizumab in metastatic breast cancer. Another major topic that has gained recent attention in the field of metastatic breast cancer is the use of PARP inhibitors. What is your interpretation of recent findings and how they may be used in patient management?

Joyce A. O'Shaughnessy, MD DNA repair pathways may be an important way for some tumor cells to resist treatment with cytotoxic chemotherapy. Poly(ADP)-ribose polymerase 1 (PARP-1)-mediated DNA repair pathways have emerged as an attractive target for drug development. These pathways are often used by tumor cells to repair chemotherapy-induced DNA damage, and inhibition of PARP-1 can prevent DNA repair. Normally, the BRCA1/BRCA2 proteins play an important role in overcoming PARP-1 inhibition. However, in the setting of BRCA1/BRCA2-deficient cells, DNA damage goes unrepaired and cell death ensues.

PARP inhibitors have been shown to be particularly potent in BRCA1/BRCA2-deficient cells. Importantly, triple-negative breast cancer shares many of the same characteristics of BRCA1/BRCA2-deficient breast tumors, including hormone receptor-negative/HER2-negative status, mutated p53, a basal-like gene expression pattern, and poorly differentiated (high-grade) tumor histology. Furthermore, many triple-negative breast tumors exhibit PARP1 upregulation and diminished expression of BRCA1.

One of the particular challenges regarding PARP inhibitors is the need to combine them with cytotoxic

chemotherapy in order for them to exert their effect. However, this combination strategy can result in higher toxicity, especially myelosuppression.

PARP inhibitors—iniparib, olaparib, and veliparib—have advanced in clinical trials; of these, iniparib has been developed the furthest. A recently published, randomized, phase II trial initially showed a significant improvement in clinical responses with the addition of iniparib to chemotherapy with gemcitabine plus carboplatin for patients with triple-negative metastatic breast cancer.¹ Median PFS and OS were also prolonged in this study. Based on these promising results, a similarly designed, randomized, phase III clinical trial of iniparib, also in triple-negative metastatic breast cancer, was initiated.² However, in a recent press release, the drug's manufacturers stated that iniparib failed to meet the prespecified criteria for significance in the primary endpoints of PFS and OS.³ No specific data have been provided, so it is not yet possible to closely scrutinize the results. The company did report that in a prespecified analysis, significant improvements in OS and PFS were noted among patients treated in the second- and third-line setting, suggesting that iniparib may still hold promise in heavily pretreated patients. The results of this study are expected to be presented in the near future.

A recent abstract presented by Ji and colleagues at the American Association for Cancer Research (AACR) annual meeting may offer an explanation for the less-than-dramatic results observed with iniparib in the phase III clinical trial.⁴ Through a series of elegant, cell line-based experiments, it was shown that olaparib and veliparib inhibited PARP1/2 in a dose- and time-dependent fashion, but iniparib did not. Furthermore, compared with olaparib, iniparib treatment of cells resulted in a dramatic difference in gene expression changes. Gene pathway analyses indicated that iniparib instead potentially inhibits the telomerase pathway. This abstract strongly suggests that iniparib has a unique mechanism of action.

Edith A. Perez, MD Again, the failure of iniparib in the phase III clinical trial, even though its design essentially mirrored that of the successful phase II study, demonstrates the challenge we have in translating preclinical and early clinical data to clinical practice. This is exactly why phase III clinical trials are so important—to confirm and corroborate a hypothesis suggested in the phase II setting. It is critical now more than ever that tissue samples be collected in clinical trials of new agents, in order to conduct the necessary sub-analyses to validate and optimize the findings in the clinic.

Hope S. Rugo, MD What agents do you think now hold the most promise for metastatic breast cancer?

Joyce A. O'Shaughnessy, MD I think the mammalian target of rapamycin (mTOR) inhibitors are particularly intriguing for metastatic breast cancer, especially with

potential for patients with endocrine resistance. Promising data have been demonstrated in the TAMRAD trial, showing that the addition of everolimus to tamoxifen resulted in significant improvement in outcomes versus tamoxifen alone for patients with HER2-negative, hormone receptor-positive metastatic breast cancer with previous aromatase inhibitor exposure.⁵ Results of the BOLERO-2 (Breast Cancer Trial of Oral Everolimus) trial, investigating the combination of everolimus with exemestane, are eagerly awaited.⁶

Edith A. Perez, MD I think one of the most exciting therapeutic candidates right now is the novel antibody-drug conjugate trastuzumab-DM1 (T-DM1). A recent report of a phase II trial of T-DM1 in metastatic breast cancer suggested that this agent may have similar activity but reduced toxicity compared with traditional trastuzumab.⁷

