Breast cancer is the most common nondermatological malignant neoplasm in women, with an estimated 232,670 new diagnoses in 2014, and is the second leading cause of cancer death in women, with an estimated 40,000 women in the United States dying from the disease in 2014. Although often curable when localized to the breast and local lymph nodes, if the disease becomes metastatic it is usually not curable. Breast cancer is a heterogeneous disease comprising several molecular subtypes, which are commonly extrapolated into clinical subtypes based on receptor status. The specific receptors that are assessed in standard clinical practice are the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2-neu (HER2) receptor. These receptors are both prognostic but also predictive of response to targeted therapy; thus, when metastasis is suspected it is crucial to perform a biopsy not only to confirm recurrent disease, but also to confirm receptor status. In addition, tissue availability may increase clinical trial access because many studies now assess targetable molecular aberrations.

Considerable advances have been made in treatment of certain subtypes of breast cancer, for example, HER2-positive disease. In this subtype, targeted therapies against HER2 have changed the clinical outcome for patients with metastatic disease by providing them with several effective therapies that can extend survival by many years. The ER- and PR-positive subtypes also have several targeted therapies available using endocrine therapies; however, when the disease becomes metastatic, all patients eventually develop endocrine resistance and eventually require cytotoxic chemotherapy. Patients with ER-, PR-, and HER2-negative tumors, the so-called triple-negative breast cancers (TNBCs), biologically tend to display an aggressive phenotype, currently do not have targeted therapy options as a standard of care, and have only a limited amount of cytotoxic agents available to treat their disease. The current standard of care of these different subtypes of breast cancer is summarized in the Figure. This review narrates and expands on some of the recent efforts in drug development for metastatic breast cancer that were highlighted at the 37th Annual San Antonio Breast Cancer Symposium (SABCS) in December 2014.

Overcoming Endocrine Resistance

Some patients with early-stage ER-positive breast cancer have considerable residual risks of recurrence. While a recent study has determined that extending endocrine therapy to 10 years can modestly reduce the risk of recurrence, the risk persists indefinitely. The long periods of time that patients may experience between initial diagnosis of early-stage ER-positive breast cancer and time to recurrence may be due to tumor dormancy, a state where cancer cells are not actively proliferating. Several mechanisms have been suggested to explain tumor dormancy implicating cancer stem cells, as have elements in the microenvironment, such as angiogenic and immune factors. At the time of clinical recurrence, the tumor cells may be genetically different compared with tumor cells at the initial diagnosis. A study has found that metastatic ER-positive tumors harbor mutations in the ER that can drive ER-independent transcription and proliferation and reduce the efficacy of standard endocrine therapies. Aberrancies in downstream effectors of the ER, especially the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) signaling pathway, are also important mechanisms of resistance to endocrine therapy. As our understanding of resistance mechanisms has grown, so have our therapeutic strategies to deliver targeted therapy overcoming resistant pathways.
The PI3K-Akt-mTOR signaling pathway is a major intracellular signaling pathway playing a significant role in cell growth and proliferation, and it is implicated in resistance to endocrine therapy, HER2-directed therapy, and cytotoxic chemotherapy. The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study demonstrated that inhibiting mTOR with everolimus in combination with exemestane compared with exemestane alone, improved progression-free survival (PFS) in patients with ER-positive metastatic breast cancer previously treated with a nonsteroidal aromatase inhibitor (AI). However, a large phase 3 study found there was no survival benefit when temsirolimus was combined with letrozole in the first-line setting, demonstrating the importance of clinical setting in trial design. While the BOLERO-2 study combination has become a standard of care in patients whose disease has progressed after treatment with a nonsteroidal AI, it is unknown if everolimus has meaningful single-agent activity that could explain results. Furthermore, it is unknown if simply adding everolimus to existing hormone therapy is enough to overcome endocrine resistance, although studies are under way (NCT00912340).

