Breast Cancer: Targets and Therapy

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REVIEW

Emerging targeted combinations in the management of breast cancer

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Abstract: The number of targeted treatments has risen exponentially over the last few years and is an important concept in the fight against cancer. This review will concentrate on some of the main treatments targeting aberrant pathways which have been tested mainly in the Phase I/II setting. These include human epidermal growth factor receptor 2 inhibitors, drug-antibody conjugates, epidermal growth factor receptor inhibitors, vascular endothelial growth factor inhibitors, reticular activating system, mammalian target of rapamycin and multi-kinase inhibitors. Further knowledge of these pathways and the predictors of response to them will enable personalized medicine to become a reality.

Keywords: breast cancer, targeted therapy, tyrosine kinase, receptor

Introduction

With the discovery of estrogen receptors, targeted treatments became a reality. Since then, attention has turned to molecular pathways and alternative receptors as potential targets. As our knowledge of the mechanisms behind cancer cell development has improved, so too has our ability to develop therapies that can inhibit aberrant pathways. This review will examine some of the main drugs that have been investigated during the last few decades.

HER-2 receptor

The neu oncogene was first discovered in 1984 by Schechter et al.[1] It is a member of the epidermal growth factor receptor family (EGFR, see Figure 1) and is encoded by the proto-oncogene "v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)." The human equivalent is *her-2,* which is found on chromosome 17q21.1.[2] HER2 overexpression, found in approximately 22% of breast cancers,[3] is a marker for a more aggressive phenotype with increased growth rates, increased likelihood of early metastasis, and decreased overall survival (OS).[2]

The discovery of HER2 has enabled a variety of targeted therapies to be developed. The first of these was trastuzumab (Herceptin®), a monoclonal antibody which binds to the extracellular juxtamembrane protein of HER2, therefore blocking its ability to promote cellular proliferation and survival.[4] Slamon et al conducted a Phase III trial in the metastatic setting which found a statistically significant improvement in overall response rate (ORR) (50% versus 32%, $P < 0.001$), progression free survival (PFS) (7.4 months versus 4.6 months $P < 0.001$) and, importantly, overall survival (OS) (25.1 months versus 20.3 months, $P = 0.046$) when trastuzumab was combined

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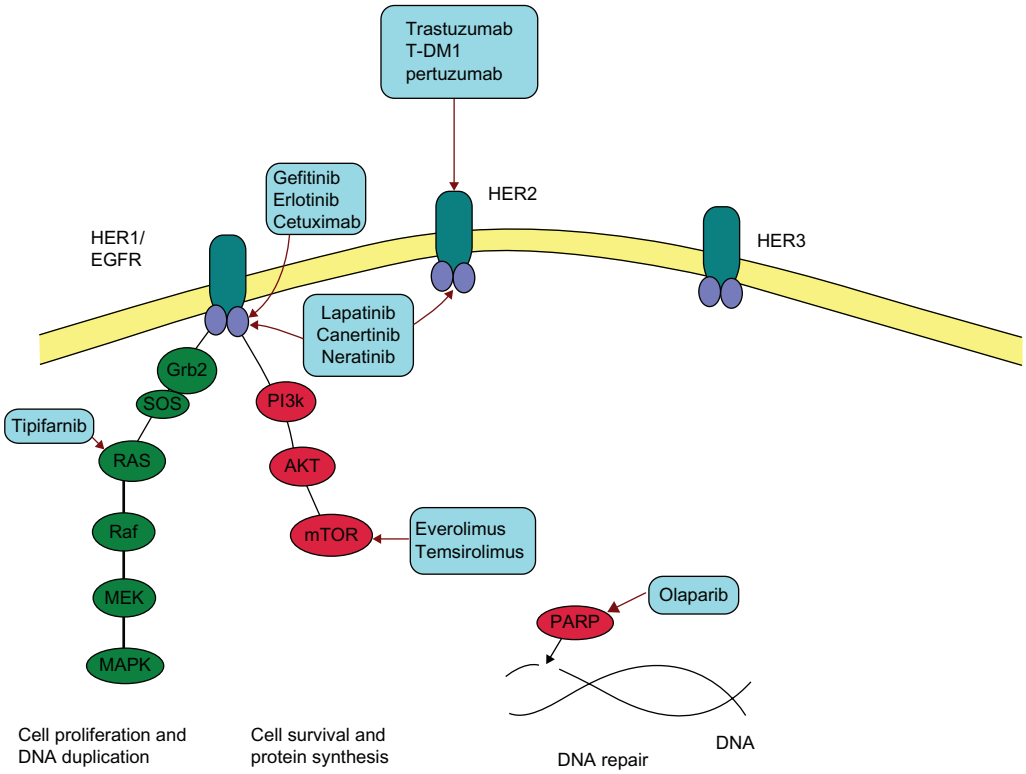

Figure 1 Human epidermal growth factor receptor (HER) and poly (ADP-ribose) polymerase (PARP).
Abbreviations: AKT, also known as Protein Kinase B (PKB), is a serine/threonine-specific protein kinase; Grb2, growth factor receptor-bound protein 2; HER, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinases; MEK (aka MAP2K), mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PARP, poly (ADP-ribose) polymerase (PARP); PI3k, phosphatidylinositol 3'-kinase; Raf, protooncogene cytoplasmic serine/threonine protein kinases; SOS, son of sevenless.

with different chemotherapy regimens.[2] As a result of this study, a new standard of care for patients with metastatic HER2 positive (HER2+) breast cancer was defined.

