Moving beyond the one-size-fits-all formula for breast cancer treatments

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Major advances in the understanding of breast cancer biology have led to new treatment options that have dramatically improved the prognosis for breast cancer patients in the past few decades. Yet, breast cancer remains a significant health problem; in 2011 it was estimated that about 2.9 million women were living with breast cancer in the United States and median survival in the metastatic setting is only 2 years. Thus, the development of new and effective treatment options remains a priority. Here, we discuss the most significant advances in recent years that are changing oncology practice today and for the future.

New agents for HER2-positive disease

After the identification of the human epidermal growth factor receptor 2 (HER2) pathway and its dysfunction in cancer, a significant focus of breast cancer research has been in HER2-positive (HER2+) disease, which accounts for about one-fifth of all breast cancers. There has been particular success in the development of targeted agents, beginning with the much lauded approval of the anti-HER2 monoclonal antibody (mAb) trastuzumab in 1998.

Since then, drug development in HER2+ disease has become an increasingly dynamic area on the forefront of breast cancer drug development, with a number of approvals in recent years (Table 1; Figure 1). Over the past decade a near doubling of overall survival (OS) in patients with metastatic HER2+ breast cancer has been achieved, primarily owing to the development of new agents, such as a second anti-HER2 mAb, pertuzumab, and an antibody–drug conjugate, ado-trastuzumab emtansine, as well as combination strategies with existing agents, such as anti-HER2 mAbs and anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).

Ado-trastuzumab emtansine (T-DM1) is an antibody–drug conjugate (ADC) that was approved by the US Food and Drug Administration (FDA) in 2013 for the treatment of HER2+ disease. ADCs essentially act as targeted chemotherapy, combining the specificity of mAbs with the potent cell-killing activity of chemotherapy by conjugating a mAb to a cytotoxic agent in a single drug. Until recently, only 2 ADCs had been approved, both for use in hematologic malignancies. T-DM1, comprised of trastuzumab conjugated to the microtubule-inhibiting agent DM-1, is the first ADC to be approved for use in solid tumors.[1]

The approval of T-DM1 was based on the phase 3 EMILIA trial in which T-DM1 was compared with the EGFR TKI lapatinib in combination with capecitabine. All of the results favored T-DM1; median progression-free survival (PFS) was 9.6 months versus 6.4 months, respectively, and median OS was 30.9 months versus 25.1 months. A number of phase 3 trials of T-DM1 are ongoing (Table 2), investigating the drug's potential in a variety of different combinations and determining where in the sequence of treatment it will prove most valuable.[1,2] The first results from the TH3RESA trial, comparing T-DM1 with physician's choice, were presented at the 2013 European Cancer Congress and indicated a significant improvement in PFS (6.2 months vs 3.3 months, respectively). Median OS had not yet been reached for T-DM1 and was 14.9 months for physician's choice.[3]

Another significant area of research in HER2+ disease has been combination therapy, particularly in light of the approval of pertuzumab. Because pertuzumab and trastuzumab target different parts of the HER2 receptor, it is believed that they might offer complementary activity. The combination of pertuzumab, trastuzumab, and docetaxel has been evaluated in the phase 3 CLEOPATRA study. Median PFS was 18.5 months, compared with 12.4 months in the control group, which received placebo plus trastuzumab plus docetaxel. Based on these findings, the combination has been approved by the FDA and has become standard of care in newly diagnosed HER2+ patients with metastatic breast cancer.[5,6]

Combinations of HER2-targeting mAbs with TKIs that target the EGFR, another member of this receptor family, are also being heavily investigated.

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TABLE 1 FDA-approved HER2-targeting therapies

