Review

Potential of overcoming resistance to HER2-targeted therapies through the PI3K/Akt/mTOR pathway

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Abstract

Human epidermal growth factor receptor 2 (HER2) overexpression occurs in up to 30% of breast cancers and is a marker of aggressive disease. While HER2-targeted therapies have improved outcomes in these tumors, resistance to these agents develops in a large proportion of patients. Determining molecular mechanisms underlying resistance might help improve outcomes for patients with HER2-positive disease by allowing development of strategies to overcome resistance. Activation of signaling pathways involving the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway might contribute to the development of resistance to HER2-targeted therapies. Several inhibitors of this pathway are under investigation in this disease setting and phase 3 data for everolimus in combination with trastuzumab and chemotherapy in trastuzumab-refractory, advanced disease are promising. In this review, molecular mechanisms underlying resistance to HER2-targeted therapies are considered and evidence for strategies to manage resistance is evaluated, including the use of inhibitors of the PI3K/Akt/mTOR pathway.

Introduction

Human epidermal growth factor receptor 2 (HER2) is a member of the ErbB family of receptor tyrosine kinases [1]. HER2 mediates signal transduction through heterodimerization with other ErbB family members, including Erb1, Erb3, and Erb4, causing auto-phosphorylation of the tyrosine kinase domain of the receptor and subsequent activation of downstream pathways, including the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) and Ras/Raf/mitogen-activated protein kinase (MAPK) pathways. Up to 30% of invasive breast cancers overexpress HER2 [2], leading to stimulation of pathways involved in cell proliferation and survival [3]. HER2 overexpression is a marker of aggressive disease [4], and is correlated with age older than 50 years and higher T stage and histologic grade [5].

Identification of the dysregulated HER2 pathway in breast cancer pathogenesis has led to the development of HER2-targeted therapies [6,7]. Trastuzumab is a monoclonal antibody that has shown improved overall survival (OS) in the first-line setting in combination with chemotherapy in patients with HER2-positive (HER2+) advanced disease [8,9] and as adjuvant therapy when used in combination with or sequentially after chemotherapy [10,11], and is recommended as part of neoadjuvant regimens in HER2+ disease [12]. Pertuzumab is a monoclonal antibody that prevents HER2 from coupling with other ErbB family members [13], and is approved for use in combination with trastuzumab and docetaxel in patients who have not received previous HER2-targeted therapy or chemotherapy for metastatic disease, based on improved OS in this setting, as well as for neoadjuvant therapy for HER2+, locally advanced, inflammatory, or early breast cancer, based on an improvement in pathologic complete response rate [14–17]. Lapatinib-based therapies have been successfully approved in estrogen receptor-negative and HER2-positive cohorts due to the effectiveness of lapatinib in combination with capecitabine as a second-line therapy and in combination with letrozole [18,19]. Also, recent improvements in OS have been seen with second-line
approaches with trastuzumab emtansine (T-DM1) [20,21]. Based on these findings, lapatinib and T-DM1 are both approved as second-line HER2-targeted therapies in patients with advanced or metastatic HER2+ breast cancer who have progressed on prior therapy with trastuzumab [19,21].

Although reports continue to emerge about the usefulness of targeted therapy for recurrent HER2+ disease in the first-line setting, including the recent improvement in OS recently reported with pertuzumab [22], nearly 70% of these patients will experience acquired resistance and some will still exhibit primary resistance [23]. Primary resistance might occur because of lack of target dependency or activation of compensatory pathways [24]. Acquired resistance, which develops in most patients with advanced disease, may result from loss of expression of the target because of continuous therapy, activation of mutations downstream from the target, or activation of mechanisms that promote cell proliferation [24]. Determination of molecular mechanisms underlying resistance is necessary to improve outcomes for patients with HER2+ tumors [3], by allowing the selection of patients who are likely to benefit from specific therapies and the development of strategies to overcome resistance [25].

