New Strategies in Estrogen Receptor–Positive Breast Cancer

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Abstract

Endocrine therapy has led to a significant improvement in outcomes for women with estrogen receptor–positive (ER+) breast cancer. Current questions in the adjuvant setting include the optimal duration of endocrine therapy, and the accurate molecular prediction of endocrine responsiveness using gene array–based assays compared with ER expression itself. In advanced disease, novel selective estrogen receptor antagonists (SERM) have failed to make an impact, although the pure ER antagonist fulvestrant may have a role, albeit optimal dose and sequence remain unclear. Overcoming de novo or acquired endocrine resistance remains critical to enhancing further the benefit of existing endocrine therapies. Recent progress has been made in understanding the molecular biology associated with acquired endocrine resistance, including adaptive “cross-talk” between ER and peptide growth factor receptor pathways such as epidermal growth factor receptor (EGFR)/human epidermal growth factor receptor 2 (HER2). Future strategies that are being evaluated include combining endocrine therapy with inhibitors of growth factor receptors or downstream signaling pathways, to treat or prevent critical resistance pathways that become operative in ER+ tumors. Preclinical experiments have provided great promise for this approach, although clinical data remain mixed. Enriching trial recruitment by molecular profiling of different ER+ subtypes will become increasingly important to maximize additional benefit that new agents may bring to current endocrine therapies for breast cancer.

Background

Currently available endocrine strategies for the treatment of estrogen receptor (ER)-positive (ER+) breast cancer include targeting the ER itself with the anti-estrogen tamoxifen, or suppressing the amount of available ligand (estrogen) for the receptor either with gonadal suppression in premenopausal women (ovariectomy or luteinizing hormone-releasing hormone agonists), or with aromatase inhibitors in postmenopausal women. Given their proven efficacy and generally favorable side effect profile, these endocrine therapies are widely used in the treatment of both early-stage and recurrent and/or metastatic breast cancer (1). Unfortunately, despite documented levels of ER in breast cancer, not all patients respond to first line endocrine treatment (de novo resistance), whereas others will eventually relapse despite an initial response (acquired resistance; ref. 2). In the last two decades there have been major efforts to understand the various biological mechanisms responsible for the development of endocrine resistance, with the ultimate aim of identifying new therapeutic strategies to enhance the efficacy of current treatment strategies for hormone receptor-positive breast cancer (3, 4). This article will review the current issues relating to the diagnosis and treatment of ER breast cancer, and then outline future strategies on the horizon that are being developed to further enhance the benefit of existing endocrine therapies.

Current Diagnosis and Treatment Strategies for ER+ Breast Cancer

Early breast cancer. In patients with early stage ER+ breast cancer, adjuvant endocrine therapy given for 5 years after primary surgery delays local and distant relapse, and prolongs overall survival (1). It also substantially reduces the incidence of contra-lateral breast cancer in patients with primary breast cancer by about 50%. Although tamoxifen has been a previous standard of care for postmenopausal women, current evidence suggests that aromatase inhibitor (AI) therapy provides added benefit both in terms of improving disease-free survival, and providing a different tolerability profile to long-term tamoxifen therapy. Clinical practice uses either up-front AI therapy for 5 years on the basis of clinical data from the ATAC study with anastrozole (5) and the BIG1-98 study with letrozole (6), or a switch strategy consisting of 2 to 3 years tamoxifen followed by 2 to 3 years of AI therapy as in the IES trial with exemestane (7). Likewise the reverse sequence...
of an AI followed by tamoxifen is as effective as an AI, as shown in BIG1-98 (6). For premenopausal women with ER+ breast cancer, tamoxifen remains the standard of care, whereas the additional role of ovarian ablation in addition to tamoxifen is still being investigated in ongoing prospective clinical trials.

