Triple-negative breast cancer (TNBC) is an aggressive immunohistochemical phenotype found in approximately 15% of women with invasive breast cancer. Although TNBC is sensitive to cytotoxic chemotherapy, it is associated with poorer outcomes. Moreover, patients with TNBC are not candidates for hormonal or human epidermal growth factor 2-targeted therapies, thus underscoring the need for new treatments for TNBC. Agents targeting aberrant DNA repair, including platinum and PARP-1 inhibitors, are under evaluation in TNBC based on its overlap with BRCA1-related breast cancer. Several other cytotoxic (e.g., ixabepilone) and targeted agents (e.g., bevacizumab, cetuximab, everolimus and dasatinib) are also being investigated clinically. Results from early clinical trials suggest the potential for improving the outcomes of patients with TNBC in the future.

Keywords: basal-like breast cancer • BRCA1-related breast cancer • PARP-1 • targeted therapy • triple-negative breast cancer
the inner layer of the breast duct. The HER2-positive phenotype is characterized by HER2 overexpression and a lack of hormone receptor expression; this subset predicts an aggressive clinical course, but is sensitive to HER2-targeted therapies. The normal breast-like subset typically lacks ER and HER2 expression and exhibits characteristics of normal mammary stromal cells. Some experts believe that this subset may be an artifact caused by contamination with a large proportion of normal breast tissue. However, more recent gene expression studies have identified other potential but less common subtypes. The claudin-low subtype is the most notable given that it typically carries a triple-negative phenotype and is enriched for features associated with stem cell function and the epithelial-to-mesenchymal transition.

The term TNBC encompasses breast cancer characterized immunohistochemically based on the lack of ER, PR and HER2 expression, whereas the molecular phenotypes are characterized by gene expression profiling. Although basal-like tumors are frequently triple negative, it is important to recognize that TNBC is not synonymous with basal-like tumors. Up to 30% of basal-like tumors do not exhibit a TNBC phenotype in that they show either hormone receptor or HER2 expression when evaluated by immunohistochemistry. More recently, other molecular subtypes, such as the claudin-low subset, may fall under the TNBC umbrella.

TNBC is associated with overexpression of the basal CKs 5, 6 and 17, reflecting its overlap with the basal-like subset. In addition, the EGFR receptor (EGFR; HER1) is overexpressed in up to 60% of TNBC tumors. Other molecular markers that are expressed at rates higher in basal-like tumors than in other molecular breast cancer subtypes, and consequently may also be associated with TNBC, include c-kit, p53 (or TP53 gene mutations), p16, cyclin E, E2F3 and α-B-crystallin. Conversely, expression levels of the retinoblastoma protein and cyclin D1 are typically reduced. TNBC has been further characterized on the basis of CK 5/6 and EGFR expression: the term ‘core basal phenotype’ has been used to identify a subset of TNBC tumors that express either CK 5/6 and/or EGFR, whereas the term ‘quintuple-negative’ has been used to refer to TNBC tumors that express neither CK 5/6 or EGFR (i.e., ER, PR, HER2, CK 5/6 and EGFR negative). It should be noted, however, that the quintuple-negative subgroup among patients with TNBC is typically very small. The clinical relevance of this additional stratification remains to be determined, but several studies suggest that it may add significance to the prognostic information conferred by TNBC status.

Histologically, TNBC generally presents as a ductal carcinoma, but some cases have mixed histology with features of metaplastic or medullary carcinomas. A large majority of tumors associated with TNBC are high-grade (Nottingham grade III). In the TNBC cohort from the Carolina Breast Cancer Study, 84% had tumors with Nottingham grade III whereas only 2% were low-grade tumors (grade I). Most TNBC tumors were noted to have marked nuclear pleomorphism (80%) and high mitotic index (>10 per 10 high-power fields; 87%) [19]. Consistent with this profile, TNBC is associated with high expression of the proliferation marker Ki-67 and exhibits pushing margins of invasion, with a stromal lymphocytic infiltrate at the tumor margins and multiple necrotic cores.

