Review
Recent advances in systemic therapy
When HER2 is not the target: advances in the treatment of HER2-negative metastatic breast cancer

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Abstract

The anti-human epidermal growth factor receptor 2 (HER2) agent trastuzumab has improved outcomes in breast cancer patients with HER2 over-expressing tumours. However, systemic treatment for patients with HER2-negative disease is still limited to endocrine and cytotoxic therapies. The increasing use of the anthracyclines and taxanes in early stage disease has reduced the available therapeutic options for patients with relapsed disease, and choices are further limited for patients with triple-negative tumours, who typically have a poor prognosis. The novel agents bevacizumab and ixabepilone were recently approved for metastatic breast cancer, and numerous other agents are currently in clinical development that may contribute further valuable therapeutic options.

Introduction

Metastatic breast cancer (MBC) remains incurable in most patients; the goals of treatment are to optimize quality of life, manage symptoms and prolong survival. A wide array of agents is available for the treatment of MBC, including endocrine therapies, cytotoxic chemotherapy (Table 1) and targeted biological agents. Treatment choice is influenced by a large number of factors [1], and careful consideration is required to strike a balance between the benefits of treatment and the associated side effects.

Despite the variety of agents currently available for the treatment of MBC, median survival remains 2 to 3 years, indicating considerable unmet need and the necessity for improvement. This review summarizes recent data for novel agents, either in development or recently approved for use in MBC, that have the potential to improve treatment outcomes for patients with human epidermal growth factor receptor 2 (HER2)-negative disease.

Endocrine therapy

Recommendations support the use of endocrine treatment as first-line therapy in patients with hormone-sensitive MBC [1,2]. Tamoxifen is approved for the treatment of MBC and has long been considered the 'gold standard' of therapy for hormone-sensitive disease in premenopausal or postmeno-pausal patients. However, this agent is associated with some serious side effects, including thromboembolic events and uterine cancer, both occurring predominantly in women aged 50 years or older [3].

More recently developed endocrine therapies, including the third-generation aromatase inhibitors (anastrozole, letrozole and exemestane) and the selective oestrogen receptor down-regulator fulvestrant, are at least as effective as tamoxifen but have improved tolerability [4-8]. The aromatase inhibitors are recommended as first-line therapy for postmenopausal women with hormone receptor-positive MBC; however, tamoxifen remains a valuable therapeutic option [1,2]. Treatment options for premenopausal patients include tamoxifen and ovarian function suppression (using a luteinizing hormone-releasing hormone agonist) or a combination of both [1,2].

Fulvestrant is recommended for second-line therapy after failure of tamoxifen and for third-line therapy after failure of tamoxifen and aromatase inhibitors. Other third-line agents that are used after other options have failed include progestins, androgens or high-dose oestrogens [1,2]. The increasing use of selective oestrogen receptor modulators and aromatase inhibitors in the adjuvant setting may limit their utility in the treatment of relapsed disease, and data on rechallenging with these agents are limited.

CNS = central nervous system; EGFR = epidermal growth factor receptors; ERK = extracellular signal-regulated kinase; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; MBC = metastatic breast cancer; MEK = mitogen-activated protein kinase kinase; mTOR = mammalian target of rapamycin; ORR = overall response rate; PARP = Poly-ADP ribose polymerase; PFS = progression-free survival; RR = response rate; TKI = tyrosine kinase inhibitor; TNBC = triple-negative breast cancer; VEGF = vascular endothelial growth factor.