The most unanswered clinical question relates to the optimal duration of endocrine therapy in the adjuvant setting; it is increasingly recognized that for women with ER+ disease the hazard ratio for recurrence remains elevated for a significant number of years beyond the 5-year time point, and extended adjuvant therapy between years 5 to 10 with the AI letrozole following 5 years of tamoxifen significantly reduced risk of recurrence and improved overall survival in those at greatest risk (i.e., node-positive disease) compared with 5 years of tamoxifen alone (8). Ongoing studies are continuing to assess the optimal duration of endocrine therapy, and what the long-term safety of AI therapy is in terms of bone loss, arthralgias, and cognitive effects. Clear consensus guidelines now exist to measure and monitor bone density by dual X-ray absorptiometry (DEXA), with appropriate management of osteopenia and/or osteoporosis with bisphosphonates (9). Until further long-term safety and efficacy data are available, in postmenopausal women a minimum of 5 years therapy that includes an AI is deemed appropriate for most patients, with the choice of an upfront AI or a tamoxifen-AI switch strategy. In clinical practice the optimal duration of therapy is determined on an individual patient basis depending on the balance between the risk of cancer recurrence versus the short and long-term tolerability of the specific therapies.

The key issue in early stage ER+ breast cancer is the diagnostic ability to predict the degree of hormone sensitivity within an individual’s tumor, and in particular whether endocrine therapy alone is sufficient adjuvant systemic therapy, or whether chemotherapy is required to provide additional risk reduction. The recurrence score (RS) assay Oncotype DX is a multigene-based molecular assay that is being used in clinical practice to determine prognosis in ER+ early breast cancer (10). Although the majority of genes are either ER (ESR1, PGR, BCL2, SCUBE2) or proliferation based (Ki-67, STK15, Survivin, CCNB1, MYBL2), additional genes are included that may modulate hormone sensitivity (HER2, GRB7, MMP11, CTSL2, GSTM1, CD68, BAG1). The RS is a continuous variable that was validated within the NSABP-B14 adjuvant trial as quantifying the likelihood of distant recurrence in postmenopausal women with node-negative ER+ breast cancer treated with tamoxifen (11). More recently, the RS has provided similar predictive outcome data for those treated with anastrozole within the ATAC trial (12). However, in clinical practice the RS is being used to assess whether chemotherapy is required, on the basis of the likely additional benefit gained from the addition of chemotherapy over tamoxifen in ER+ tumors that might be less hormone sensitive. Data from both the node-negative NSABP-20 trial (13) and the node-positive SWOG 8814 trial (14) have shown the prognostic and predictive benefit of the RS, and may predict the magnitude of the additional benefit from chemotherapy in those with ER+ tumors that have higher RS values. This benefit is now being assessed in a large prospective study called the Trial Assigning Individual Options for Treatment (TAILORx), which will specifically test the value of chemotherapy for those with an intermediate RS (15). Additional gene arrays such as Mammaprint also exist that assess overall prognosis. As such, molecular profiling has become an additional diagnostic tool to help determine optimal treatment strategies in ER+ early stage breast cancer, and provide additional independent prognostic information over classical clinical-pathological features that have been traditionally used in treatment decision making (16).

**Advanced disease.** In patients with ER+ metastatic breast cancer, endocrine treatments in general achieve a response rate of between 20% to 40% according to the type of therapy and prior exposure to endocrine treatment. Predictors of response to hormone therapy include a previous response to endocrine treatment and/or a prolonged treatment-free interval, the site of metastases (i.e., soft tissue and bone versus visceral metastases), quantitative level of ER expression and co-expression of progesterone receptor, and the age of the patient. The median response duration to endocrine therapy in advanced disease is about 8 to 14 months, although for some patients response duration can last several years. For postmenopausal women with ER+ metastatic breast cancer, AIs have become standard first-line therapy on the basis of randomized trials confirming enhanced efficacy over tamoxifen and/or progesterins (17). Now as AIs become an integral component of adjuvant therapy, novel endocrine drugs are required for ER+ metastatic breast cancer.

During the 1990s significant efforts were made to develop novel selective estrogen receptor antagonists (SERM) that might be more effective than tamoxifen for breast cancer with fewer agonist side effects. These SERMs included triphenylethylen derivatives such as toremifene, droloxifene and idoxifene, and benzothiophene derivatives such as raloxifene and arzoxifene (18). However, despite the preclinical promises that each compound showed, phase II and III trials in advanced breast cancer failed to establish SERMs as an effective new endocrine therapy in advanced disease. In contrast, fulvestrant was developed as a novel type of ER antagonist that binds to the receptor and prevents ER dimerization, leading to rapid degradation and loss of cellular ER (19). In particular fulvestrant delayed the emergence of acquired resistance compared with tamoxifen in an MCF-7 hormone-sensitive xenograft model, thus suggesting it could have advantages over tamoxifen in the clinical setting (20). However, despite this profile fulvestrant was no more effective than either tamoxifen or aromatase inhibitors in various first-line phase II clinical trials (21).