There are multiple ongoing studies investigating blockade of the PI3K-Akt-mTOR pathway in patients using PI3K inhibitors as well (NCT01610284). The FERGI phase 2 study recently presented at the 2014 SABCS randomized 168 postmenopausal women with ER-positive metastatic breast cancer to fulvestrant with or without pictilisib. In the intention-to-treat (ITT) analysis, median PFS was improved from 3.8 to 6.2 months in the experimental arm (hazard ratio [HR], 0.77; 95% CI, 0.5-1.19). Although PI3K mutational status was assessed, it was not associated with an increased PFS in patients treated with pictilisib compared with placebo (6.2 vs 5.1 months, respectively; HR, 0.92; 95% CI, 0.48-1.76), albeit less than half of patients had a mutation (37 of 84 in the ITT population). Thus, while the FERGI study demonstrates the relevance of PI3K inhibition in breast cancer, it also highlights the difficulties in developing effective predictive biomarkers.

At a Glance

- Advances in treatment of endocrine receptor-positive cancers include combination aromatase inhibitor therapy with everolimus and palbociclib; many ongoing studies are investigating other mechanisms of overcoming endocrine resistance.
- The treatment repertoire for HER2-positive metastatic breast cancers includes trastuzumab, pertuzumab, lapatinib, and trastuzumab-emptansine; many more are in development.
- While nontargeted therapy is approved for triple-negative breast cancer, ongoing research is investigating targetable novel cell surface receptors, the use checkpoint inhibitors, and identifying subgroups likely to benefit from platinum-based therapies and poly(adenosine diphosphate-ribose) polymerase inhibitors.
- Integration of clinical trial participation in oncologic care is a critical element in the development of new treatment options for patients with advanced disease.

Another strategy used to overcome resistance to single-agent endocrine therapy has been to target the ER in different ways. Fulvestrant binds to the ER, causing its downregulation; thus, estradiol may compete for receptor site occupancy. Preclinical studies have suggested that the antitumor effects of fulvestrant can be increased in a low-estrogen environment, and studies in breast cancer xenografts have found the combination of an AI with fulvestrant to have synergistic antitumor effects. Combination endocrine therapy using AIs and fulvestrant in the metastatic setting have been studied in large randomized clinical trials with discordant results. The Southwest Oncology Group (SWOG) 0226 study demonstrated a median PFS of 13.5 months (95% CI, 12.1-15.1 months) for the anastrozole arm compared with 15 months (95% CI, 13.2-18.4 months) for the combination arm (HR, 0.8; 95% CI, 0.68-0.94; P = .007), with overall survival (OS) favoring the combination arm.

Figure. Schematic for Standard of Care Therapeutic Options for the Treatment of Metastatic Breast Cancer

- Aromatase inhibitor with or without palbociclib
- Tamoxifen
- Exemestane and everolimus
- Fulvestrant
- Other hormone
- Chemotherapy
- Taxane, trastuzumab, and pertuzumab
- TDM-1
- Lapatinib and chemotherapy
- Trastuzumab and chemotherapy