Table 1

Preferred chemotherapy and endocrine agents and regimens for HER2-negative metastatic breast cancer

Type of therapy	Type of regimen/class of agent	Agents
Cytotoxic chemotherapies[a]	Single agents	Anthracyclines: doxorubicin (A), epirubicin (E), pegylated liposomal doxorubicin Taxanes: paclitaxel (T), docetaxel (T), *nab*-paclitaxel Fluoropyrimidines: capecitabine Others: vinorelbine, gemcitabine (G)
	Combination chemotherapy	Anthracycline based: CAF/FAC, FEC, AC, EC Taxane-based: T/cisplatin, TG, T/carboplatin, T/capecitabine Anthracycline/taxane: AT Other: CMF
	Combinations with targeted or specific anti-VEGF agents	Bevacizumab + paclitaxel
Endocrine therapies	Aromatase inhibitors	Steroidal (type I): exemestane Nonsteroidal (type II): anastrozole, letrozole
	SERMs (anti-oestrogens)	Tamoxifen Toremifene
	SERD	Fulvestrant
	Progestin	Megestrol acetate
	Androgen	Fluoxymesterone
	High-dose oestrogen	Ethinylestradiol

Adapted from Beslija and coworkers [1] and the National Comprehensive Cancer Network [2]. [a]Additional active agents are as follows: oral etoposide, vinblastine, 5-fluorouracil (F) continuous infusion, ixabepilone, and ixabepilone plus capecitabine. AC, doxorubicin, cyclophosphamide; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; EC, epirubicin, cyclophosphamide; FAC/CAF, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; HER2, human epidermal growth factor receptor 2; SERD, selective oestrogen receptor downregulator; SERM, selective oestrogen receptor modulator; VEGF, vascular endothelial growth factor.

Chemotherapy

Cytotoxic chemotherapy is the treatment modality of choice for patients with aggressive or symptomatic visceral disease, a short disease-free interval since adjuvant treatment, hormone receptor-negative disease, endocrine therapy-refractory hormone receptor-positive disease, or rapidly progressive hormone receptor-positive disease.

Anthracyclines and taxanes, used as single agents or in combination, are the most popular cytotoxic agents for the treatment of MBC [1]. Partly because of the increasing use of these agents in the adjuvant setting, an issue currently facing physicians is the choice of treatment in patients with anthracycline-resistant or taxane-resistant disease. Agents including capecitabine and vinorelbine have demonstrated clinical benefit as monotherapy and combination therapy in such patients. Gemcitabine and ixabepilone have demonstrated clinical benefit only when used in combination with taxanes and capecitabine, respectively [1].

Triple-negative breast cancer

The term 'triple-negative' breast cancer (TNBC) refers to a subgroup of patients whose tumours do not express HER2 or hormone receptors. Gene expression analysis has defined five distinct subtypes of breast cancer, with predictive and prognostic implications [9]. One of these, the basal-like subtype, shares numerous clinical and pathological features with the triple-negative phenotype, but - although there is significant overlap between the two groups - they are not synonymous [10].

Although patients with TNBC show some sensitivity to taxane and anthracycline-based regimens, they generally are at greater risk for early systemic recurrence and poorer survival than are their non-TNBC counterparts [11,12]. Interestingly, recent clinical trial data indicate that adjuvant tandem high-dose chemotherapy may be more effective than standard-dose therapy in improving 5-year event-free survival and overall survival in patients with the triple-negative phenotype [13].

Recent evidence suggests that TNBC may have increased susceptibility to platinum-based therapies relative to other breast cancers, and this has revived interest in their use [14,15]. Triple-negative tumours are known to have reduced levels of the DNA repair protein BRCA1, increasing their sensitivity to the DNA-damaging effects of platinum compounds [16]. Further information on this subject is expected from an ongoing phase III trial (NCT00532727), which is comparing platinum therapy (carboplatin) with taxane therapy

Table 2

Novel cytotoxic agents under investigation or approved for metastatic breast cancer

Agent	Drug class	Stage of development in breast cancer
Nanoparticle albumin-bound (*nab-*) paclitaxel	Taxane	Approved
Larotaxel	Taxane	III
Ixabepilone	Epothilone	Approved
Patupilone	Epothilone	II
ZK-EPO	Epothilone	II
BMS-310705	Epothilone	I
KOS-862	Epothilone	Discontinued
Vinflunine	Vinca alkaloid	II
Eribulin	Mitotic inhibitor	III
Trabectedin	Nucleotide excision repair inhibitor, cell cycle inhibitor	III

(docetaxel) in patients with triple-negative MBC. The estimated completion date of this trial, which aims to recruit around 400 patients, is 2012.