Early clinical data from phase II studies in advanced breast cancer suggested some modest efficacy for fulvestrant in a second- and/or third-line setting (22, 23). This
efficacy was confirmed in the large randomized phase III Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) study that showed similar efficacy for fulvestrant versus exemestane in patients who have progressed on treatment with nonsteroidal AIs (24). However, the efficacy of fulvestrant, especially in the setting of endocrine resistance in which activated ER signaling may be dominant, may critically depend on the background estrogen environment in which the cells exist (25, 26). In a xenograft model with aromatase-transfected MCF-7 cells combined therapy of an aromatase inhibitor plus fulvestrant was significantly more effective than either alone, delaying emergence of resistance (27, 28). On the basis of these findings, an ongoing phase III trial (SoFEA) will compare progression-free survival in patients who have progressed on a nonsteroidal AI, and who are subsequently treated with either fulvestrant plus continued anastrozole, or with fulvestrant alone, whereas two first-line phase III studies (FACT and SWOG SO226) have compared anastrozole and fulvestrant versus anastrozole alone in endocrine-sensitive advanced breast cancer. Although in the first-line setting previous studies suggested that fulvestrant 250 mg once monthly had similar efficacy to the AI anastrozole (29), recent results of a randomized phase II trial suggest that a higher intramuscular dose of fulvestrant (500 mg/month, plus 500 mg on day 14 of month 1) may be required to improve efficacy over AIs (30). Ultimately, fulvestrant may be an effective option because it also can eliminate ER+-dependent cells that start to operate in a ligand-independent fashion secondary to growth factor-induced cross-talk, as discussed below.

**On the Horizon**

**Understanding endocrine resistance.** In order to enhance the current benefit of existing endocrine therapies and improve outcomes in ER+ breast cancer, recent efforts have been directed toward understanding the molecular basis for endocrine resistance. Experimental and clinical observations have suggested that even following the development of endocrine resistance, ER signaling continues to play an important role (31, 32). For example sequential biopsies from breast cancer patients who relapsed on tamoxifen showed that functional ER expression was retained in more than 50% of cases (33). However, loss of ER either due to the clonal selection of ER negative cells or transcriptional suppression of ER gene expression may also account for acquired endocrine resistance associated with progressive disease (34, 35). The use of de-methylating agents or histone deacetylase inhibitors can reactivate expression of a functional ER in cell lines in which ER silencing exists because of promoter methylation (35).
Table 1. Clinical trials of combinations of endocrine therapies with targeted biological agents in ER+ breast cancer