* Premenopausal women may receive regimens indicated for postmenopausal women if they are treated with ovarian ablation.
* Consideration of front-line therapy should be based on previous therapy received for early-stage disease.
* Palbociclib may be considered in the front-line setting in combination with letrozole.
* Chemotherapy may be considered at any point if a visceral crisis is suspected.
* Patients with ER/HER2-positive disease may be treated with either endocrine or HER2-targeted therapies alone or in combination as clinically indicated.
* In particular, endocrine therapy can be considered as monotherapy when patients have bone or soft-tissue disease or are asymptomatic.
* Preferred first-line regimen; patients treated without pertuzumab may receive it in combination with trastuzumab with or without chemotherapy as future-line therapy.
* Preferred second-line treatment for patients progressing on a trastuzumab-based regimen. TDM-1 indicates trastuzumab emtansine.
as well (HR, 0.81; 95% CI, 0.65-1.00; P = .049). However, subgroup analysis demonstrated that the benefit was restricted to patients who had not received prior tamoxifen (HR, 0.74; 95% CI, 0.59-0.92; P = .006) rather than those previously treated with tamoxifen (HR, 0.89; 95% CI, 0.69-1.15; P = .39).21 The Fulvestrant and Anastrozole Combination Therapy (FACT) study20 and the Study of Faslodex with or without concomitant Arimidex vs Exemestane following progression on nonsteroidal Aromatase inhibitors (SoFEA),19 on the other hand, showed no difference in median PFS. These results therefore have had limited applicability in clinical practice. However, neither the SWOG 0226 study nor the FACT study investigated fulvestrant alone as a control arm, although data from SoFEA suggest that fulvestrant vs exemestane were equivalent in patients whose disease was progressing during treatment with a non-steroidal AI (HR, 0.95; 95% CI, 0.79-1.14; P = .56). Notably, these studies used the 250-mg dose of fulvestrant, which has subsequently been shown to be inferior to the 500-mg dose in the Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) study, which is now the standard of care dose.22 In addition, in the front-line setting the Fulvestrant fiRst-line Study comparing endocrine Treatments (FIRST) suggests that 500 mg of fulvestrant compared with anastrozole may improve median time to progression (HR, 0.63; 95% CI, 0.39-1.0; P = .049), and recent update at the 2014 SABCS suggests a similar benefit in median OS (HR, 0.7; 95% CI, 0.5-0.98; P = .04). The results from a confirmatory phase 3 study are anticipated because these findings may ultimately affect clinical practice. (NCT01602380).23,24

A new strategy in treating patients with ER-positive breast cancer is to target cyclin-dependent kinases 4 and 6 (CDK4/6), a key pathway involved in regulation of the G1/S transition of the cell cycle. Preclinical studies combining tamoxifen with the CDK4/6 inhibitor, palbociclib, demonstrated synergistic antitumor effects, which led to a phase 2 study randomizing 165 women with ER-positive metastatic breast cancer to front-line letrozole alone or in combination with palbociclib. This study showed a significant difference in PFS between the letrozole arm (10.2 months; HR, 5.7-12.6 months) and the combination arm (20.2 months; 95% CI, 13.8-27.5 months) (HR, 0.488; 95% CI, 0.139-0.748; P < .001).25 These impressive results led to accelerated approval by the US Food and Drug Administration as the corresponding phase 3 study is anticipated, and palbociclib in combination with an AI is now an option for front-line therapy in postmenopausal patients with metastatic ER-positive breast cancer. Interestingly, part of the trial recruited patients with cyclin D1 (CCND1) and/or loss of p16; however, enriching for patients with these molecular abnormalities did not improve outcomes. While additional molecular correlative biomarkers are currently being studied, additional research will be needed to identify those most likely to benefit from this therapy.

Next-Generation Anti-HER2 Therapies

The development and approval of trastuzumab changed the treatment paradigm of HER2-positive breast cancer.26 Shortly thereafter, several drugs targeting HER2 were developed and approved, including lapatinib, pertuzumab, and trastuzumab emtansine (TDM-1), and these drugs are now considered a standard of care (Figure).27-29 Despite the important advances in developing these potent anti-HER2 therapies, these drugs are generally not curative in the metastatic setting, likely owing to several mechanisms of anti-HER2 therapy resistance. Preclinical and translational studies have helped elucidate several mechanisms of resistance, including loss of the trastuzumab epitope from the extracellular domain of HER2, activating HER2 mutations, loss of HER2 expression, and constitutive activation of downstream effectors, such as the phosphatase and tensin homologue (PTEN) and PI3K pathways.30-32