Novel cytotoxic chemotherapy agents
Novel taxane formulations
Nanoparticle albumin-bound paclitaxel
Polyethoxylated castor oil is required to make the chemotherapy agent paclitaxel water soluble before administration. Unfortunately, this excipient is also associated with hypersensitivity reactions, frequently necessitating pretreatment with steroids and ultimately compromising drug delivery to the tumour [17]. A new formulation of nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel, ABI-007; Table 2) is available as an alternative to paclitaxel, with the aim of reducing the potential for allergic reactions and improving penetration of the drug into the tumour. Indeed, in a phase III study comparing *nab*-paclitaxel with polyethoxylated castor oil-based paclitaxel in 454 patients with MBC, a significantly higher response rate (RR; 33% versus 19%, respectively; $P = 0.001$) and a longer time to progression (hazard ratio [HR] = 0.75; $P = 0.006$) was reported with *nab*-paclitaxel [18]. In addition, the incidence of grade 4 neutropenia was significantly lower among patients receiving *nab*-paclitaxel than in those receiving standard paclitaxel ($P < 0.001$), although febrile neutropenia occurred at a similar incidence with both treatments. Grade 3 sensory neuropathy was more common in the *nab*-paclitaxel arm than in the standard paclitaxel arm but, despite the fact that premedication was not used in patients receiving *nab*-paclitaxel, no hypersensitivity reactions occurred with this agent.

These findings have led to the approval of *nab*-paclitaxel in the USA, Canada and Europe for use in patients with MBC who are not suitable candidates for anthracyclines, after first-line therapy has failed. Elsewhere, studies are currently investigating combinations of *nab*-paclitaxel with other agents, including the novel anti-angiogenic agents sorafenib and bevacizumab. Preliminary data suggest that the latter agent is active and well tolerated in combination with *nab*-paclitaxel [19-21].

Larotaxel
Larotaxel is a novel semisynthetic taxane that was selected for clinical development based on preclinical efficacy against multidrug-resistant tumours and its ability to cross the blood-brain barrier (Table 2). Larotaxel has subsequently shown good clinical activity, manageable toxicity and a favourable therapeutic index in a phase II trial conducted in 130 patients who had received prior taxane therapy for MBC [22]. In general, clinical outcomes in this study were better among non-taxane-resistant patients compared with those who were taxane resistant, with overall response rates (ORRs) of 42% and 19%, median durations of response of 5.3 months and 5.0 months, median times to progression of 5.4 months and 1.6 months, and median survival times of 22.6 months and 9.8 months, respectively.

Epothilones
The epothilones are a novel class of microtubule-stabilizing anticancer drugs that prevent cell division, leading to cell cycle arrest [23]. Preclinical studies indicate that these agents have a relatively broad spectrum of activity in paclitaxel-resistant breast cancer models [24]. Several members of this drug class are currently in clinical development [25] (Table 2).

Ixabepilone
Ixabepilone, a semisynthetic derivative of epothilone B, is the only approved therapeutic agent in this class of drug and has shown significant clinical activity in patients with taxane-resistant and anthracycline-resistant tumours. Combination

therapy with ixabepilone and the oral fluoropyrimidine capecitabine significantly prolonged progression-free survival (PFS) compared with capecitabine alone in a phase III study of 752 patients with MBC resistant to anthracyclines and taxanes (HR = 0.75; $P = 0.0003$) [26]. However, the incidences of grade 3/4 fatigue (9% versus 3%) and neutropenia (68% versus 11%) were higher in the combination arm. Also, grade 3/4 sensory neuropathy occurred in 21% of patients given ixabepilone plus capecitabine, but this was not reported among patients receiving capecitabine alone. These data have been confirmed in other clinical studies of ixabepilone.