<table>
<thead>
<tr>
<th>Molecular target and clinical setting</th>
<th>Trial phase and no. patients</th>
<th>Intervention</th>
<th>Clinical endpoints</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>MBC II n = 15</td>
<td>ANA + GEF</td>
<td>PR = 0</td>
<td>(47)</td>
</tr>
<tr>
<td>Hormone-refractory MBC</td>
<td>MBC II n = 150</td>
<td>LET + ERL</td>
<td>CBR = 11/20 so far</td>
<td>(48)</td>
</tr>
<tr>
<td>Hormone-sensitive MBC</td>
<td>MBC II RCT n = 206 Stratum 1</td>
<td>TAM vs. TAM + GEF</td>
<td>PFS 10.9 mo (TAM + GEF) vs. 8.8 mo (TAM) HR 0.84</td>
<td>(51)</td>
</tr>
<tr>
<td>Hormone-sensitive MBC</td>
<td>MBC II RCT n = 93</td>
<td>ANA vs. ANA + GEF</td>
<td>CBR 50.5% (TAM + GEF) vs. 45.5% (TAM)</td>
<td>(52)</td>
</tr>
<tr>
<td>Hormone-sensitive MBC</td>
<td>MBC II RCT n = 93</td>
<td>ANA vs. ANA + GEF</td>
<td>PFS 14.6 mo (ANA + GEF) vs. 8.2 mo (ANA) HR 0.55, CBR 48.8% (ANA + GEF) vs. 34.0% (ANA)</td>
<td>(53)</td>
</tr>
<tr>
<td>HER2+ MBC</td>
<td>HER2+ MBC n = 33</td>
<td>TRAS + LET</td>
<td>PR = 26%</td>
<td>(56)</td>
</tr>
<tr>
<td>(note: all patients were TRAS and AI naive)</td>
<td></td>
<td>SD = 26%</td>
<td>PFS = 2.4 mo (ANA) vs. 4.8 mo (ANA + TRAS), HR 0.63, P = 0.0016</td>
<td>(57)</td>
</tr>
<tr>
<td>HER2 + MBC</td>
<td>HER2 + MBC III n = 207</td>
<td>ANA vs. ANA + TRAS</td>
<td>ORR = 6.8% (ANA) vs. 20.3% (ANA + TRAS), P = 0.018</td>
<td>(57)</td>
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<tr>
<td>(All patients were IHC 3+ or FISH+)</td>
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<tr>
<td>HER2 + MBC</td>
<td>HER2 + MBC III n = 219</td>
<td>LET vs. LET + LAP</td>
<td>PFS = 3.0 mo (LET) vs. 8.2 mo (LET + LAP), HR 0.71, P = 0.019</td>
<td>(57)</td>
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<tr>
<td>(All patients were IHC 3+ or FISH+)</td>
<td></td>
<td></td>
<td>CBR = 29% (LET) vs. 48% (LET + LAP), OR 0.4, P = 0.003</td>
<td>(57)</td>
</tr>
<tr>
<td>Downstream signaling (FT; mTOR)</td>
<td>MBC II RCT n = 120</td>
<td>LET vs. LET + TIP</td>
<td>PR = 38% (LET) vs. 30% (LET + TIP)</td>
<td>(63)</td>
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<tr>
<td>Tamoxifen resistant MBC</td>
<td>MBC II n = 92</td>
<td>LET vs. LET + TEM 10 mg daily vs. LET + TEM 30 mg intermittent</td>
<td>CBR = 62% (LET) vs. 49% (LET + LAP) ORR = 45% (LET) vs. 33% (LET + TEM10), vs. 40% (LET + TEM10) v. 45% (LET + TEM30)</td>
<td>(65)</td>
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<tr>
<td>MBC</td>
<td></td>
<td></td>
<td>PFS = 11.6 mo (LET) vs. 11.5 mo (LET + TEM10) vs. 13.2 mo (LET + TEM30)</td>
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Strategies in ER+ Breast Cancer

There is also evidence that in ER+ breast cancer cells that have developed endocrine resistance, ER expression may be suppressed directly by enhanced peptide growth factor receptor signaling from overexpression of the type I growth factor receptors such as epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), with subsequent downstream mitogen activated protein kinase (MAPK) activation that inhibits ER transcriptional expression (36). Preclinical studies with the dual EGFR/HER2 tyrosine kinase inhibitor (TKI) lapatinib have shown that inhibition of growth factor activity in endocrine-resistant cells could then be associated with an adaptive increase in ER signaling, and subsequent restoration of sensitivity to endocrine agents such as tamoxifen or estrogen deprivation (37, 38). This dynamic interaction between ER and EGFR/HER2 certainly supports using ER and growth factor targeted therapies in combination in the setting of endocrine resistance.

Although loss or suppression of ER may occur in some tumors that develop endocrine resistance especially to tamoxifen, resistance following long term estrogen deprivation (LTED; i.e., prolonged aromatase inhibitor therapy) may be associated with retention and indeed enhanced ER signaling. In vitro models of adaptation to LTED have shown an increase in ER expression and E2 hypersensitivity to very low levels of residual estrogen (39–41). In part this finding is caused by an adaptive increase in ER levels, but in addition, enhanced "cross-talk" occurs with ER becoming phosphorylated and super-sensitized by a number of different signaling pathways including HER2/HER3, downstream MAPK activation, or signaling through the insulin-like growth factor (IGF)/AKT pathway (Fig. 1). In experimental models of LTED various approaches to interrupting these signaling pathways restored endocrine responsiveness, including EGFR TKI gefitinib, use of MEK inhibitors, or the ER down-regulator fulvestrant, providing a clear rationale for use of these agents to prevent resistance to aromatase inhibitors in the clinic (see below).