**Mechanisms of resistance to HER2-targeted therapy**

Various factors associated with resistance to HER2-targeted therapies have been proposed [25,26], which may be generally classified as factors associated with receptor-level effects or those of downstream signaling components.

Receptor-level factors affecting drug binding and action might contribute to resistance. p95HER2, a HER2 fragment lacking the extracellular binding domain, is unable to bind trastuzumab but might retain sensitivity to other HER2-targeted therapies that bind intracellularly [27,28]. Also, loss of HER2 amplification has been reported in patients with significant residual disease after neo-adjuvant trastuzumab therapy and is associated with poor recurrence-free survival [29]. Increased activation of HER3 has also been proposed as a contributor to resistance because increased HER-family activating ligands have been detected in cells resistant to trastuzumab, which does not inhibit HER2-HER3 heterodimerization [30], and inhibiting HER2 has been shown to reactivate HER3 [31–33].

Factors associated with downstream signaling components have also been investigated as factors related to resistance to HER2-targeted therapies. Alterations in regulation of downstream signaling might lead to aberrant activation of signaling pathways downstream of HER2 [34,35]. Also, compensatory crosstalk with other pathways, such as between HER2 and HER3, epidermal growth factor receptor (EGFR)/HER1, and insulin-like growth factor 1 receptor (IGF-1R), has been reported to reduce the effectiveness of trastuzumab [36–38], and crosstalk between the estrogen receptor pathway and HER2 and the PI3K/Akt/mTOR pathway has been implicated in endocrine resistance [39].

**Current management options for resistance to HER2-targeted therapy**

Disease will eventually progress in patients with HER2+ metastatic breast cancer who initially respond to HER2-targeted therapy [40]. Various treatment strategies to overcome resistance to HER2-targeted therapy have been assessed.

One strategy is to maintain trastuzumab therapy beyond progression because there have been several reports of the benefits of continued trastuzumab therapy with progressive disease [41–48], which might be attributed to an additive action of trastuzumab in combination with chemotherapy. However, additional prospective and larger clinical studies are necessary to elucidate the role of continued use of HER2-targeted therapy and the appropriate concomitant chemotherapeutic agents to use after disease progression.

Because some tumors resistant to HER2-targeted therapy depend on HER2-mediated signaling, another approach to managing resistance is to switch HER2-targeted therapy. Data are available for novel agents in the setting of trastuzumab resistance. A phase 3, randomized, open-label study evaluating the dual HER2-specific and EGF/HER1-specific tyrosine kinase inhibitor (TKI) lapatinib in combination with capecitabine versus capecitabine alone reported significant improvements in time-to-progression (TTP) (8.4 vs 4.4 months; hazard ratio [HR], 0.49; 95% confidence interval [CI] = 0.34–0.71; p < 0.001) and progression-free survival (PFS) (8.4 vs 4.1 months; HR, 0.47; 95% CI, 0.33–0.67; p < 0.001) at a planned interim analysis, prompting early termination of the study and subsequent crossover of the study treatment arms [18]. Based on this phase 3 data, lapatinib is approved in combination with capecitabine for use in HER2+ metastatic breast cancer that progresses with trastuzumab therapy [18,19]. T-DM1 is an antibody–drug conjugate with the anti-tumor properties of trastuzumab and the cytotoxic activity of DM1, a DNA topoisomerase inhibitor (maytansine derivative). T-DM1 monotherapy is approved for the management of HER2+ metastatic breast cancer in patients who previously received trastuzumab and a taxane [21]. This approval was based on phase 3 data from a randomized, open-label study that reported a prolonged PFS (9.6 vs 6.4 months; HR, 0.65; 95% CI, 0.55–0.77; p = 0.001) and OS (30.9 vs 25.1 months; HR, 0.68; 95% CI, 0.55–0.85; p < 0.001) for T-DM1 versus combination therapy with lapatinib and capecitabine [20]. The findings of this study was confirmed by a recently published, phase 3, randomized, open-label trial comparing T-DM1 and physician’s choice of therapy in patients with HER2+ advanced breast cancer who had received two or more HER2-targeted therapies [49]. T-DM1 was associated with a significant improvement in PFS compared with physician’s choice of therapy (6.2 vs 3.3 months; HR, 0.528; 95% CI, 0.422–0.661; p < 0.0001); an interim OS analysis showed a trend in favor of T-DM1 (HR, 0.552; 95% CI, 0.369–0.826; p = 0.0034), but the efficacy-stopping boundary was not crossed [49].