In the adjuvant setting, a number of large Phase III studies again showed benefit for adding trastuzumab to standard chemotherapy.[5] The NCCTG, N9831, and NSABP B-31 trials examined doxorubicin, cyclophosphamide, and paclitaxel with or without trastuzumab following surgery for HER2+ breast cancers.[5] In the combined analysis, for a total of 3969 participants at median follow up of 2.9 years (range up to 6.4 years), the 4-year disease-free survival (DFS) rate was 85.9% in the trastuzumab arm compared with 73.1% in the non-trastuzumab arm; hazard ratio (HR) 0.49 ($P < 0.0001$; 95% confidence interval [CI]: 0.41–0.58). The four-year OS for the combination with trastuzumab was 92.6% versus 89.4% without; HR 0.63 ($P = 0.0004$; 95% CI 0.49–0.81).[5]

The multicenter HERA trial randomized 5102 women who had received locoregional therapy and a minimum of four courses of adjuvant or neoadjuvant chemotherapy to receive either observation alone (number [n] = 1698), trastuzumab for 1 year (n = 1703) or 2 years (n = 1701).[6] At median follow up of 23.5 months (range 0–48 months), the 1-year trastuzumab arm had a 3-year DFS of 80.6% compared with 74.3% in the observation arm; HR 0.63 (95% CI 0.53–0.75; $P < 0.0001$). The 3-year OS was 2.7% better with 1-year trastuzumab compared with observation; HR 0.63 (0.45–0.87; $P = 0.0051$).[6]

Finally, the BCIRG 006 study compared combinations of trastuzumab with anthracycline or non-anthracycline based chemotherapy.[7] The investigators randomized 3222 women with early stage breast cancer HER2+ following surgery to receive either docetaxel, cyclophosphamide, and doxorubicin (AC-T) or AC-T plus trastuzumab or docetaxel, carboplatin and trastuzumab (TCH). Both trastuzumab containing regimens had significantly improved PFS and OS compared with AC-T alone. There was no significant difference in OS or PFS between the two trastuzumab regimens, but there was greater congestive cardiac failure seen in the anthracycline containing regimen compared with TCH (2.0% versus 0.4% $P < 0.001$).[7] Loss of mean left ventricular ejection fraction (defined as >10% relative loss) was 18.6% in the AC-T plus trastuzumab arm versus 9.4% in the TCH arm ($P < 0.001$) and this was still present in 33% of those patients at 4 years.[7]

Pertuzumab

The monoclonal antibody pertuzumab (Perjeta®) also targets HER2 but binds to a different epitope to trastuzumab

(subdomain II compared to subdomain IV) preventing dimerization of HER2.[8] Normally, subdomain II is responsible for dimerization of HER2 with either other HER2 receptors (homodimerization) or HER1/HER3 receptors (heterodimerization).[8] The pairing of receptors results in a cascade of signaling that promotes tumor growth[8] and may also affect tumor resistance to therapies.[9]

A Phase II study comparing two doses of pertuzumab in 78 women with HER2 negative metastatic breast cancer (MBC) whose disease had progressed through up to two lines of previous therapy resulted in limited efficacy.[10] Only two patients had a partial response (PR) with 44% (18/41) of patients in the 420 mg dose arm having stable disease (SD) and 38% (14/37) of patients in the 1050 mg arm having SD lasting >12 weeks.[10] The authors recommended that pertuzumab should not be used as a single agent in unselected patients.[10] However, as pertuzumab and trastuzumab have different mechanisms of action with pertuzumab acting as a dimerization inhibitor of HER2 compared with trastuzumab which inhibits HER2 cleavage, it was hypothesized that they would work synergistically. A Phase II study performed in 66 patients with HER2+ MBC who had previously had trastuzumab in which they received pertuzumab in combination with trastuzumab demonstrated an ORR of 24.2% with 7.6% patients experiencing complete remission (CR) and 16.7% a PR, despite the documented resistance to single agent trastuzumab.[11]

These results led to the Phase III CLEOPATRA study which randomized 808 patients with previously untreated HER2+ MBC to receive placebo, trastuzumab, and docetaxel or pertuzumab, trastuzumab, and docetaxel.[12] The investigators demonstrated a median PFS of 12.4 months in the control arm versus 18.5 months in the pertuzumab group (HR 0.62; 95% CI 0.51–0.75; $P < 0.001$).[12] Interim analysis at median 30 months follow up and 267 deaths (69% of planned events for the final analysis), demonstrated a median OS of 37.6 months for the placebo arm and had not yet been reached for the pertuzumab arm. The HR was significantly in favor of pertuzumab (HR = 0.66; 95% CI 0.52–0.84; $P = 0.0008$).[13] Dual targeting of a single receptor is superior, for HER2 at least, to monotherapy.