Combining endocrine and growth factor receptor therapies: a future strategy to prevent resistance? Based on the preclinical evidence in a hormone-sensitive MCF-7 xenograft model that cotargeting ER and EGFR signaling might treat or delay endocrine resistance (42), a number of early trials were conducted with the EGFR TKIs gefitinib or erlotinib either alone or in combination with endocrine therapy (Table 1; ref. 43). The monotherapy phase II studies with the EGFR TKI gefitinib in patients with advanced breast cancer were all relatively disappointing (44–46), and two additional phase II studies that explored the potential benefit for combining either gefitinib or erlotinib with an aromatase inhibitor in unselected patients with ER+ advanced breast cancer showed little significant clinical efficacy (47, 48). In primary ER+ postmenopausal breast cancer a randomized neo-adjuvant trial of anastrozole alone or in combination with gefitinib given for 3 months prior to surgery showed no improvement in tumor response rate or antiproliferative effect as determined by Ki-67 (49), although a pre-operative trial of gefitinib versus gefitinib combined with anastrozole for 4 to 6 weeks prior to surgery

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<td>Pre-operative EBC</td>
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<tr>
<td>II RCT</td>
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<tr>
<td>LET</td>
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<tr>
<td>ORR = 65% (LET) vs. 59% (LET + EVE) (98)</td>
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<td>PFS = 9.2 mo (LET) vs. 9.2 mo (LET + EVE) (98)</td>
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<td>II RCT</td>
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<td>LET</td>
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<td>ORR = 24% (LET) vs. 24% (LET + TEM) (66)</td>
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<td>Abbreviations: MBC, metastatic breast cancer; EBC, early (primary) breast cancer; RCT, randomized controlled trial; RT, partial response; SD, stable disease &gt; 6 mo.; ORR, objective response rate (PR + CR); CBR, clinical benefit rate (ORR + stable disease &gt; 6 mo.); USS, ultrasound; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; OR, odds ratio; FT, farnesyltransferase; TAM, tamoxifen; EVE, everolimus; TEM, temsirolimus; TP, tipifarnib; TRAS, trastuzumab; ANA, anastrozole; LET, letrozole; GEF, gefitinib; ERL, erlotinib; LAP, lapatinib.</td>
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in women with ER+ EGFR+ primary breast cancer did report that combined treatment induced the greatest reduction in tumor cell proliferation (50). As such these early studies failed to define a clear role for blockade of EGFR as a means to enhance endocrine responsiveness.

In the setting of ER+ve first-line hormone-sensitive advanced breast cancer, the primary endpoint for any combined therapy trial has been to investigate whether time to disease progression can be significantly prolonged by the addition of a targeted therapy to endocrine treatment, thus delaying the emergence of resistance because of any activation of the molecular target in question. A double-blind placebo-controlled phase II trial of tamoxifen with or without gefitinib was conducted in 290 patients as first-line endocrine therapy in postmenopausal women with ER+ve metastatic breast cancer (51). There was a numerical increase in progression-free survival from 8.8 to 10.9 months [hazard ratio 0.84, 95% confidence interval (CI) 0.59-1.18, P = 0.31]. A second randomized trial of gefitinib and anastrozole versus anastrozole alone in a similar first-line patient population of women with ER+ve advanced breast cancer reported a prolongation of progression-free survival from a median of 8.2 months with anastrozole to 14.6 months with the combination (hazard ratio 0.55, 95% CI 0.32-0.94; ref. 52). No information was available on how many patients had received prior adjuvant endocrine therapy, and thus which patients derived benefit from the combination. Furthermore, this initial nonstatistical benefit seen with gefitinib plus anastrozole was not observed in a second randomized phase II trial with the combination (53).