Combining HER2 inhibitors has also been used as a strategy to manage resistant disease because there is preclinical evidence of a synergistic effect of the agents when used in combination [50–52]. In a phase 3, randomized, open-label study of patients with HER2+ early breast cancer, the pathologic complete response rate associated with lapatinib in combination with trastuzumab (51.3%) was higher than that with either trastuzumab (29.5%) or lapatinib (24.7%) given alone (p = 0.0001 for combination vs trastuzumab; p = 0.34 vs lapatinib), resulting in an odds ratio of 2.6 (97.5% CI, 1.50–4.58; p = 0.0001) for combination therapy versus trastuzumab alone [53]. The findings of another phase 3, randomized, open-label study in patients with metastatic breast cancer resistant to trastuzumab demonstrated a significant improvement in PFS with trastuzumab in combination with lapatinib versus lapatinib monotherapy (12.0 vs 8.1 weeks; HR, 0.73; 95% CI, 0.57–0.93; p = 0.008), although no significant difference in OS (51.6 vs 39.0 weeks; HR, 0.75; 95% CI, 0.53–1.07; p = 0.106) was seen between the two treatment groups [54]. Combination therapy with trastuzumab and pertuzumab was assessed in a phase 2 study of patients with advanced breast cancer that progressed during trastuzumab therapy [55]. Trastuzumab and pertuzumab reported an objective response rate (ORR) of 24%, a clinical benefit rate (CBR) of 50%, a median PFS of 5.5 months (80% CI, 18–31), and a median TTP of 3.9 months [55]. Another analysis of patients with prior trastuzumab treatment who received pertuzumab...
monotherapy compared to pertuzumab plus trastuzumab determined that the combination of pertuzumab and trastuzumab showed a greater benefit than pertuzumab monotherapy (ORR 17.6% vs 3.4%; CBR 41.2% vs 10.3%; median PFS 17.4 vs 7.1 weeks; median TTP 17.4 vs 7.1 weeks) [56].

Investigational management options for resistance to HER2-targeted therapy

A number of novel HER2-targeted treatment options are currently undergoing clinical investigation in patients with HER2-resistant breast cancer. Pertuzumab is being assessed in HER2-resistant breast cancer, with an ongoing phase 2 trial of pertuzumab in combination with trastuzumab and paclitaxel (ClinicalTrials.gov identifier NCT01276041) reporting a preliminary 6-month PFS rate of 81% (95% CI, 67–91) based on data from 36 evaluable patients (53 patients were enrolled) [57]. A recent phase 2 study of eribulin in combination with trastuzumab for locally recurrent or metastatic HER2+ breast cancer demonstrated the acceptability of this treatment option in this setting, reporting an ORR of 71.2% (95% CI, 56.9–82.9), a disease control rate of 96.2% (95% CI, 86.8–99.5), a CBR of 84.6% (95% CI, 71.9–93.1), and a median PFS of 11.6 months (95% CI, 9.1–13.9) [58]. Another phase 2 trial is currently assessing pertuzumab in combination with eribulin and trastuzumab in recurrent HER2+ breast cancer (ClinicalTrials.gov identifier NCT01912963). A phase 3 trial comparing combined treatment with trastuzumab and capcitabine with or without pertuzumab in patients with HER2+ metastatic breast cancer that has progressed on prior trastuzumab therapy is currently ongoing (ClinicalTrials.gov identifier NCT01026142).