Drug development has focused on targeting several of these mechanisms of resistance. A small phase 2 study, investigating adding everolimus to paclitaxel and trastuzumab in women with HER2-positive breast cancer whose disease had progressed while they were treated with trastuzumab and who were previously treated with a taxane, found an overall response rate (ORR) of 21.8%, suggesting biologic activity with the addition of the mTOR inhibitor.33 At the 2014 SABCS Annual Meeting, however, the phase 3, double-blind, placebo-controlled randomized counterpart, the BOLERO-1 trial, did not show an improved PFS in HER2-positive patients, although the endocrine receptor negative subset did seem to have a benefit of 7.2 months in median PFS.34 The phase 3 BOLERO-3 trial investigated the addition of everolimus to trastuzumab and vinorelbine in women with metastatic HER2-positive breast cancer, and found a modest but significant improvement in PFS from 5.78 to 7.0 months (HR, 0.78; 95% CI, 0.65-0.95; P = .007), although at the cost of significant toxic effects (serious adverse events in 42% of the everolimus group compared with 20% of the control group).35 To date, no OS data are available in these studies, and these combinations are not considered to be a standard of care at this time. These studies demonstrate how translational science can inform clinical trial design and how biologic activity can translate into clinical efficacy; however, pharmacological specificity is crucial because off-target toxic effects hinder clinical applicability.

Next-generation tyrosine kinase inhibitors (TKIs) of HER2 are also being developed. The small molecule HER2 inhibitor, ONT-380, is being studied in 3 phase 1 studies in combination with other anti-HER2 therapies (NCT01921335, NCT01983501, and NCT02025192), and results are needed before moving forward with next-phase studies. Afatinib, an irreversible TKI of HER1 and HER2, has been studied in a phase 2 study in patients whose disease had progressed during treatment trastuzumab in the metastatic setting.36 That study found that 46% of patients had clinical benefit, suggesting antitumor effects. Another promising anti-HER2 TKI being developed is neratinib, an irreversible, pan-HER TKI. This drug has been tested in a phase 2 study in both trastuzumab-naïve and trastuzumab-treated patients with metastatic HER2-positive breast cancer with statistically significant response rates seen in both populations.37 Neratinib is currently being studied in combination with capecitabine compared with lapatinib with capecitabine in a large phase 3 study (NCT01808573). While it seems to be a promising agent that will expand the repertoire of anti-HER2 therapy, management of diarrhea will be critical to patient acceptance and clinical utility of this agent.

Antibody-drug conjugates are conceptually a very simple method of overcoming trastuzumab resistance, and one that has shown tremendous promise in patients with advanced HER2-positive breast cancers, particularly with the approval of TDM-1.29 Nanotechnology is being used in a similar manner to deliver cytotoxic drugs specifically to HER2-positive cells. MM-302, which is a...
HER2-targeted anthracycline-loaded nanoparticle, is currently under investigation in a multicenter phase 2 study in patients whose disease has progressed during treatment with trastuzumab and TDM-1 (NCT02213744). 38

HER2-positive breast cancer treatment is also a paradigm example of the importance of the immune system in breast cancer therapy. 49 In efforts of harnessing the immune system, HER2-targeted, bispecific antibodies have been developed, targeting both HER2 and immune cells. Preclinical studies have identified a trastuzumab-based, bispecific antibody, which activates T cells and binds HER2-positive cells and has significant antitumor effects in xenograft models. Interestingly, programmed death ligand-1 (PDL-1) was found to limit effect of this bispecific antibody; however, this resistance could be overcome by PDL-1 inhibition. 40 Ertuzumab, a bispecific antibody targeting HER2 and cluster of differentiation 3 (CD3), which also activates immune cells, has already been tested in a phase 1 study with one-third of patients having antitumor responses. 41

Targeting TNBC

Triple-negative breast cancer is more commonly seen in premenopausal and African American women and tends to have an aggressive phenotype with higher recurrence rates and lower survival rates. 42 To date, there are no approved therapies specifically for this subtype of breast cancer; however, many are in development.