Agent (brand name)	Sponsor	FDA-approved indication(s)
Trastuzumab (Herceptin)	Genentech	▪ In patients with HER2+ MBC as first-line therapy in combination with paclitaxel or as single-agent therapy for patients who have received 1 or more chemotherapy regimens ▪ In patients with HER2+, locally advanced, inflammatory or early-stage BC in combination with trastuzumab and docetaxel as neoadjuvant therapy
Lapatinib (Tykerb)	GlaxoSmithKline	▪ In patients with HER2+ advanced breast cancer or MBC in combination with capecitabine after prior therapy including trastuzumab ▪ In postmenopausal women with HER2+/HR+ MBC in combination with letrozole
Pertuzumab (Perjeta)	Genentech	▪ In patients with HER2+ MBC who have had no prior anti-HER2 or chemotherapy in combination with trastuzumab and docetaxel ▪ In patients with HER2+, node-positive or node-negative advanced breast cancer as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel, with docetaxel and carboplatin, or as a single agent following multimodality anthracycline-based therapy
Ado-trastuzumab emtansine (Kadcyla)	Genentech	▪ In patients with HER2+ MBC as a single agent after prior trastuzumab and taxane-based therapy for metastatic disease or development of disease recurrence within 6 months of completing adjuvant therapy

FDA, US Food and Drug Administration; HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor-positive; MBC, metastatic breast cancer

The combination of lapatinib with trastuzumab or pertuzumab initially seemed promising, but recent results presented at the 2014 annual meeting of the American Society of Clinical Oncology (ASCO) suggested that the combination was not superior to trastuzumab monotherapy in either the adjuvant or neoadjuvant settings and resulted in an increased risk of adverse events (AEs).[5,7]

Hormone therapy: aromatase inhibitors outperform tamoxifen

About 70% of breast cancers express estrogen receptors (ER) and their uncontrolled growth can be stimulated by estrogen produced primarily by the ovaries in premenopausal women and by other tissues, including the adipose tissue and skin, in both pre- and postmenopausal women.

TABLE 2 Ongoing phase 3 clinical trials of T-DM1

Trial name (clinicaltrials.gov identifier)	Description
MARIANNE (NCT01120184)	T-DM1 with or without pertuzumab vs trastuzumab and a taxane
TH3RESA (NCT01419197)	T-DM1 vs physician's choice
KATHERINE (NCT01772472)	T-DM1 vs trastuzumab for women with residual tumor
NCT01966471	T-DM1 and pertuzumab vs trastuzumab, pertuzumab and a taxane following anthracyclines as adjuvant therapy
NCT02311064	T-DM1 and pertuzumab vs chemotherapy, trastuzumab and pertuzumab
NCT02144012	T-DM1 vs trastzumab and docetaxel
NCT01702571	T-DM1 in patients with HER2+ breast cancer who have received prior anti-HER2 and chemotherapy-based treatment

T-DM1, ado-trastuzumab emtansine; HER2+, human epidermal growth factor receptor 2-positive

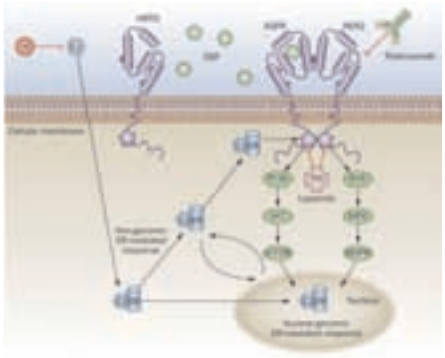

FIGURE 1 Key targeted therapies in HER2+ and ER+ breast cancer. Key targets for practice-changing therapies that have been developed for the treatment of HER2+ and ER+ breast cancers. AIs such as exemestane and letrozole inhibit the generation of estrogen, tamoxifen inhibits the action of the ER, and mTOR inhibitors such as everolimus inhibit its kinase activity and may have an important role in patients that develop resistance to both HER2-targeted and hormonal therapies. A number of HER2-targeted agents have been developed since the initial approval of the monoclonal antibody trastuzumab, including a second antibody pertuzumab, an antibody-drug conjugate T-DM1 and TKIs such as the dual inhibitor of HER2 and epidermal growth factor receptor, lapatinib. (Reproduced with permission. Originally adapted from Cortes J, Saura C, Bellet M, et al. HER2 and hormone receptor-positive breast cancer – blocking the right target. Nat Rev Clin Oncol. 2011;8:307-311.]