Trastuzumab-DM1

Trastuzumab-DM1 (T-DM1) or trastuzumab-emtansine as it is alternatively known, represents an interesting development in targeted chemotherapy delivery. It is an antibody-drug conjugate containing trastuzumab, which is covalently bonded to the chemotherapy agent emtansine.[14] Emtansine is derived from maytansine, which binds to microtubules, thereby preventing mitosis. It has previously been shown to have good cytotoxic activity, but its clinical utility was limited by its toxicity. It has however been possible to covalently bind emtansine to trastuzumab with the linker molecule (*N*-maleimidomethyl) cyclohexane-1-carboxylate.[14]

In a Phase I trial Krop et al demonstrated a confirmed objective tumor response (OR) in 5/24 heavily pretreated patients with HER2+ metastatic breast cancer (MBC).[15] Of the 15 patients treated at the maximum tolerated dose of 3.6 mg/kg, 73% achieved either OR or SD.[15]

Evidence of its activity was further validated in a Phase II trial of 112 patients with HER2+ MBC, whose disease had progressed through prior treatment with both trastuzumab and chemotherapy (median number of prior treatments was 8, range 2–19).[16] ORR in this heavily pretreated population was 25.9% (95% CI 18.4%–34.4%) by independent assessment with a follow up of greater than 12 months. Median PFS was 4.6 months (95% CI 3.9–8.6 months). It was generally well tolerated with the majority of events being grade 2 or less. The commonest grade 3 adverse events (AE) were hypokalemia (8.9%), thrombocytopenia (8.0%), and fatigue (4.5%).[16]

EMILIA, a Phase III trial comparing T-DM1 with lapatinib combined with capecitabine in 991 HER2+ patients with MBC was recently published.[17] Patients had received both prior trastuzumab and a taxane. PFS was significantly better in the T-DM1 arm (9.6 months versus 6.4 months $P < 0.001$).[17] At the second interim analysis of OS at 331 deaths, T-DM1 median OS was 30.9 months versus 25.1 months with lapatinib plus capecitabine $P < 0.001$. ORR was also greater in the T-DM1 arm (43.6%) than in the lapatinib capecitabine arm (30.8%) $P < 0.001$. Frequently occurring toxicities were fatigue (45.4%), nausea (42.3%), headache (28.7%), thrombocytopenia (28.7%), and constipation (25.5%).[18] The main grade 3 or 4 toxicities seen with T-DM1 were thrombocytopenia (12.9%) with 2% of patients discontinuing the treatment, increased bleeding risk (29.8% for T-DM1 versus 15.8% for lapatinib plus capecitabine) and increased serum transaminases with three patients discontinuing treatment due to this.[17]

Another Phase III trial, MARIANNE, has recently closed for recruitment and its results are awaited. It is examining T-DM1 plus placebo versus T-DM1 plus pertuzumab versus trastuzumab plus a taxane.[19]

EGFR inhibitors

EGFR has previously been found to promote tumor cell proliferation. EGFR is also more commonly expressed in triple negative breast cancers and is associated with a poor prognosis.[20] A number of EGFR inhibitors have been extensively

investigated as both monotherapies or in combination with other treatments.

Gefitinib

Gefitinib is a selective small molecule inhibitor of EGFR, which blocks signaling pathways involved in cell proliferation and growth.

Baselga et al performed a Phase II study examining the efficacy and pharmacodynamics of 500 mg gefitinib daily in 31 patients with MBC which had progressed through one or two previous lines of treatment, with at least 50% of patients having tumors which were EGFR receptor positive.[21] Despite finding that at that dose all the tumor biopsies analyzed (16 samples at day 28) had EGFR phosphorylation completely inhibited, none of the patients had CR or PR. SD was observed in 38.7% (12/31) patients and median time to progression (TTP) was 55 days (95% CI 42–88).[21] Other studies examining gefitinib monotherapy had a comparable low response rate.[22–24]

Gefitinib has also been investigated in combination with other agents. In a study by Ciardiello et al,[25] patients received gefitinib 250 mg daily with three cycles of docetaxel either at 75 mg/m^2 or 100 mg/m^2, increasing to six cycles if they had SD/PR/CR after three cycles. Those who had a response continued on gefitinib monotherapy until disease progression or unacceptable toxicity. They found an ORR of 54%, 22/41 patients (95% CI 45%–75%). Interestingly, the majority of responses occurred in estrogen receptor (ER) positive (ER+) tumors (70% of ER+ versus 21% ER; $P = 0.01$). The main toxicities were grade 3 or 4 neutropenia in 49% of patients, diarrhea in 10%, and rash in 5%. This is in contrast to a study by Engebraaten et al which terminated early due to toxicities including diarrhea and dehydration experienced with combining weekly docetaxel and gefitinib.[26]