The efficacy of platinum agents in TNBC seen in the neoadjuvant setting has made them attractive agents to consider in the metastatic setting. 42 A retrospective study 43 has shown that in patients with metastatic TNBC, platinum-based chemotherapy is associated with improved survival. The Triple-Negative Breast Cancer Trial (TNT), recently presented at the 2014 SABCS, randomized 376 unselected patients with metastatic TNBC to carboplatin vs docetaxel. In the overall analysis, median PFS was not statistically significant (P = .29; 3.1 vs 4.5 months for the carboplatin and docetaxel arms, respectively). However, for patients with breast cancer susceptibility gene (BRCA) germline mutations, the ORR for the carboplatin arm was more than double that of the docetaxel arm (ORR, 68.0 vs 33.3%; P = .03); homologous recombination deficiency (HRD) scores did not predict benefit. 44 Moving forward, it will also be important to delineate which patients are most likely to derive benefit from platinum-based therapy, and whether BRCA germline mutations or HRD biomarkers can predict who is most likely to benefit.

The effectiveness of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors has been of great interest in TNBC, especially in women with BRCA germline mutations. Iniparib, initially thought to be a PARP inhibitor, was studied in a phase 2 study in an unselected population of patients with metastatic TNBC and showed improved PFS (3.6-5.9 months) and OS (7.7-12.3 months), prompting a larger phase 3 study, which did not show improved PFS or OS. 45,46 Definitive preclinical studies afterward, however, demonstrated that in fact iniparib has weak, if any PARP, inhibitory effects. 47 While these studies almost put an end to developing PARP inhibitors in breast cancer, several agents, including olaparib and veliparib among many others, are now actively being developed. 48 Already, in women who have a BRCA germline mutation with metastatic ovarian cancer, the first PARP inhibitor, olaparib, has been approved based of a phase 2 study and compelling ORR. 49

The androgen receptor (AR) has been identified as a possible predictive biomarker for antiandrogen therapy in breast cancer. The Translational Breast Cancer Research Consortium (TBCRC) 011 study, 50 a phase 2 study investigating bicalutamide in AR-positive, ER-negative, breast cancer, found the clinical benefit rate (defined as complete or partial response, or stable disease for >6 months) to be 19% (95% CI, 7%-39%), suggesting antitumor effect despite only 12% of the 424 patients tested having AR positivity. Several other studies have since been launched evaluating enzalutamide in patients with AR-positive disease, and results are awaited (NCT01889238, NCT02091960).

Another strategy targeting TNBC is through the glycoprotein NMB (gpNMB), a transmembrane protein expressed in approximately 40% to 60% of breast cancers. A recent phase 1/2 study investigated a fully humanized anti-gpNMB monoclonal antibody conjugated to monomethyl auristatin in patients with metastatic breast cancer. Progression-free survival was particularly improved in gpNMB-positive and TNBC, and phase 2 studies are under way (NCT01997333). 51

New Directions in Targeting Angiogenesis

While numerous studies investigating 52 anti–vascular endothelial growth factor (VEGF) therapy in the neoadjuvant setting suggest improved pathologic complete response rates, especially in TNBC, studies to date 52 have not demonstrated a survival benefit in the adjuvant setting or metastatic setting. Multiple studies have now been conducted in unselected patients with metastatic breast cancer. The Eastern Cooperative Oncology Group (ECOG) 2100 study 53 found that adding bevacizumab to paclitaxel in unselected patients with metastatic breast cancer improved PFS (11.8 vs 5.9 months; HR, 0.60; P < .001) but not OS (26.7 vs 25.2 months; HR, 0.88; P = .16). The Regimens in Bevacizumab for Breast Oncology-1 (RIBBON-1) trial 54,55 showed that adding bevacizumab to chemotherapy in HER2-negative metastatic breast cancer also improved PFS but not OS in the first-line setting; the RIBBON-2 study had similar results in the second-line setting. Subgroup analysis, however, suggested that in patients with TNBC there may be a trend to OS benefit (HR, 0.624; 95% CI, 0.39-1.01; P = .05). The phase 3 IMELDA study randomized patients with HER2-negative metastatic breast cancer to bevacizumab with or without capecitabine after an induction of docetaxel and bevacizumab, and found that the addition of capecitabine improved PFS (11.9 vs 4.3 months; P < .001) and OS (39.0 vs 23.7 months; P = .003) despite premature termination of the study. 57 A recent update 58 at the 2014 SABCS meeting found no differences among different subgroups in terms of OS, and no significant changes in quality of life measures. These results are difficult to apply to clinical practice because there was no control arm investigating capecitabine without bevacizumab. The TANIA phase 3 study, an investigation of bevacizumab continuation through second-line therapy in patients with HER2-negative metastatic breast cancer, reported that PFS was improved in those continuing bevacizumab (6.3 vs 4.2 months; P = .007); however, OS has not been reported to date. 60 Recent subgroup analysis of the TANIA study presented at the 2014 SABCS meeting suggested a slight benefit in the TNBC populations (median PFS, 4.9 vs 2.1 months) and that plasma-based VEGF biomarkers did not predict efficacy. 61,62 The fact there are no data suggesting an
Promises of Immune Therapies