AI, aromatase inhibitors; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; T-DM1, ado-trastuzumab emtansine; TKI, tyroskine kinase inhibitors

As a result, hormone therapy, which involves the use of drugs that block the production of hormones or prevent their action on hormone receptors, is the principal treatment for patients with estrogen receptor-positive (ER+) breast cancer, both in the early and advanced stages of the disease. The selective ER modulator tamoxifen alone or in combination with ovarian function suppression has become the standard of care for adjuvant hormonal therapy in ER+ patients.[8]

A more recent addition to hormonal therapy are the aromatase inhibitors (AIs), which work by blocking the activity of the enzyme aromatase that converts androgens into estrogens, thereby resulting in a rapid decrease in circulating estrogen levels. A number of AIs have been developed, but the third-generation agents anastrozole and letrozole (nonsteroidal inhibitors) and exemestane (an irreversible steroidal inhibitor) are the most potent.[9-11]

The efficacy of AIs in comparison with tamoxifen in ER+ postmenopausal women with breast cancer has been evaluated in 7 major studies (Table 3) and although there is no difference in efficacy among the 3 third-generation AIs, all of them show consistent superiority to tamoxifen.10 As a result, these agents have become standard adjuvant endocrine therapy for postmenopausal women with ER+ breast cancer in recent years and in 2010, the ASCO released a practice guideline recommending the use of AIs at some point during adjuvant hormonal therapy.[19]

A number of these trials also examined the comparative efficacy of AI monotherapy and sequential treatment with an AI for 2-3 years followed by tamoxifen for 2-3 years for a total of 5 years. Both strategies were found to be equally effective and both were superior to tamoxifen monotherapy.[10]

An important question that has yet to be answered is the optimal duration of hormonal therapy. The ATLAS study showed that 10 years of tamoxifen is superior to 5 years, and other study findings suggest that extending the duration of AI therapy may also be beneficial.20 Several ongoing trials (eg, MA.17 extension trial [NCT00754845] and NSABP B-42 trial [NCT00382070]) are evaluating the use of extended AI or tamoxifen therapy, as well as the effects of adding an AI after 5 years of tamoxifen (eg, MA-17 trial [NCT00003140] and ABCSG-6a trial [NCT00300508]).9,10 The use of AIs is also being evaluated in the neoadjuvant setting; letrozole has been shown to be superior to tamoxifen, while there is no difference between anastrozole and tamoxifen and the relative efficacy of exemestane compared with tamoxifen in this setting remains unclear.[9,10]

Although AIs have primarily been used in postmenopausal women because they require lower estrogen levels, their success in this setting has prompted their evalua-

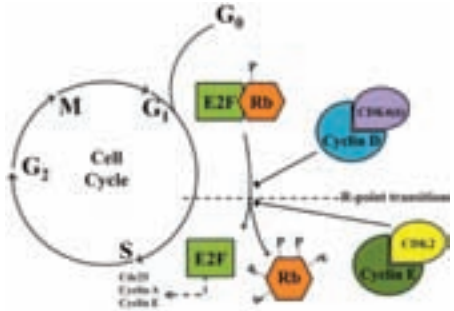

FIGURE 2 Role of cyclin D-dependent kinases 4 and 6 in the cell cycle. The cyclin D-dependent kinases, CDK4 and CDK6, are the primary regulators of the transition G1 to S phase, the restriction point, or R-point, at which the cell commits to entering the cell cycle. CDK4 and CDK6 are activated by cyclin D and subsequently phosphorylate the pRb, among other targets. Phosphorylation of pRB removes its repressive activity on the E2F transcription factors and allows activation of E2F target genes, including many that drive the G1/S transition. (Used with permission. From Biggar KK, Storey KB. Perspectives in cell cycle regulation: lessons from an anorexic vertebrate. Curr Genomics. 2009;10:573-584.)

pRb, retinoblastoma protein

TABLE 3 Key phase 3 trials comparing third-generation AIs and tamoxifen in postmenopausal women with breast cancer