Another open-label, phase III trial randomized 1,221 patients with MBC to receive either ixabepilone plus capecitabine or capecitabine alone [27]. In both arms, 74% of patients had previously received taxanes in the metastatic setting. Haematological and nonhaematological toxicities were comparable to those in the aforementioned study, and cardiovascular events (1.8%) and toxic deaths (0.7%) were similar between treatment arms. A statistically significant improvement in PFS was seen in the ixabepilone arm but, like the previous study, overall survival was not significantly different in the combination arm.

Ixabepilone has also shown efficacy in patients with TNBC. In a subgroup analysis of data from two studies of patients with anthracycline-pretreated MBC, patients with triple-negative disease receiving ixabepilone achieved similar response rates to patients with other disease subtypes [28]. As a result of these studies, ixabepilone is approved in the USA but not in the European Union in combination with capecitabine for the treatment of anthracycline- and taxane-pretreated MBC, or for use as a monotherapy in the treatment of anthracycline-, taxane- and capecitabine-pretreated disease.

Patupilone
Patupilone (EPO-906) is structurally similar to ixabepilone but it has a different activity and toxicity profile, and is currently under investigation in MBC patients with central nervous system (CNS) metastases [29]. This dual-centre, open-label, phase II study aims to enroll 45 patients, and has a primary end-point of 3-month CNS PFS. Preliminary results from 17 patients, all of whom had received prior chemotherapy and irradiation, indicate that patupilone has modest activity in this patient group, with a 3-month PFS in the CNS of 8% [29].

Other novel cytotoxic agents
Vinflunine
The third-generation vinca alkaloid vinflunine (Table 2) has demonstrated clinical efficacy in the treatment of MBC. In a phase II trial, 31% of patients receiving vinflunine as second-line therapy for anthracycline-pretreated and taxane-pretreated disease achieved a partial response, and median PFS was 4.2 months [30]. Tolerability was generally considered to be manageable by the study investigators, although 64% of

patients developed grade 3/4 neutropenia. A similar study demonstrated clinical activity in the third-line setting [31]. Another phase II trial is planned, which will assess efficacy and safety of vinflunine in combination with capecitabine in patients with previously treated MBC; this study is not yet open for recruitment.

Eribulin
Eribulin is a synthetic analogue of halichondrin B, a naturally occurring microtubule inhibitor isolated from a marine sponge (Table 2). Eribulin monotherapy has shown clinical activity in phase II studies of heavily pretreated MBC patients, while exhibiting a relatively favourable toxicity profile, with neutropenia, fatigue and neuropathy being the most frequently reported grade 3/4 adverse events [32-34]. Phase III studies are currently underway to compare the efficacy and safety of eribulin with commonly used treatment regimens in patients with pretreated MBC.

Trabectedin
Trabectedin is another novel agent of marine origin, which interacts with DNA leading to transcriptional inhibition (Table 2) [35]. A small phase II study has reported a confirmed RR of 14% for single-agent trabectedin in 21 MBC patients who had received one or two prior chemotherapy regimens [36]. The most frequently occurring adverse event was transaminitis, which was observed in most patients; 33% of patients experienced grade 4 neutropenia. A phase III open-label trial is ongoing to investigate trabectedin in different subtypes of pretreated MBC, including one cohort of patients with triple-negative disease.

Anti-angiogenic agents
For a tumour to survive and grow, it needs to develop and maintain a network of blood vessels. Angiogenesis, the growth of new blood vessels, is therefore regarded as a key target for the development of new therapeutic strategies for breast cancer, as well as many other cancer types. A number of agents have been developed to inhibit the vascular endothelial growth factor (VEGF) pathway, which plays a key role in both normal and tumour angiogenesis (Table 3). To date, the most successful strategies have been based on direct inhibition of the VEGF ligand with a specific monoclonal antibody, or inhibition of the VEGF receptor using small-molecule tyrosine kinase inhibitors (TKIs).