Other novel, targeted therapies are also undergoing clinical development in the setting of HER2-resistant breast cancer. Phase 1/2 trials evaluating the IGF-1R inhibitors BMS-754807 and cixutumumab are being conducted in patients with HER2-resistant breast cancer (ClinicalTrials.gov identifiers NCT00788333 and NCT00684983, respectively). The results of a recent phase 2 study comparing the irreversible multi-TKI neratinib with lapatinib plus capcitabine did not demonstrate improvements in PFS (4.5 vs 6.8 months; HR, 1.19; 95% CI, 0.89–1.60; p = 0.231) or OS (19.7 vs 23.6 months; p = 0.280) [59]. Monotherapy with another irreversible TKI, afatinib, was also assessed in a phase 2 study of patients with HER2+ metastatic breast cancer who progressed on trastuzumab, providing a PFS of 15.1 weeks (95% CI, 8.1–16.7) and OS of 61.0 weeks (95% CI, 56.7–not evaluable) [60]. A series of ongoing phase 2 and 3 trials are being conducted to assess afatinib in combination with chemotherapy in trastuzumab- or lapatinib-resistant breast cancer (ClinicalTrials.gov identifiers NCT01125566, NCT01271725, and NCT01441596) [61–63]. In trastuzumab-refractory, HER2+ breast cancer, promising results of a phase 2 study were previously reported for tanespimycin (CBR 59%; PFS 6 months; OS 17 months) [64], although development of this agent has since been discontinued. Finally, combination therapy with the vascular endothelial growth factor (VEGF) inhibitor pazopanib and lapatinib in a phase 2 study of relapsed or refractory HER2+ inflammatory breast cancer reported a numerical improvement in ORR between the combination therapy and lapatinib monotherapy groups (58% vs 47%), but did not demonstrate an improvement in PFS (both 16.0 weeks) [65]. Therapies targeting downstream signaling pathways, such as the PI3K/Akt/mTOR pathway, have also shown great promise in overcoming resistance to HER2-targeted therapy in breast cancer. The role of this pathway in HER2+ breast cancer and the use of PI3K/Akt/mTOR inhibitors in HER2-resistant breast cancer will be discussed next.

Role of PI3K/Akt/mTOR pathway in HER2+ breast cancer

Resistance to HER2-targeted therapy might occur as a result of aberrant activation of signaling pathways downstream of the receptor [25,34,35]. Because HER2 mediates signal transduction through the PI3K/Akt/mTOR pathway [1], inhibition of components of the PI3K/Akt/mTOR pathway might be a reasonable way to overcome resistance and restore sensitivity to HER2-targeted therapy (Fig. 1) [25,66,67]. Dysregulation of PI3K/Akt signaling causes upregulation of the downstream mTOR pathway and enhancement of messenger RNA translation and increased cellular proliferation [68,69], which are mediated by growth factor receptor overexpression and loss of the phosphatase and tensin homolog (PTEN) tumor suppressor gene [70].

Breast cancer models of constitutively active PI3K/Akt/mTOR pathway have shown resistance to HER2-targeted therapy [36], and hyperactivity of the pathway associated with breast cancer includes gain-of-function mutations in genes encoding PIK3CA, which encodes the catalytic subunit of PI3K, as well as mutations in AKT1, amplification of AKT2, and loss of PTEN [26], PTEN was identified as the only gene of the 8000 tested in which suppression led to trastuzumab resistance [34], and patients with HER2+ tumors and loss of PTEN function are more often resistant to trastuzumab therapy and have shorter survival times [71]. The association of PTEN loss and trastuzumab and lapatinib resistance has also been reported [35,72]. PIK3CA gene mutations acquired during disease progression are suggested to reflect increased activation of the PI3K pathway [25], and in vitro data show that HER2 gene amplification and PIK3CA gene mutations are associated with resistance to HER2-targeted agents [35,73–75]. Poorer clinical outcomes are reported after...
HER2-targeted therapy in patients with activated PI3K pathway because of PTEN loss or PIK3CA gene mutations [34].