In the neoadjuvant setting Smith et al examined whether adding gefitinib to anastrozole would overcome development of endocrine resistance through observing changes to Ki67 during treatment.[27] They found no clinical/biological effect. Carlson et al[28] investigated adding gefitinib to fulvestrant (n = 69) or anastrozole (n = 73) as treatment for endocrine therapy naive patients with MBC. They found that the anastrozole arm had greater efficacy with an OS of 30.2 versus 23.8 months in the fulvestrant arm.[28]

Erlotinib

Erlotinib binds intracellularly to the adenosine triphosphate binding site of the EGFR receptor, blocking downstream signaling and therefore inhibiting cell proliferation and inducing apoptosis.[29,30] A number of Phase II studies examining erlotinib have been conducted and are summarized in Table 1.[29–33] There are currently no Phase III trials examining the role of erlotinib in breast cancer.

Cetuximab

Two Phase II trials have examined cetuximab; a monoclonal antibody against EGFR. Hobday et al enrolled 19 patients with MBC previously treated with a taxane/anthracycline to receive cetuximab 400 mg/m^2 in combination with irinotecan.[34] The ORR was 11% (95% CI 1%–33%) with 12 patients progressing within two cycles; therefore the study terminated early.[34] Carey et al randomized 102 patients with triple negative MBC to receive either cetuximab alone (n = 31) or in combination with carboplatin (n = 71).[35] In the cetuximab monotherapy

Table 1 Phase II studies examining erlotinib

Study	Treatment arms	Number per arm	ORR (CR/PR)	CBR (CR/PR/SD)	Median PFS/TTP (weeks)	Median OS (months)	Comment
Dickler et al[30]	Erlotinib/bevacizumab	37	3%	14%[a]	11	–	
Kaur et al[27]	Erlotinib/weekly docetaxel	31	55%[b]	90%[b]	–	23[b]	Dose reduced due to hematological toxicity
Montagna et al[28]	Metronomic capecitabine and cyclophosphamide plus bevacizumab and erlotinib	26	62%[c]	75%[c]	TTP 43	–	
Twelves et al[29]	Capecitabine/docetaxel/erlotinib	24	67%[d]	–	–	–	Dosing varied between three arms
Graham et al[33]	Gemcitabine/erlotinib	59	14%	–	2.8 months	–	

Notes: [a]At 26 weeks on the study; [b]20 patients evaluable; [c]24 patients evaluable; [d]21 patients evaluable.
Abbreviations: CBR, clinical benefit rate; CR, complete response; ORR, objective response rate; OS, overall survival; PFS/TTP, progression free survival/time to progression; PR, partial response; SD, stable disease for 6 months.

arm ORR was 6% compared with 17% in the combined arm.[35] Median OS was 7.5 months (95% CI 5.0–11.6) and 10.4 months (95% CI 7.7–13.1) respectively. Both arms were well tolerated with the main AEs being rash, infusion reactions, and fatigue.[35]

Based on the evidence from Baselga,[21] it may be that not all tumors may be EGFR-dependent despite having EGFR receptors. To date, studies of EGFR inhibitors in breast cancer have been disappointing.

HER1/HER2 dual inhibitors

Lapatinib

Lapatinib is a dual tyrosine kinase inhibitor of both HER1 and HER2. It is thought that inhibiting both pathways overcomes tumor resistance to blockade of HER2 alone by agents such as trastuzumab.

Three Phase III studies have been conducted examining lapatinib in combination with other treatments.[36–39] The international, multicenter, open-label NeoALTTO trial randomized women with HER2+ early stage, >2 cm disease in the neoadjuvant setting to receive either lapatinib (n = 154), trastuzumab (n = 149) or combination treatment for 6 weeks followed by 12 weeks with the addition of paclitaxel.[37] Patients had definitive surgery within 4 weeks of completion of treatment. The combination arm achieved significantly better pathological complete response (pCR) 51.3% (95% CI 43.1–59.5 $P = 0.0002$ versus trastuzumab alone) than the trastuzumab arm 29.5% (22.4 –37.5) or lapatinib arm 24.7% (18.1–32.3 $P = 0.74$ compared with trastuzumab arm) suggesting that dual-targeting of the HER2 receptor may be a superior approach. Because the primary endpoint of the study was pCR at time of surgery, whether higher pCR rates correlate with improved survival for this population of women is uncertain. The combination was, however, well tolerated though rates of discontinuation of treatment were higher in the lapatinib containing arms and were mainly due to excess diarrhea and transaminitis.[37]

The MA31 Phase III trial has recently published its interim analysis comparing taxane plus lapatinib to taxane plus trastuzumab as first line treatment of HER+ MBC.[38] At median follow up of 13.6 months, data were available for 636 patients which showed a decreased PFS with the lapatinib combination versus the trastuzumab combination median PFS 8.8 months versus 11.4 months (HR = 1.33; 95% CI 1.06–1.67; $P = 0.01$).[38]