Anti-VEGF monoclonal antibodies: bevacizumab
Bevacizumab is a humanized monoclonal antibody directed against VEGF and, to date, is the only inhibitor of the VEGF pathway to have received regulatory approval for use in MBC. This approval was based on the findings of a large phase III trial (E2100) that compared the clinical efficacy of bevacizumab (10 mg/kg every 2 weeks) plus weekly paclitaxel with paclitaxel alone in 722 patients with locally recurrent or MBC who had not received prior chemotherapy [37]. Patients receiving the combination regimen showed significant

Table 3

Specific or targeted anti-angiogenic agents under investigation or approved for metastatic breast cancer

Agent	Class of agent	Target	Stage of development in breast cancer
Bevacizumab	Monoclonal antibody	VEGF	Approved
Pazopanib	TKI	VEGF receptor-1, -2, -3 PDGFR-β c-Kit	III
Sunitinib	TKI	VEGF receptor-1, -2, -3 PDGFR-β c-Kit FLT3 RET CSF-1R	III
Axitinib	TKI	VEGF receptor-1, -2, -3 PDGFR-β c-Kit	II
Sorafenib	TKI	VEGF receptor-2, -3 PDGFR-β c-Kit FLT3 RET Raf	II
Vandetanib	TKI	VEGF receptor-2 RET EGFR	II

CSF-1R, colony-stimulating factor-1 receptor; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

improvements in PFS (HR = 0.42; $P < 0.0001$) and RR (48% versus 23%; $P < 0.0001$) compared with those receiving paclitaxel monotherapy. More than 90% of patients enrolled in this trial had HER2-negative disease. These investigator-assessed data were confirmed by an independent review facility, validating the original observations [37].

A subsequent phase III trial, AVADO, has studied the efficacy of bevacizumab when combined with another widely used taxane, docetaxel [38]. This study compared two doses of bevacizumab (7.5 or 15 mg/kg every 3 weeks) plus docetaxel versus placebo plus docetaxel. PFS was significantly increased with both doses of bevacizumab plus docetaxel (7.5 mg/kg: median 8.7 months; HR = 0.69, $P = 0.0035$; 15 mg/kg: median 8.8 months; HR = 0.61, $P = 0.0001$) compared with docetaxel plus placebo (median 8.0 months), as was RR (7.5 mg/kg: 55%; 15 mg/kg: 63%; placebo: 44%). All patients enrolled in this trial had HER2-negative disease.

In addition to its well described efficacy profile in MBC, bevacizumab is also well tolerated, and when it is combined with a taxane it does not impact greatly on the known safety profile of these agents. Previously reported adverse events of special interest for bevacizumab include hypertension, proteinuria, gastrointestinal perforations, wound-healing complications, haemorrhage, thromboembolic events, neutropenia, abscesses/fistulae, congestive heart failure and reversible posterior leukoencephalopathy syndrome. Although some of these adverse events of special interest were seen more frequently in the bevacizumab-containing treatment arms of both phase III studies, they were generally manageable [38,39]. Of note, in AVADO gastrointestinal perforations, arterial and venous thromboembolic events, congestive heart failure, fistula/abscess, bleeding events, proteinuria and wound-healing complications were not more common in the bevacizumab arms than in the placebo arm [38].

VEGF receptor tyrosine kinase inhibitors
Several small-molecule receptor TKIs are currently under investigation for use in MBC, including sunitinib, sorafenib, vandetanib and axitinib. These agents are multitargeted, inhibiting numerous other receptor tyrosine kinases in addition to the VEGF receptors (Table 3).

Preliminary data indicate that sunitinib, an oral multitargeted TKI with both anti-angiogenic and antitumour activities, has some activity in patients with pretreated MBC [40]. A small phase II trial of 23 patients receiving sunitinib reported a partial response rate of 17%, but haematologic toxicity was high and dose modification was required in approximately 50% of patients [40]. No data are currently available for sunitinib in combination with chemotherapy in MBC, but four phase II studies are underway, though two have been suspended following futility analyses.