mTOR is a serine/threonine kinase that integrates multiple signals from growth factors and hormones, thereby controlling cell growth, proliferation, and angiogenesis [6]. Positive regulators of mTOR activity include IGF-1, IGF-1R, members of the ErbB family and associated ligands, and VEGF receptors and associated ligands [69]. Negative regulators of mTOR include PTEN, which inhibits signaling through the PI3K/Akt pathway, and tuberous sclerosis complex 1 (TSC1) and TSC2. Phosphorylation of TSC2 by Akt upregulates mTOR activity. Dysregulated mTOR activation is implicated in oncogenesis, angiogenesis, and drug resistance [6], and HER2 overexpression is associated with activation of the mTOR pathway and subsequent poor prognosis [76,77]. As multiple upstream components of the mTOR pathway become dysregulated in breast cancer and are thought to be involved in oncogenesis, mTOR inhibition has the potential to interfere with tumor progression at several levels, and targeting multiple pathways with different agents might be more effective than monotherapy strategies [6,78]. Because of the cytostatic nature of mTOR inhibitors, their combined use with cytotoxic agents is suggested [36].

**PI3K/Akt/mTOR inhibitors in HER2-resistant breast cancer**

Preclinical data support the use of inhibitors of the PI3K/Akt/mTOR pathway after resistance to HER2-targeted therapy. Trastuzumab in combination with everolimus, an mTOR inhibitor, restored sensitivity and inhibited growth of trastuzumab-resistant breast cancer and are thought to be involved in oncogenesis, mTOR inhibition has the potential to interfere with tumor progression at several levels, and targeting multiple pathways with different agents might be more effective than monotherapy strategies [6,78]. Because of the cytostatic nature of mTOR inhibitors, their combined use with cytotoxic agents is suggested [36].

**Table 1**

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<thead>
<tr>
<th>Trial (phase)</th>
<th>Number of evaluable patients</th>
<th>Study treatment</th>
<th>Efficacy results</th>
<th>Safety results (adverse events)</th>
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<tr>
<td>NCT00426556</td>
<td>33 patients enrolled, 27 had measurable disease and were evaluable for efficacy</td>
<td>Everolimus + trastuzumab + paclitaxel</td>
<td>ORR, 44%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Most common hematologic events: neutropenia (21%), lymphopenia (14%), and leukopenia (14%)</td>
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<td>DCR, 74%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Median PFS, 34 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Most common nonhematologic events: stomatitis (27%), asthenia/fatigue (22%), and diarrhea (16%)</td>
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<tr>
<td>NCT00426556</td>
<td>55</td>
<td>Everolimus + trastuzumab + paclitaxel</td>
<td>CBR, 36%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Most common hematologic events: neutropenia (36%), anemia (35%), and leukopenia (22%)</td>
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<td>ORR, 22%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Median PFS, 5.5 months</td>
<td>Most common nonhematologic events: stomatitis (76%), diarrhea (56%), and asthenia (51%)</td>
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<tr>
<td>NCT00426530</td>
<td>50 patients enrolled, 47 patients were evaluable for efficacy</td>
<td>Everolimus (5, 20, or 30 mg/week) + vinorelbine (25 mg/m² on days 1 and 8 of 21-day cycle) + trastuzumab (2 mg/kg weekly)</td>
<td>ORR, 19%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Most common hematologic event: neutropenia (92%)</td>
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<td>CBR, 50%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Median PFS, 30.7 weeks&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Most common nonhematologic event: stomatitis (70%)</td>
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<td>BOLERO-3</td>
<td>569</td>
<td>Everolimus + vinorelbine + trastuzumab vs placebo + vinorelbine + trastuzumab</td>
<td>PFS, 7.00 vs 5.78 months, ORR, 41% vs 37% (p = 0.2108)</td>
<td>Most common hematologic events in the everolimus arm: neutropenia (82%), anemia (49%), leukopenia (46%), febrile neutropenia (17%), and thrombocytopenia (15%)</td>
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<td>CR, 3% vs 2%</td>
<td>PR, 38% vs 35%</td>
<td>Most common nonhematologic events in the everolimus arm: stomatitis (62%), fatigue (43%), pyrexia (39%), diarrhea (38%), nausea (36%), and decreased appetite (32%)</td>
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<td>SD, 48% vs 41%</td>
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CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