Trial name (clinicaltrials.gov identifier)	Description	Results
ATAC (NCT00849030)	Anastrozole vs tamoxifen alone and in combination as adjuvant treatment in postmenopausal women with breast cancer	Demonstrated superiority of anastrozole as initial adjuvant treatment for postmenopausal women with hormone-sensitive, early breast cancer[12]
BIG 1-98 (NCT00004205)	Letrozole vs tamoxifen as adjuvant therapy in postmenopausal women with breast cancer	Demonstrated superiority of letrozole monotherapy over tamoxifen monotherapy, but no benefit from sequential treatments involving tamoxifen and letrozole compared with letrozole monotherapy[13]
ABCSG-8 (NCT00291759)	Primary treatment with tamoxifen for 2 years followed by randomization to tamoxifen or anastrozole for further 3 years as adjuvant endocrine therapy in postmenopausal women with breast cancer	Demonstrated a small outcome and toxicity benefit to sequence strategy of 2 years of tamoxifen followed by 3 years of anastrozole[14]
ARNO95 (NCT00287534)	3 years of anastrozole following 2 years of tamoxifen vs 5 years of tamoxifen in postmenopausal women with early breast cancer	Demonstrated a reduction in the risk of recurrence and improved OS in patients who switched to anastrozole after 2 years of tamoxifen compared with those who continued on tamoxifen[15]
ITA (NCT00286117)	Comparison of anastrozole vs tamoxifen as adjuvant therapy in postmenopausal women with breast cancer already being treated with tamoxifen for at least 2 years	Demonstrated safety and long-term improvement in RFS and EFS following switch from tamoxifen to anastrozole after 2 years of tamoxifen treatment[16]
IES (NCT00038467)	Comparison of sequential administration of exemestane with administration of further tamoxifen until 5 years in postmenopausal women with breast cancer who have already received 2-3 years of adjuvant tamoxifen	Demonstrated a reduction in risk of relapse or death and OS benefit following switch to anastrozole vs continuing therapy with tamoxifen[17]
TEAM (NCT00036270)	Comparison of exemestane for 5 years vs tamoxifen and exemestane given sequentially over 5 years in the adjuvant treatment of postmenopausal women with breast cancer	Demonstrated equal efficacy of exemestane given alone and in combination with tamoxifen[18]

EFS, event-free survival; OS, overall survival; RFS, regression-free survival

tion in premenopausal women in combination with ovarian function suppression (OFS), which mimics the lower estrogen environment of postmenopausal women.

The current standard adjuvant therapy for premenopausal women with ER+ breast cancer is tamoxifen and OFS or tamoxifen alone and these regimens have been compared with an AI and OFS in a number of phase 1 and 2 studies. Two large phase 3 trials (TEXT [NCT00066703] and SOFT [NCT00066690]) are ongoing, both evaluating the combination of exemestane and OFS.[11]

A joint analysis of these trials was recently presented at the 2014 ASCO annual meeting involving almost 5,000

TABLE 4 Key phase 3 trials of mTOR inhibitors in breast cancer

Agent (brand name)	Sponsor	Trial	Description (clinicaltrials.gov identifier)
Everolimus (Afinitor)	Novartis	BOLERO-1	Everolimus in combination with trastuzumab and paclitaxel in the treatment of HER2+, locally advanced or MBC (NCT00876395)
		BOLERO-2	Everolimus in combination with exemestane in postmenopausal women with ER+, locally advanced or metastatic breast cancer who are refractory to AIs (NCT00863655)
		BOLERO-3	Everolimus in combination with trastuzumab and vinorelbine in HER2+ women with locally advanced or metastatic BC (NCT01007942)
		S1222	Fulvestrant alone vs fulvestrant and everolimus vs fulvestrant, everolimus and anastrozole in postmenopausal women with stage IV BC (NCT02137837)
Temsirolimus (Torisel)	Pfizer	HORIZON	Temsirolimus in combination with letrozole in patients with HR+ BC (NCT00083993; terminated)

ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor-positive; MBC, metastatic breast cancer

premenopausal women with ER+ breast cancer. Over a median follow-up period of 5.7 years, there was a higher disease-free survival (DFS) rate for the exemestane arm than for the tamoxifen arm (91.1% vs 87.3%, respectively). There was a reduction of 34% in the risk of breast cancer recurrence and of 28% in the risk of having invasive disease in the exemestane arm. OS was also higher in the study group, although this was not statistically significant – the survival data are not yet mature. Studies are also underway in the neoadjuvant setting.[21]

mTOR inhibitors: outsmarting resistant tumors

Despite the success of endocrine therapy in ER+ breast cancers, not all ER+ tumors are sensitive to endocrine therapy, and some tumors that do initially respond to the therapy, eventually develop resistance. The development of acquired resistance is an important issue for most targeted therapies, and researchers have sought to understand the molecular mechanisms that drive it. Multiple mechanisms of acquired resistance to endocrine therapy have been described and among them is the activation of the mammalian target of