Another multitargeted agent, sorafenib, has also been investigated in patients with pretreated MBC. In a phase II trial in 56 patients, one patient (2%) receiving sorafenib achieved a partial response and 19 patients (35%) had stable disease [41]. Dose reductions due to skin rash, hand-foot syndrome, hypertension and cramping of the hands and feet were required. Further phase II studies of this agent in combination with cytotoxic chemotherapy and endocrine agents are underway.

Combination therapy with axitinib plus docetaxel has demonstrated superior efficacy to docetaxel plus placebo in a phase II trial conducted in 168 patients who had not previously received chemotherapy for MBC [42]. The ORR was 40% for the docetaxel plus axitinib arm and 23% for the docetaxel plus placebo arm ($P = 0.038$). Grade 3/4 adverse events that were increased with axitinib plus docetaxel versus docetaxel plus placebo included febrile neutropenia (16% versus 7%), fatigue (13% versus 5%), stomatitis (13% versus 2%), diarrhoea (11% versus 0%) and hypertension (5% versus 2%). Axitinib is currently undergoing further evaluation in patients with MBC.

Two phase II trials of vandetanib in patients with MBC have been completed without yielding any firm evidence of efficacy. One study, a comparison of vandetanib plus docetaxel with placebo plus docetaxel in 62 patients with MBC, did not meet its primary end-point (number of progression events) [43]. The second study investigated single-agent vandetanib in 46 patients, but it reported no objective responses [44]. A phase II study of this agent in combination with the aromatase inhibitor anastrozole is currently recruiting. Elsewhere, no clinical trials have been reported with pazopanib in MBC, but a phase II study is underway to assess the activity of this agent as a monotherapy. Ultimately, given the success of the anti-angiogenic approach using bevacizumab in patients with HER2-negative disease, further investigation of these small-molecule TKIs in this patient group is warranted.

Targeting the epidermal growth factor receptor family

The epidermal growth factor receptors (EGFRs) are a family of transmembrane proteins that trigger intracellular pathways responsible for cell growth via tyrosine kinase activation. Four receptors have been identified and given the acronym HER (human epidermal growth factor receptor): EGFR/HER1, HER2/neu, HER3 and HER4.

The development of trastuzumab, an antibody against HER2 (Table 4), significantly improved the outcome for patients with HER2 over-expressing breast cancer, and is now a widely recognized treatment option in this patient group. Indeed, combination therapy with trastuzumab plus chemotherapy is the current standard first-line treatment for HER2-positive MBC, and breast cancer patients are routinely tested to determine their HER2 status. A recent retrospective analysis revealed that some patients with HER2-negative disease may also benefit from the addition of trastuzumab to their chemotherapy regimen [45]. Response to trastuzumab in these patients may be linked to polysomy of chromosome 17 [46].

EGFR over-expression has been noted in some breast tumours, most frequently in the basal subtype [47], and has been linked to poor prognosis [48]. However, EGFR expression is not a reliable marker of response to EGFR inhibitors, and EGFR status is not yet routinely tested in breast cancer [49].

Lapatinib is a dual inhibitor of EGFR and HER2 (Table 4) and is approved in combination with capecitabine for second-line or later-line treatment (after anthracyclines and taxanes) of patients with HER2-positive disease who have received prior trastuzumab therapy. However, lapatinib appears to offer little, if any, benefit to patients with HER2-negative disease. In a large phase III study investigating the combination of lapatinib and paclitaxel versus placebo and paclitaxel, the lapatinib combination failed to show any benefit over paclitaxel alone in patients with HER2-negative disease [50].