Geyer et al conducted a Phase III study randomizing women with locally advanced (LA) or metastatic HER2+ breast cancer which had progressed following a regimen which included an anthracycline, a taxane, and trastuzumab, to receive capecitabine alone (n = 163) or capecitabine and lapatinib (n = 161).[36] After 121 disease progression events, an interim analysis found that the combination group was superior with 49 events compared with 72 in the capecitabine monotherapy group HR 0.49 (95% CI 0.34–0.71; $P < 0.001$). Median TTP was 8.4 months in the combination group compared with 4.4 months for monotherapy ($P < 0.001$). ORR was 22% (95% CI 16%–29%) with combination therapy versus 14% (95% CI 9%–21%) with monotherapy ($P = 0.09$).[36] AEs did not lead to significantly more treatment discontinuations in the combination arm, although more diarrhea, rash, and dyspepsia were seen.[36] It demonstrated that targeting of the HER2 receptor beyond progression was a useful treatment option and the combination of lapatinib and capecitabine is one standard of care.

This study also demonstrated a lower risk of developing brain metastases (a major clinical problem for patients with HER2+ breast cancer) as the first site of disease progression on the combination arm (4 versus 13 months, $P = 0.045$).[39] It is thought that as it is a small molecule, lapatinib may cross the blood–brain barrier more effectively than other larger agents. A Phase II study investigated the use of lapatinib in patients with HER2+ breast cancer who had progressive brain metastases and had been previously treated with trastuzumab and whole brain radiotherapy.[40] The ORR was only 6% but a fifth of patients had a volumetric reduction of >20% in the volume of their brain metastases. On progression, patients were treated with lapatinib and capecitabine in combination with an ORR of 20%, though this improvement may have been due to capecitabine alone.

The CEREBEL trial examined the use of lapatinib as prophylaxis against brain metastases in patients with HER2+ MBC and no central nervous system (CNS) involvement at baseline.[41] Patients were randomized to receive either trastuzumab plus capecitabine (n = 218) or lapatinib plus capecitabine (n = 218). Approximately 40% of patients had not received prior trastuzumab. The primary endpoint of CNS relapse was 3% for the lapatinib arm and 4% for trastuzumab. However, both median PFS and OS were reduced in the lapatinib arm compared with trastuzumab; therefore the study was terminated early.[41] The efficacy of lapatinib in patients with brain metastases remains of interest, but uncertain. An ongoing study in the United Kingdom (LANTERN) is randomizing patients post radiotherapy for brain metastases to lapatinib and capecitabine or trastuzumab and capecitabine, which may provide further evidence.

Neratinib

Neratinib is an irreversible pan ErbB tyrosine kinase receptor inhibitor. A Phase II study by Burstein et al[42] compared patients with MBC who had received prior trastuzumab therapy (n = 66) and those who were trastuzumab naive (n = 70). They were given 240 mg neratinib and the primary endpoint of PFS at 16 weeks was evaluated. ORR was 24% in pre-treated patients (95% CI 14%–36%) and 56% in trastuzumab naive patients (95% CI 43%–69%). The treatment was generally well tolerated with diarrhea as the main grade 3/4 AE. Diarrhea improved as patients received further weeks of treatment. Further studies are ongoing.

mTOR inhibitors

The mTOR protein kinase integrates signaling from Ras and phosphatidylinositol-3-OH kinase (PI3K) resulting in further phosphorylation of downstream proteins in growth signaling pathways which, when behaving abhorrently, drive tumorigenesis.[43] Furthermore, mTOR signaling pathways are thought to contribute to anticancer drug resistance.[44]

Everolimus

Everolimus inhibits mTOR through allosteric binding to mTOR complex 1 (mTORC1). Phase II studies have investigated it in combination with hormone therapy in order to exploit its potential for overcoming hormone resistance.[45,46] The BOLERO-2 Phase III randomized study compared exemestane in combination with placebo (n = 239) or everolimus (n = 485) in women with hormone receptor positive in advanced breast cancer which had progressed while receiving prior nonsteroidal aromatase inhibitors.[47] The investigators found that the combination treatment had improved median PFS (based on central assessment) of 10.6 months versus 4.1 months with placebo (HR 0.36; 95% CI 0.27–0.47; $P < 0.001$).[47] Data for OS are yet to be presented, although at 12.5 months there were fewer deaths reported with combination treatment; 17.2% versus 22.7% with placebo.[48] The improved PFS was at the expense of more grade III toxicities for the combination arm with 19% of patients on the combination arm discontinuing treatment compared to 3% on the placebo/exemestane. The commonest grade III toxicity was stomatitis (8% versus 1%).