TABLE 5 Key phase 3 trials of CDK inhibitors in breast cancer

Agent (brand name)	Sponsor	Trial name (clinicaltrials.gov identifier)	Description
Palbociclib (PD0332991)	Pfizer	PEARL (NCT02028507)	Palbociclib plus exemestane vs chemotherapy in HR+/HER2- patients with MBC
		PALOMA-2 (NCT01740427)	Palbociclib plus letrozole vs letrozole alone for postmenopausal women with ER+/HER2- advanced breast cancer
		PALOMA-3 (NCT01864746)	Palbociclib plus fulvestrant in HR+/HER2- advanced breast cancer
		PENELOPE-B (NCT01958021)	Palbociclib plus standard endocrine treatment in HR+/HER2- patients with residual disease after neaodjuvant chemotherapy and surgery
Bemaciclib (LEE011)	Novartis	MONALEESA-2	Bemaciclib plus letrozole vs letrozole alone in HR+/HER2- advanced breast cancer
LY2835219	Eli Lilly	NCT02107703	LY2835219 plus fulvestrant in HR+/HER2- breast cancer

HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor 2-negative; MBC, metastatic breast cancer

rapamycin (mTOR) protein, a serine–threonine kinase that acts downstream of numerous signaling pathways and is a central regulator of cell growth and proliferation.[22]

Several mTOR inhibitors have been developed and have been evaluated in combination with endocrine therapy in breast cancer. Consistent efficacy of everolimus has been reported in a number of trials in combination with letrozole, tamoxifen, and exemestane. For example, the phase 3 BOLERO-2 trial demonstrated improved PFS for the combination of everolimus and exemestane compared with exemestane and placebo (7.8 months vs 3.2 months, respectively) at a median follow-up of 18 months. As a result of those findings, the combination was approved by the FDA in 2012 for the treatment of patients with advanced ER+/HER2-negative breast cancer after failure of an AI.23 The role of everolimus in premenopausal women and endocrine-sensitive patients has yet to be established and, as such, a number of trials are underway (Table 4).

Common mechanisms of resistance to trastuzumab are loss of phosphatase and tensin homolog (PTEN) expression and mutation in the phosphatidylinositol-3-kinase (PI3K) gene, both of which activate mTOR. Therefore, it has been suggested that mTOR inhibition may also help to overcome trastuzumab resistance and mTOR inhibitors are being evaluated in patients with HER2+ breast cancer (eg, BOLERO-3; Table 4).[24-26]

Targeting the cell cycle: CDK inhibitors

Cyclin-dependent kinases (CDKs) act as gatekeepers of the cell cycle, regulating the transition between the different phases (Figure 2). The CDKs and the cyclins that regulate their activity are often dysregulated in cancer; cyclin D1, which regulates the activity of CDK4 and CDK6, is overexpressed in 50% of breast cancers. Experimental breast cancer models established an oncogenic role for cyclinD1/CDK4/CDK6 and suggested that these proteins may be involved in the development of resistance to hormonal therapy.[27-30]

Thus, the development of CDK inhibitors as breast cancer therapeutics has been pursued, focusing on CDK4/6. Several of these agents have reached advanced stages of clinical testing (Table 5), in particular in hormone receptor-positive (HR+) disease in combination with hormonal therapy. The results of several trials were recently presented at the 2014 annual meeting of the American Association for Cancer Research (AACR).

In the phase 2 PALOMA-1 study, the combination of palbociclib and letrozole compared with letrozole alone was evaluated in postmenopausal women with HR+/HER2-, locally advanced breast cancer. The combination demonstrated a near-doubling of PFS (20.2 vs 10.2 months, respectively), in addition to superiority in the duration of treatment and clinical benefit rate. This combination received a breakthrough therapy designation from the FDA in 2013. A phase 1 study of LY2835219 was also presented at the AACR meeting, and the agent showed durable monotherapy activity, particularly in patients with HR+ disease.[31,32]

A deeper understanding of the biology underlying the development of breast cancer and resistance to targeted therapies has led to the development of new treatment strategies in recent years. Long-gone are the days of a one-size-fits-all approach to breast cancer therapy, and the expansion of our armamentarium is bringing us closer to the goal of individualized therapies that more specifically address the needs of the patient.

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