The EGFR inhibitor erlotinib (Table 4) is an effective treatment for patients with pancreatic or non-small-cell lung cancer; however, its efficacy in MBC remains unclear. In a phase II trial, single-agent erlotinib had minimal activity in heavily pretreated patients with MBC, with only one partial response and three cases of stable disease (≥12 weeks) among 69 treated patients [51]. In another phase II study of 37 patients receiving erlotinib with the anti-angiogenic agent bevacizumab, one partial response was reported and four patients achieved stable disease (>9 months) [52]. Another study suggests that greater clinical success may be achieved by combining erlotinib with gemcitabine, yielding a 14% response rate [53]. Further phase II trials with erlotinib in MBC are ongoing.

In a phase II study, patients with triple-negative MBC received combination therapy with the EGFR inhibitor cetuximab (Table 4) and carboplatin [54]. In arm 1 of the trial, patients were treated with single-agent cetuximab until disease progression, and then carboplatin was added; patients in arm 2 received combination therapy throughout. The ORR was low in both arms but favoured combination therapy (arm 1: 6%; arm 2: 18%). Adverse events occurred more frequently in the combination arm, most commonly rash, fatigue and nausea. Phase II studies of cetuximab in combination with other agents in MBC are ongoing.

A phase II study of single-agent gefitinib (Table 4) in 58 patients with taxane-pretreated and anthracycline-pretreated MBC produced an ORR of only 1.7% [55]. Gefitinib was well tolerated, but it was not efficacious as a single agent in this setting. Two randomized phase II trials of gefitinib in

Table 4

Agents targeting the EGFR family under investigation or approved for metastatic breast cancer

Agent	Class of agent	Target	Stage of development in breast cancer
Trastuzumab	Monoclonal antibody	HER2	Approved
Lapatinib	TKI	EGFR, HER2	Approved
Erlotinib	TKI	EGFR	II
Cetuximab	Monoclonal antibody	EGFR	II
Gefitinib	TKI	EGFR	Discontinued

EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; TKI, tyrosine kinase inhibitor.

combination with docetaxel also produced disappointing results [56,57]: one showed no efficacy benefit, but increased toxicity versus docetaxel alone, and the other was closed early due to treatment-related toxicity. Development of gefitinib in breast cancer has been discontinued.

Considerable interest has been expressed in modulation of resistance to endocrine therapies by concomitant inhibition of the EGFR pathway [58]. Preclinical studies have shown that combining fulvestrant with gefitinib may result in greater antitumour activity than fulvestrant alone in patients with hormone receptor-positive advanced breast cancer [59,60]. It is hoped that ongoing trials will determine whether conco-mitant targeting of the EGFR pathway will delay the onset of resistance to fulvestrant in this setting [61]. Another ongoing phase III trial is examining the effect of letrozole with or without lapatinib in patients with hormone receptor-positive MBC.

Overall, the success of EGFR inhibitors in MBC has been mixed. Although trastuzumab remains an agent of choice for patients with HER2-positive disease, there remains a lack of treatment options for patients with HER2-negative disease, and new therapeutic options for this patient population are required.

Mammalian target of rapamycin inhibitors
Mammalian target of rapamycin (mTOR) is a serine/threonine-protein kinase that is vital to the regulatory mechanisms of cell growth. mTOR inhibitors that have been, or are being, studied in breast cancer include sirolimus, temsirolimus, everolimus and deforolimus (Table 5).

The most promising data in this class have been reported from studies of temsirolimus; data with other agents remain limited. An ORR of 9.2% was reported in a phase II study of 106 patients with MBC receiving temsirolimus [62], whereas in another phase II study there was an improvement in PFS in postmenopausal women with locally advanced or MBC receiving temsirolimus combined with letrozole [63]. In a preliminary analysis of this study, median PFS in patients receiving temsirolimus plus letrozole was 13.2 months, as

compared with 11.6 months in patients who received letrozole alone. A phase III randomized, double-blind study that planned to evaluate this combination further has been discontinued.