<sup>a</sup>Data are for the overall population.

<sup>b</sup>Data are for the everolimus 5-mg/day cohort.

<sup>c</sup>Data are for all grades.
not receiving trastuzumab at study entry). Everolimus in combination with weekly vinorelbine and trastuzumab was well tolerated and manageable; neutropenia was the most common hematologic AE (92%) and stomatitis the most common non-hematologic AE (70%). Based on DLT findings, everolimus 5 mg/day was chosen as the optimal daily dose in combination with weekly trastuzumab and vinorelbine for further clinical development. In the 5-mg/day everolimus cohort, the ORR was 19% and the CBR was 50%. The median PFS in the 5-mg/day cohort was 30.7 weeks. In the extension phase of the study, in which patients were allowed to continue everolimus and vinorelbine could be discontinued at the investigator’s discretion, two additional patients achieved complete response, one achieved a partial response, and the overall PFS was 41 weeks [91]. In patients receiving everolimus 5 mg/day in combination with weekly trastuzumab and vinorelbine, neutropenia (grade 1/2, 10%; grade 3/4, 83%) was the most common hematologic AE and stomatitis (grade 1/2, 70%; grade 3/4, 17%) the most common non-hematologic AE related to study treatment.

A post hoc analysis of these two phase 1/2 trials evaluated the efficacy of everolimus in patients pretreated with lapatinib [92]. Among 101 evaluable patients, the ORR was 21% for those who received previous lapatinib therapy and 29% in those who did not; the disease control rate was 88% and 81%, respectively; and mean PFS was 29.0 and 36.1 weeks, respectively [92], suggesting that everolimus in combination with trastuzumab and chemotherpay has promising efficacy in HER2+ metastatic breast cancer, regardless of prior lapatinib therapy.

BOLERO-3 (ClinicalTrials.gov number NCT01007942) is a phase 3, randomized, double-blind, placebo-controlled, multicenter, international clinical trial assessing the efficacy of everolimus in combination with trastuzumab and vinorelbine in 569 patients with HER2+ advanced breast cancer resistant to trastuzumab who have been previously treated with a taxane [90,93]. The primary endpoint was DFS, and secondary endpoints include OS, ORR, and safety. Study treatment was continued until progressive disease or intolerable toxicity.

At the time of the first reported analysis of the BOLERO-3 study (data cutoff: March 15, 2013), the median duration of follow-up was 20 months, and 61 patients were continuing study treatment, including 12% in the study arm and 10% in the control arm [90]. The most common reason for discontinuation was disease progression, with fewer patients discontinuing treatment because of disease progression in the everolimus arm (68%) than in the control arm (78%), while 10% of patients in the everolimus arm discontinued treatment because of AEs, compared with 5% in the control arm. The study population was heavily pre-treated, with all patients having prior exposure to both trastuzumab and taxane therapies, approximately 27% of patients having prior lapatinib exposure, and 42% of patients receiving at least two prior lines of chemotherapy for metastatic disease. The median duration of exposure was highly comparable across treatment groups for the individual drugs used in the respective combinations.