As previously stated, mTOR inhibitors may also be effective at overcoming drug resistance to other anti-cancer therapies. BOLERO-1 is looking at the use of everolimus in addition to trastuzumab and paclitaxel in patients with metastatic HER2+ cancer in the first line setting, with BOLERO-3 randomizing patients with metastatic HER2+ breast cancer who have received no more than three lines of cytotoxic therapy to trastuzumab and vinorelbine with or without everolimus. Results from these studies are awaited.

Temsirolimus

Although Phase II studies showed some antitumor activity and a tolerable safety profile, HORIZON, the recent Phase III study of temsirolimus versus placebo in combination with letrozole, was terminated early by the independent data monitoring committee due to lack of efficacy. Patients with hormone receptor positive MBC and no prior exposure to aromatase inhibitors were randomized to receive letrozole in combination with either temsirolimus or placebo. There was no improvement in median PFS with the addition of temsirolimus (HR 0.90 95% CI 0.76–1.07), however more grade 3/4 events were seen (37% versus 24% for placebo).[49] Trials of temsirolimus in combination with other drugs are ongoing.

PI3K inhibitors

The PI3K pathway plays an essential role in cell survival, differentiation and growth.[50] PI3Ks are activated by cell membrane receptors such as HER2 and insulin-like growth factor receptor resulting in phosphorylation of phosphatidylinositol bisphosphate to phosphatidylinositol triphosphate.[50] This enables Protein kinase B or AKT to bind, which activates mTOR resulting in further downstream signaling. Mutations in PI3K are found in 20%–30% of breast cancers, most frequently in hormone receptor positive cancers and less commonly in triple negative tumors.[51]

In addition, there may be an association between PI3K mutations and hormone therapy resistance,[52] which is being investigated further in the Phase I/II study randomizing patients to receive letrozole in combination with XL147 or XL765.[50] Phase I/II trials of other PI3K inhibitors are also currently recruiting.

Ras inhibitors

Tipifarnib

Growth factor receptor pathways are integral to cellular signal transduction and growth. A component of these pathways is the attachment of Ras proteins to cell membranes, which enables interaction with membrane receptors and downstream signaling to occur. In order to attach to cellular membranes, new Ras proteins must be modified by farnesylation which involves covalent attachment of farnesyl to a COOH-terminal amino acid sequence on the Ras protein.[53] This process is catalyzed by farnesyl protein transferase which is inhibited by tipifarnib. In addition, tipifarnib inhibits estrogen signaling pathways and theoretically may overcome resistance to hormone therapies.[54] Therefore, many of the Phase II trials in the metastatic

setting have combined tipifarnib with hormone therapy (see Table 2).[54–57] Phase III trials are yet to be conducted.

PARP inhibitors

Poly(ADP-ribose) polymerase (PARP) is an enzyme responsible for repair of single stranded DNA breaks. Olaparib is a PARP inhibitor which has been investigated in two Phase II studies. Gelmon et al treated 26 patients with advanced triple-negative breast cancer with olaparib 400 mg twice daily.[58] There were no ORs, however, in patients who had *BRCA* mutated cancers; 63% (5/8) had SD for >8 weeks. For those who were BRCA wild type, 30% (7/23) had SD. The most common AEs reported were fatigue, decreased appetite, nausea, and vomiting.[58]

In another Phase II study examining olaparib in 56 women with BRCA1 or BRCA2 positive breast cancers, an ORR of 41% (95% CI 25%–59%) was achieved in patients receiving a 400 mg twice daily dose (11/27) and 22% (95% CI 11%–41%) in those receiving 100 mg twice daily (7/27).[59] Similar AEs were reported and were mainly low grade. A Phase III trial has yet to be developed in breast cancer. Another inhibitor, iniparib which was initially thought to act on PARP, did not show significant improvement of PFS or OS when combined with carboplatin/gemcitabine in a Phase III study in women with pretreated MBC.[60] It has subsequently been demonstrated that iniparib is not an inhibitor of PARP and its development has been put on hold.

VEGF inhibitors

Tumor angiogenesis is thought to play a critical role in the growth and metastasis of tumors in order to supply cancerous cells with the nutrients and oxygen they need to survive. VEGF mediates formation of blood vessels and is known to be over expressed in breast cancer cells (see Figure 2).[61]

Bevacizumab

Bevacizumab is a monoclonal antibody which blocks VEGF from binding to its receptor on endothelial cells inhibiting their proliferation.[62] To date, unfortunately, clinical trials using the drug in breast cancer have been relatively disappointing. In the Phase III setting, four large randomized trials have been conducted.[63–66]

The AVADO trial randomized 736 patients with a local recurrence or metastatic HER2 negative breast cancer or on an intention to treat (ITT) basis to receive docetaxel with either placebo or bevacizumab at 7.5 or 15 mg/kg doses.[63] Bevacizumab at 15 mg/kg combined with docetaxel showed a statistically significant (but clinically small) improvement in PFS of median 10.1 months versus 8.2 months with docetaxel plus placebo (HR 0.77 95% CI 0.64–0.93 $P = 0.006$).[63] AEs of hypertension, bleeding, and proteinuria were more commonly seen in the bevacizumab arm, however there were similar numbers of AEs leading to death in both arms (2% in both bevacizumab arms, 3% placebo arm).[63]