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Slide Library

Metastatic Breast Cancer

- Approximately 30% of breast cancer patients will subsequently develop metastatic disease¹
- Patients tend to be younger and to present with more locally advanced disease, although recurrence can occur at any age
- Approximately one-quarter of patients with lymph node-negative breast cancer and one-half with lymph node-positive breast cancer will ultimately develop distant, recurrent disease²
- Approximately 5% of women are not diagnosed until they have already developed metastatic breast cancer³

1. QIP Breast Cancer. Oncologist. 2009;14(10):1207-1211. 2. Heres DF. An overview of treatment for locally advanced, recurrent, and metastatic breast cancer. 2009. http://www.uptodate.com. 3. National Cancer Institute. SEER Stat Fact Sheets: Breast. http://seer.cancer.gov/factsheets/breast.html

Single-Agent Therapy: The FIRST Trial

Trial Design	Multicenter, randomized, open-label, phase II study comparing the efficacy and safety of the ER antagonist fulvestrant with anastrozole
Patient Population	205 postmenopausal women with previously untreated hormone receptor-positive locally advanced or metastatic breast cancer
Results	The median TTP was significantly prolonged in the fulvestrant arm compared with the anastrozole arm (23.4 vs 13.3 months, HR, 0.66, 95% CI, 0.47-0.92; P=.001)

Chowdhury M, et al. Breast Cancer (London, England). First Fulvestrant Post-Line Study With or Without Letrozole in Postmenopausal, Hormone Receptor-Positive, Locally Advanced or Metastatic Breast Cancer: Results of the First Randomized, Open-Label, Phase II Study. J Clin Oncol. 2009;27(12):2011-2017.

Single-Agent Therapy: Nab-Paclitaxel

Trial Design	Randomized, phase II trial comparing nab-paclitaxel (at 3 different dosages) and docetaxel
Patient Population	377 patients with first-line metastatic breast cancer
Results	Overall survival was 33.8 months in the 140 mg/m ² weekly nab-paclitaxel arm (n=94) and 25.6 months in the docetaxel arm (HR, 0.68, n=93). PFS was 14.5 months in the 140 mg/m ² weekly nab-paclitaxel arm and 7.8 months in the docetaxel arm (HR, 0.58; P<.01). Among patients in the 140 mg/m ² weekly nab-paclitaxel arm, the overall response rate was 74%, as compared with 39% in the docetaxel arm (P<.002).

PPH Progression Free Interval. Gosselin M, et al. J Clin Oncol. 2010;28(10):1667-1674.

Single-Agent Therapy: The EMBRACE Trial

Trial Design	An international, multicenter, open-label, randomized, phase III clinical trial comparing eribulin with treatment of physician's choice
Patient Population	764 patients with locally recurrent or metastatic breast cancer
Results	Median OS was significantly improved among patients who received eribulin compared with patients who received treatment of physician's choice (13.4 vs 10.5 months, respectively, HR, 0.81, 95% CI, 0.66-0.99; P=.002). In an independent review, no significant difference was observed in median PFS between the eribulin arm and the treatment of physician's choice arm (3.2 vs 2.8 months, respectively; HR, 0.87, 95% CI, 0.74-1.02; P=.137). However, the difference in PFS as assessed by study investigators was statistically significant (HR, 0.76, 95% CI, 0.64-0.90; P<.003).

Chowdhury M, et al. Breast Cancer (London, England). Eribulin Versus Physician's Choice in Locally Recurrent or Metastatic Breast Cancer: Results of the EMBRACE Trial. J Clin Oncol. 2010;28(10):1675-1682.

NCCN-Recommended Combination Chemotherapy Regimens for Metastatic Breast Cancer

Preferred Options Cyclophosphamide, doxorubicin, and fluorouracil Fluorouracil, epirubicin, and cyclophosphamide Doxorubicin plus cyclophosphamide Epirubicin plus cyclophosphamide Doxorubicin plus docetaxel or doxorubicin plus paclitaxel Cyclophosphamide, methotrexate, and fluorouracil Docetaxel plus capecitabine Gemcitabine plus paclitaxel	Other Options Isabaptine plus capecitabine Preferred Combination Options With Trastuzumab for HER2-Positive Disease Trastuzumab plus: Paclitaxel + carboplatin Docetaxel Vinorelbine Capecitabine Lapatinib plus* Trastuzumab plus* Other first-line agents Capecitabine Lapatinib
Preferred Combination Options With Bevacizumab Bevacizumab plus: Paclitaxel	

*Trastuzumab is not approved for use in combination with bevacizumab. National Comprehensive Cancer Network. Breast Cancer Clinical Practice Guidelines in Oncology. Version 1.2011.

Bevacizumab in Metastatic Breast Cancer

- In June 2011, an advisory committee to the US Food and Drug Administration concluded that bevacizumab should not be approved for use in metastatic breast cancer
- It has become increasingly evident that the most effective use of antiangiogenic therapy is likely to be in treating patients with a clearly defined tumor biology or a specific patient population

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