The primary efficacy analysis based on local radiologic assessment resulted in an estimated 22% risk reduction for DFS (HR, 0.78; 95% CI, 0.65–0.95; p = 0.0067) with everolimus therapy, corresponding to a 1.22-month prolongation in median PFS, from 5.78 months in the control arm to 7.00 months in the everolimus arm [90]. The PFS benefit of everolimus was observed across patient subgroups, defined by demographic characteristics, prior therapy, and disease characteristics. Patients with negative hormone receptor status had better PFS outcomes with everolimus therapy. The ORR was similar between treatment arms. OS data are not yet mature.

The nonhematologic AE profile of combination therapy with everolimus was consistent with the known safety profile of the individual drugs, and no new unexpected AEs were observed [90,93]. AEs typical of mTOR inhibitors occurred more frequently with everolimus therapy and included stomatitis, noninfectious pneumonitis, rash, and hyperglycemia, whereas the incidence and grade of other nonhematologic AEs were similar between arms, with the exception of grade 3/4 stomatitis (everolimus, 13%; placebo, 1%) and fatigue (everolimus, 12%; placebo, 4%). The most common hematologic AEs in the everolimus treatment groups were neutropenia (82%), anemia (49%), leukopenia (46%), febrile neutropenia (17%), and thrombocytopenia (15%).

Other mTOR inhibitors under development in HER2-resistant breast cancer include temsirelimus and INK128 (MLN0128), both undergoing phase 1/2 clinical investigation (ClinicalTrials.gov numbers NCT01111825 and NCT01351350, respectively). Investigational PI3K inhibitors under development include buparlisib (BKM120), BYL719, pictilisib (GDC-0941), and XL147, and investigational AKT inhibitors include MK2206, all currently under phase 1/2 clinical investigation in patients with HER2+ breast cancer who either experienced disease progression with or received previous trastuzumab therapy. In a phase 1/2 study of buparlisib in combination with trastuzumab in patients resistant to trastuzumab-containing therapy, the maximum tolerated dose (MTD) of BKM120 was 100 mg/day, and, in the 17 enrolled patients, two achieved a partial response, and there were seven occurrences of disease stabilization of at least 6 weeks in duration (ClinicalTrials.gov number NCT01326644) [94]. Common AEs with the combination therapy included rash (39%), hyperglycemia (33%), and diarrhea (28%).

Conclusions

Therapies targeting HER2 have resulted in improved outcomes for patients with HER2+ breast cancer. However, intrinsic and acquired resistance to these therapies is an ongoing clinical challenge. Elucidation of the molecular mechanisms underlying resistance is leading to the identification of therapies and strategies to manage resistance to HER2-targeted therapies.

As HER2-overexpressing tumors use the PI3K/Akt/mTOR pathway to develop resistance to HER2-targeted therapies, therapy with inhibitors of this pathway is a rational approach. The combination of everolimus, an mTOR inhibitor, with HER2-targeted therapies is a promising therapeutic strategy to overcome resistance in patients with HER2+ advanced breast cancer, a strategy that is supported by phase 3 data from the BOLERO-3 study. Other promising inhibitors of the PI3K/Akt/mTOR are undergoing clinical development.

As described by the authors of the BOLERO-3 study, everolimus is thought to be the first non-HER2–targeted therapy to specifically address the postulated underlying molecular mechanism of trastuzumab resistance [90]. The positive findings from BOLERO-3 suggest that aberrant intracellular signaling pathways contribute to the genesis of trastuzumab resistance, and justify investigation of additional treatment strategies, including mTOR inhibitors in combination with other HER2-targeted therapies.

Ongoing clinical investigation should provide further insight into the appropriate management of HER2-resistant breast cancer. As well, to achieve maximum clinical efficacy through individualized administration of targeted agents, there is a need to identify predictive biomarkers. This could result in optimization of treatment strategies for individual patients, allowing both patient stratification based on previous treatment exposure or sensitivity and identification of tumor phenotypes in responding patients.
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Conflict of interest statement

No conflicts of interest.

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