Another open-label trial randomized 722 women with MBC to receive either paclitaxel (n = 354) or paclitaxel plus bevacizumab (n = 368) as first line treatment (prior adjuvant chemotherapy/hormone therapy/trastuzumab was allowed).[66] The primary endpoint was PFS and after 624 events, the combined arm had a median PFS of 11.8 months versus 5.6 months in the paclitaxel monotherapy arm (HR 0.60, $P < 0.001$). ORR was 36.9% for the combination compared to 21.2%, for paclitaxel ($P < 0.001$).[66] Importantly, neither study showed an improvement in OS with the addition of bevacizumab to standard chemotherapy.

Miller et al conducted an open label study which randomized 462 patients with heavily pretreated MBC equally to receive capecitabine alone or in combination with bevacizumab.[64] Although they found that there were increased ORRs with the addition of bevacizumab (19.8% versus 9.1%, $P = 0.001$), this did not translate into improved PFS (4.9 versus 4.2 months, HR 0.98) or OS (15.1 versus 14.5 months). The only more frequent grade 3 or 4 toxicity with the combined arm was hypertension.[64]

Table 2 Phase II studies of tipifarnib in MBC

Study	Treatment arms	Number of patients per arm	ORR (CR/PR)	CBR	Median PFS/TTP (months)
Dalenc et al[54]	Tipifarnib/tamoxifen	20	5%	50%	5.7
Li et al[55]	Tipifarnib/capecitabine	63	9.5%	32%	2.6
Li et al[56]	Tipifarnib/fulvestrant	31	35.5%	51.6%	TTP 7.2
Johnston et al[57]	Tipifarnib/letrozole	80	30%	49%	TTP 5.6
	Letrozole/placebo	40	38%	62%	TTP 10.8

Abbreviations: CBR, clinical benefit rate; CR, complete response; MBC, metastatic breast cancer; ORR, objective response rate; PFS/TTP, progression free survival/time to progression; PR, partial response.

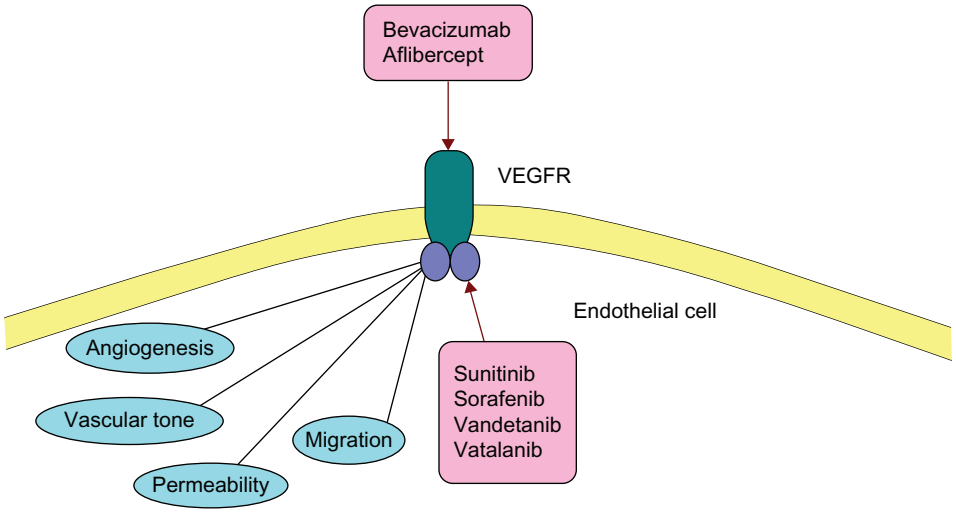

Figure 2 Role of VEGFR (vascular endothelial growth factor receptor) in vascularization/angiogenesis and its inhibitors.

The RIBBON-1 study examined whether the addition of bevacizumab to chemotherapy as first line treatment in locally advanced or metastatic HER2 negative breast cancer improved efficacy.[65] Before 2:1 randomization, investigators allocated a patient to receive either capecitabine (n = 615), a taxane based regimen (n = 307), or an anthracycline based combination (n = 315). The addition of bevacizumab improved PFS; in the capecitabine group PFS was 6.2 months with placebo versus 9.8 months with bevacizumab (HR, 0.68; 95% CI 0.54–0.86), in the taxane/anthracycline group PFS was 8.3 months with placebo versus 10.7 months with bevacizumab (HR 0.77; 95% CI 0.60–0.99).[65] There was no significant difference in 1 year OS.[65] RIBBON-2 examined the addition of bevacizumab to chemotherapy as second line treatment in the setting of HER2 negative locally advanced or MBC; 684 patients were randomized to receive chemotherapy and placebo (n = 225) or chemotherapy and bevacizumab (n = 459).[67] The median PFS was improved from 5.1 months with placebo to 7.2 months with bevacizumab (HR 0.78 $P = 0.0072$).[67]