The immune system can identify tumor antigens through immunosurveillance, a process in which antigen-presenting cells present non-self-antigens to T cells, allowing them to recognize and destroy cells expressing such antigens. A hallmark of oncogenesis is that tumor cells can develop mechanisms to evade such immune recognition. The success of immune checkpoint blockade in certain cancers has served as proof-of-concept that immune therapy is a viable therapeutic strategy. Cytotoxic T-lymphocyte antigen (CTLA) inhibitors have shown significant and sustained antitumor activity in melanoma. Blockade of the programmed cell death 1 (PD-1) and PD-L1 has also been found to have antitumor activity in certain cancers, with 6% to 17% overall response rates. The effects of single-agent checkpoint blockade are modest, with only a small fraction of patients having clinically significant responses; however, recently combination checkpoint blockade with CTLA and PD-L1 inhibitors has demonstrated synergistic activity with an ORR of 40%, and 31% of patients achieving greater than 80% reduction in their tumors by 12 weeks. These results suggest that combination immune therapy may improve antitumor responses.

Approximately 20% of TNBCs express PD-L1, and expression of PD-L1 is associated with poor prognosis in patients with breast cancer, particularly those with luminal B and basal-like subtypes, thus making aggressive phenotype ER-positive and TNBC attractive subtypes in which to investigate PD-L1 blockade. A recent early-phase study presented at the 2014 SABCS meeting demonstrated clinical activity of the anti-PD-L1 monoclonal antibody, pembrolizumab, in patients with heavily treated TNBC. Numerous studies are currently being launched investigating immune checkpoint blockade in breast cancer (NCT02129556, NCT02303366, NCT02309177).

Expanding Treatment Options

As patients progress through standard of care therapy, expanding their treatment options through clinical trials is a vital component of modern clinical oncology. Clinical trials have greatly improved cancer outcomes; however, accrual nationwide is generally low. Many factors weigh into low accrual, including trials available, sufficient clinical research staffing, and low accrual of minority populations. Accrual of patients with metastatic breast cancer to early-phase trials is particularly low, despite data suggesting patients with metastatic TNBC enrolling in phase 1 trials may have improved survival outcomes.

Advances in tumor genetics have changed the landscape of how we treat breast cancer, and identifying targetable mutations may help select which drugs are more likely to have efficacy in specific intrinsic tumor types. As next-generation sequencing techniques are made more accessible, it is important to learn how to use these in clinical practice, especially in consideration of clinical trial eligibility and expanding therapeutic options. However, the wealth of information obtained by these tests many times has little or no clinical use in treatment decision making, either because there are no drugs available (either approved or in clinical trial) to target certain mutations, or logistical aspects of ordering the test in a timely manner Therefore, identifying the correct clinical setting is crucial when considering tumor genomic profiling.

Conclusions

An understanding of the biology of breast cancer has led to important advances in developing targeted therapies; however, metastatic breast cancer still remains an incurable disease for most patients. Targeted combination therapies are needed to eradicate certain bacterial and viral infections, such as tuberculosis and human immunodeficiency virus, and this may be an important historical lesson as we develop therapies for cancer. As we learn to use genomic medicine and harness the immune system to guide drug development, it is important to start combining drugs using biologically informed translational science to optimize patient outcomes.