 Likewise, targeting HER2 in hormone receptor-positive breast cancer has been explored as a means of improving endocrine responsiveness. This targeting may involve re-expression of a silenced or suppressed ER as outlined in preclinical data (54), and some clinical evidence exists that trastuzumab can restore both ER expression and endocrine responsiveness in patients with original ER−ve HER2+ve advanced breast cancer (55). A phase II clinical trial of letrozole and the monoclonal antibody trastuzumab in patients with ER+/HER2+ metastatic breast cancer revealed that the combination was well tolerated and had a clinical benefit rate (partial response and stable disease) of 50% (56). Subsequently, the randomized phase II TAnDEM trial in 207 patients with known ER+/HER2+ metastatic breast cancer recently reported a doubling of progression-free survival with the addition of trastuzumab over anastrozole alone (4.8 months versus 2.4 months, P = 0.0016; ref. 57).

Subsequently laptatinib, a potent oral TKI of both EGFR and HER2, has been explored in combination with endocrine therapy on the basis of in vitro data that suggested benefit for combined therapy in models of endocrine-resistant breast cancer (37, 38). Results from a phase III trial of 1,286 patients with metastatic ER+ breast cancer who were randomized to receive either letrozole alone or letrozole combined with laptatinib were recently reported (58). In patients with known ER+/HER2+ tumors (n = 219), the addition of laptatinib to letrozole significantly reduced the risk of progression [hazard ratio 0.71, 95% CI 0.53-0.96, P = 0.019], improving the median progression-free survival from 3.0 months for letrozole to 8.2 months for the combination. The clinical benefit was also significantly greater for the combination (48% versus 29%, P = 0.003). There were 952 patients with ER+/HER2− tumors, in which the hypothesis was that any development of acquired resistance to letrozole due to adaptive EGFR or HER2 up-regulation might be prevented and/or delayed by the combination. However, in the ER+/HER2−ve population overall there was no improvement in PFS, although potential benefit from the addition of laptatinib may exist for that subset of patients that relapsed during adjuvant tamoxifen therapy. This result is consistent with previous data relating to tamoxifen resistance being associated with HER2 upregulation and early relapse. However, the lack of benefit for cotargeting HER2 and ER in hormone-sensitive breast cancer from the outset suggests that this approach may not delay resistance in all cases. Indeed this was shown preclinically by the failure of trastuzumab and letrozole when combined from the outset to delay endocrine resistance in hormone receptor-positive xenografts, albeit that combined therapy was effective at the time resistance to letrozole had developed (59). Thus whereas combined endocrine-HER2 targeted therapy may be effective in tumors with endocrine resistance and/or established co-expression of both receptors, the promising strategy of co-blockade from the outset to delay endocrine resistance may be significantly harder to deliver in the clinic.

Future strategies to co-target endocrine therapies with downstream signaling inhibitors. Although most work has been undertaken with growth factor receptor therapies, combinations of endocrine therapies with drugs that target relevant downstream signaling pathways have also been attempted, including farnesyltransferase inhibitors (tipifarnib) and mammalian target of rapamycin (mTOR) antagonists (everolimus, temsirolimus). Farnesyl-transferase inhibitors (FTI) were developed in an effort to interrupt Ras/Raf/MAPK signaling, and on the basis of encouraging results in cell line and tumor xenograft models (60), several trials were conducted in combination with tamoxifen (61) or aromatase inhibitors (62). Unfortunately the randomized phase II study of letrozole ± tipifarnib in 120 women with tamoxifen-resistant disease was negative (Table 1; ref. 62). One key reason why this strategy failed may relate to the inability to truly identify the oncogenic molecular target for FTIs in ER+ breast cancer, and as such, trials were unable to enrich for patients that could benefit from the addition of an FTI.

Other important downstream targets in ER+ breast cancer include the PI3K/Akt/mTOR pathway that is activated by a number of growth factors, including IGF-1, basic fibroblast growth factor, EGF, and vascular epidermal growth factor (VEGF). Mutations in the catalytic domain of PI3K have been identified in 20% to 25% of breast cancers, especially in ER+ disease (63). Although PI3K...