There are a number of trials not yet reported, examining bevacizumab in the adjuvant setting based on the hypothesis that anti-angiogenic agents may be most effective as adjuvant treatment through preventing angiogenesis before metastases are established. E5103 is examining how the use of bevacizumab plus taxane and anthracycline chemotherapy after surgery may reduce the risk of recurrence and whether further bevacizumab maintenance adds benefit. BETH has randomized patients with HER2+ cancer to receive trastuzumab and standard chemotherapy plus bevacizumab or placebo. Preliminary results of the BEATRICE trial looking at the addition of bevacizumab to anthracycline/taxane based chemotherapy as adjuvant treatment for triple negative early breast cancer were recently presented at the San Antonio Breast cancer Symposium. At a median follow-up of 32 months, the hazard ratio for invasive disease-free survival was 0.87 (95% CI 0.72–1.07) in favor of patients assigned to chemotherapy and bevacizumab randomizes patients with triple negative breast cancer to receive standard chemotherapy plus placebo or bevacizumab as adjuvant therapy following surgery.[68]

Aflibercept

Aflibercept is a soluble decoy protein which has high affinity for the family of VEGF which bind to VEGFR-1 and VEGFR-2.[20] The only Phase II study reported was terminated early due to lack of efficacy and a PFS of only 2.4 months.[20]

Multikinase inhibitors

Sorafenib

Sorafenib is a multikinase inhibitor which targets a number of receptors including VEGF receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3, Flt-3, platelet-derived growth factor receptor (PDGFR), Raf kinase, and c-Kit producing both anti-angiogenesis and anti-proliferative effects. Two Phase II studies have examined its potential efficacy in breast cancer. Moreno-Aspitia et al examined the effect on tumor response of sorafenib monotherapy.[69] None of the 20 patients assessable for response achieved a CR/PR although two had SD for >6 months.[69]

Baselga et al randomized 229 patients with HER2 negative LA/MBC to receive capecitabine plus placebo or sorafenib. They found that sorafenib significantly improved PFS; 6.4 months versus 4.1 months (HR 0.58; 95% CI 0.41 to 0.81; $P = 0$ .001).[70] Toxicities of sorafenib at a dose of 400 mg twice daily were unacceptable with 20% of patients discontinuing due to AEs; therefore it was recommended that a lower dose be used in future studies.[70]

Sunitinib

Sunitinib is also a multikinase inhibitor, blocking VEGFR, ckit, and PDGFR. Three Phase III trials have investigated its use in breast cancer. Barrios et al conducted an open label trial comparing sunitinib with capecitabine in HER2 negative advanced disease. The trial was terminated early when the independent review committee deemed that it would not reach its primary endpoint of improved PFS with sunitinib compared to capecitabine.[71] Nor was PFS or OS improved when used in combination with capecitabine versus capecitabine alone in another Phase III trial randomizing patients with HER2+/– advanced disease.[72] Finally, Bergh et al also reported negative results in their Phase III study in patients with HER2– LA/MBC comparing sunitinib in combination with paclitaxel (n = 296) versus paclitaxel alone (n = 297).[73] Although ORR was significantly increased with the addition of sunitinib (55% versus 42% $P = 0.001$), there was no significant increase in PFS or OS.[73] RESILIENCE, a Phase III trial examining sunitinib in combination with capecitabine is currently recruiting.

Vandetanib

Vandetanib is an inhibitor of VEGFR and EGFR as well as RET tyrosine kinase. Two trials have investigated it in the Phase II setting and further studies are ongoing. Miller et al enrolled 46 patients with previously treated MBC to receive vandetanib in a dose-finding study.[74] They found that it was well tolerated with the main toxicities reported as rash, prolongation of QTc interval, and diarrhea which appeared to be dose dependent. There were no ORs and one patient had SD for >24 weeks.

Boér et al randomized 64 patients with pretreated MBC on an ITT basis to receive docetaxel with vandetanib (n = 35) or docetaxel with placebo (n = 29).[75] They found no clinical benefit for the addition of vandetanib, however it was generally reasonably tolerated with 15 patients discontinuing due to AEs including diarrhea and neutropenia in the vandetanib arm compared to 10 with placebo.[75]

Vatalanib

Vatalanib is a VEGFR inhibitor and at higher concentrations inhibits other tyrosine kinases such as PDGF, c-kit, and c-Fms.[76] The Hoosier oncology group conducted a Phase I/II study of vatalanib in combination with trastuzumab in patients with HER2+ MBC, but the trial was terminated due to low patient enrolment and toxicities.[77]

Future aims

The evolution of targeted therapies is an important step in the creation of individualized cancer management. The possible targets for therapies multiply, at the same time as our understanding of the mechanisms underlying cancer improves. However, better understanding of which patients will gain most benefit from targeted treatments is still required. Focus is currently on developing robust biomarkers in order to aid prediction of response so that in future, patients will receive only treatments that will confer an advantage.

Disclosure

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