A number of phase I and II studies are planned or ongoing investigating everolimus in combination with chemotherapy, endocrine agents, or erlotinib [64]. Although further clinical study of these agents is required, the downstream location of mTOR in relation to activated receptor tyrosine kinases, plus the relatively mild toxicity profile of these agents, makes them attractive clinical candidates for the treatment of patients with MBC.

Targeting the Ras/Raf/MEK/ERK pathway
The Ras/Raf/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) signalling cascade conveys mitogenic input to the cell nucleus through sequential phosphorylation, controlling growth regulatory functions [65]. Although Ras mutations are infrequent in breast cancers, this signalling pathway is known to play a role in endocrine therapy resistance [66]. Preclinical studies combining endocrine agents with farnesyl transferase inhibitors, which target this pathway, have reported synergistic effects [66,67]. Therefore, drugs that inhibit the Ras/Raf/MEK/ERK pathway may have important clinical ramifications for breast cancer therapy [65]. A phase II trial of two doses of the farnesyl transferase inhibitor tipifarnib (Table 5) in patients with MBC reported response rates at 6 months of 10% and 14%, and stable disease in 15% and 9% of patients [68]. Further studies combining tipifarnib with chemotherapy and endocrine agents are ongoing.

Poly-ADP ribose polymerase inhibitors
Poly-ADP ribose polymerase (PARP) is a nuclear enzyme that is involved in repairing DNA damage, and it is activated when damage of the type caused by chemotherapy and/or radio-therapy occurs [69]. Targeting PARP may prevent tumour cells from repairing DNA, a mechanism by which they develop drug resistance. Indeed, PARP inhibitors may make tumour cells more sensitive to cancer therapies [70-72]. As PARP inhibition appears to be particularly effective against

Table 5

Other agents under investigation in metastatic breast cancer

Agent	Class of agent	Stage of development
Tipifarnib	Farnesyl transferase inhibitor Inhibits Ras activation	II
Deforolimus	mTOR inhibitor	II
Everolimus	mTOR inhibitor	II
Sirolimus	mTOR inhibitor	I
Temsirolimus	mTOR inhibitor	Discontinued
KU-59436	PARP inhibitor	II
BSI-2011	PARP inhibitor	II
AG-14699	PARP inhibitor	II

mTOR, mammalian target of rapamycin; PARP, poly-ADP ribose polymerase.

BRCA1-deficient or *BRCA2*-deficient cells, PARP inhibitors may be particularly useful for the treatment of hereditary cancer with *BRCA* mutations [73,74]. Several PARP inhibitors are currently being investigated in phase II trials in patients with MBC, including KU-59436, BSI-201 and AG-14699 (Table 5). Of note, BSI-201 is currently undergoing evaluation in a multicentre, open-label, randomized phase II trial in 120 patients with triple-negative MBC. Patients receive gemcitabine plus carboplatin, either alone or in combination with BSI-201; intriguing data were presented at ASCO 2009 (O'Shaughnessy *et al.*, unpublished data) with final analysis expected in 2010.

Conclusions
Although there are many agents available for the treatment of MBC, long-term responses are infrequent and prognosis remains poor. Increasing use of anthracyclines and taxanes for early breast cancer may have reduced the usefulness of these highly active agents in the metastatic setting. Patients with HER2-negative tumours are unlikely to benefit from therapy with trastuzumab or lapatinib, and treatment options are more limited for patients with triple-negative tumours. Further study of platinum therapy and the epothilone ixabepilone in these patients is required to determine their value in this setting.

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Phase III clinical data suggest that bevacizumab may be a valuable treatment option for patients with HER2-negative MBC. Given the success of this anti-angiogenic approach, further investigation of VEGF receptor TKIs in this patient group is warranted.

In conclusion, several agents have shown promising results in clinical trials of patients with HER2-negative MBC. The new biological agents offer the potential to provide additive and synergistic therapeutic effects when used in combination with chemotherapy, and will potentially offer improved outcomes for MBC patients in the next few years.

Competing interests
DWM has received honoraria from Roche, GSK and Sanofi Aventis for invited presentations and advisory boards.

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