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inhibitors are still in the early stages of development, mTOR inhibitors have been tested in breast cancer in combination with endocrine therapies. A large randomized phase III trial of the mTOR inhibitor temsirolimus plus letrozole versus letrozole alone was undertaken in >1,000 unselected ER+ postmenopausal women with advanced breast cancer, but was halted early because of lack of benefit (64). At a molecular level, concern has also been expressed that mTOR inhibition may release the negative feedback loop via S6kinase and IRS-1 (65), which then enhances further Akt activation and thus overcomes the effects of mTOR inhibition. An alternative clinical approach to understand which patients may benefit from mTOR inhibition when combined with aromatase inhibitors has been to study biomarker changes in vivo in the pre-operative neo-adjuvant setting. In a randomized phase II trial in 270 postmenopausal women with ER+ve primary operable breast cancer the combination of letrozole 2.5 mg/day and oral everolimus 10 mg/day for 4 months presurgery resulted in a significantly greater tumor shrinkage as judged by ultrasound (Table 1; ref. 66). Elevated levels of one of the downstream biomarkers of mTOR activation (pS6240 kinase), together with specific mutations in PIK3CA were found to be associated with a greater likelihood of an antiproliferative response to the combination of an mTOR antagonist plus letrozole. The true role of PI3K mutations in modulating endocrine responsiveness is unclear, as evidence exists that they may predict for a good outcome (67).

**Molecular profiling: implications for future clinical trials in ER+ breast cancer.** Although overexpression of any given oncogene or molecular target may identify the best group of ER+ patients to treat with a novel targeted therapeutic in a combination strategy to enhance endocrine responsiveness, it remains likely that only a proportion will gain benefit because of other co-existing mutations and molecular alterations within the complex web of inter-related signaling networks that will determine response and/or resistance to inhibition of any key target (e.g., either loss of the PTEN tumor suppressor gene or activating mutation of PI3-kinase may modulate response to trastuzumab in HER2+ve breast cancer). As such, translational studies in samples from patients will remain crucial in optimizing clinical benefit from these new therapies, whether it is the original primary tumor or the relapsed sample in which the molecular profile may have changed.

In the future all clinical studies should make a greater effort to enrich their trial population with the most appropriate patients, with a tumor molecular profile likely to benefit from targeting the given pathway. In the absence of the ability to identify the molecular target in samples of metastatic disease (i.e., only the original primary tumor is available, as often is the case), understanding the inherent biology in the primary tumor that accounts for relapse and/or resistance may become crucial in determining which population to select for these studies. Genomic profiling in ER+ve breast cancer may help identify those more likely to develop resistance to endocrine therapy, or indeed the pathways that these tumors are most likely to use as escape mechanisms, which in turn may guide appropriate selection of target therapies to add in at the time of relapse. Recent studies have started to show common oncogenic pathways that intrinsic subtypes of breast cancer will use, thus allowing strategies to be developed for combinations of various signaling agents to be used in an attempt to enhance responsiveness to current therapies (68). In particular in ER+ve breast cancer, gene expression profiling has identified that in the luminal B subtype, activation of growth factor signaling pathways occurs, often independent of HER2 overexpression, thus contributing to their poorer prognosis (69). Selection of this subgroup for future combination strategies may yield answers faster than treating a more heterogeneous unselected group of patients with ER+ breast cancer.

There are now a multitude of targeted therapeutics in various stages of clinical development for breast cancer, all based on a rationale that the target in question is valid in the pathogenesis of the disease. Although the integration of these therapies with conventional therapeutics has been pioneered by the combination of trastuzumab with chemotherapy, substantial research is ongoing into combining targeted therapeutics with endocrine therapy to enhance responsiveness and delay resistance (70). The emphasis is now shifting to targeting networks and pathways with combinations of various signaling agents to be used in parallel (so-called combined horizontal blockade) or in series (combined vertical blockade). Selection of which approach is valid depends on key preclinical studies that need to be undertaken in various relevant models, in order to guide which combinations need testing in early phase clinical trials. This selection will ensure rapid and efficient transition from proof of concept studies into pivotal efficacy studies, thus maximizing the likelihood of success.

**Disclosure of Potential Conflicts of Interest**

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