Clinical features

Population-based studies indicate that women with TNBC are younger at diagnosis and more likely to be African-American than those with non-TNBC [9,21,22]. In the California Cancer Registry, for example, women with TNBC were 53% more likely to be diagnosed at 40 years of age or younger and 77% more likely to be African-American compared with non-TNBC cases [21]. Similarly, in the Carolina Breast Cancer Study, women with basal-like breast cancer were diagnosed at a significantly younger age and had a higher proportion of African-Americans compared with the luminal subtypes [19]. TNBC is also associated with obesity among premenopausal women [22]. However, the higher incidence of TNBC among African-Americans appears unrelated to patient age or body mass index [23].

BRCA1 mutations – a risk factor for early-onset familial breast cancer – are also seen more frequently in TNBC than non-TNBC cases [24–27]. In a cohort of 491 breast cancer patients who underwent genetic testing for BRCA1/2 mutations, TNBC was identified in 57% of the BRCA1-positive patients compared with 23 and 18% of BRCA2-positive and BRCA-negative patients, respectively [25]. Although a family history of breast cancer among first-degree relatives is associated with increased risk of breast cancer, it is not associated with a preferential risk increase for TNBC compared with other molecular subtypes based on recent data from the Breast Cancer Surveillance Consortium [28].

Prognosis & outcome

Early-stage TNBC is highly sensitive to neoadjuvant cytotoxic chemotherapy; however, TNBC has a paradoxical poor prognosis with increased risk of early...
relapse, different patterns of metastasis (visceral > bone), and reduced survival compared with other breast cancer subtypes. In a cohort of 1601 women with early-stage breast cancer, the risk of distant recurrence in the subset with TNBC peaked at 1–3 years following diagnosis, after which it declined and matched the lower-risk levels seen in non-TNBC patients [29]. The poor survival of patients with TNBC is illustrated by data from the California Cancer Registry, which compared 6370 women with TNBC with 44,704 women with other breast cancer types [21]. Survival at 5 years following diagnosis was significantly lower among patients with TNBC compared with patients without TNBC (77 vs 93%); this survival difference was evident regardless of the disease stage at diagnosis (Figure 2). Several other smaller studies have consistently shown similar findings of shorter survival for TNBC compared with non-TNBC [24,29–31].

When classified by expression profiling, the survival of patients with basal-like tumors is comparable to those with HER2-overexpressing tumors, both of which are significantly shorter than survival of patients with luminal A or B tumors [32]. However, the advent of adjuvant trastuzumab has significantly improved the prognosis of patients with early-stage HER2. No such targeted therapy exists yet for early-stage TNBC; however, early developments in adjuvant clinical trials with PARP-1 inhibitors are promising.

TNBC continues to confer a survival disadvantage even after development of distant metastases. In a cohort of 3726 patients initially diagnosed with early-stage breast cancer between 1986 and 1992 (median follow-up time of 14.8 years) and having archival tumor specimens for expression analysis, median survival following distant metastasis was 0.5 years for patients with basal-like tumors compared with 0.7 years for those with HER2-overexpressing tumors and 1.6–2.2 years for those with luminal A or B tumors [33]. Similarly, in another study, median survival from the time of distant recurrence was significantly shorter for patients with TNBC compared with patients without TNBC (9 vs 20 months; p = 0.02) [29]. This poorer survival in the metastatic disease setting associated with TNBC may reflect higher rates of visceral metastases and lower rates of bone metastases compared with non-TNBC cases [33–35]. Additionally, patients with metastatic TNBC are at increased risk of developing brain metastases.

**Figure 1. Overlap among triple-negative breast cancer, basal-like and BRCA1-related tumors.**

CK: Cytokeratin; EGFR: EGF receptor; TNBC: Triple-negative breast cancer.

**Traditional cytotoxic therapies for TNBC**
The primary treatment for TNBC is cytotoxic chemotherapy [2,16]. TNBC is highly sensitive to anthracyclines and anthracycline/taxane combinations, but patients have a relatively high risk of relapse, and as noted previously, a poorer outcome when compared with patients without TNBC. Evidence for the chemosensitivity of TNBC has been shown in several neoadjuvant and adjuvant clinical studies. In a cohort of 1118 women with early-stage breast cancer (including 255 patients with TNBC), neoadjuvant chemotherapy, consisting primarily of an anthracycline-based or anthracycline/taxane-based regimen, produced higher pathologic complete response (pCR) rates in women with TNBC compared with other breast cancer subtypes (22 vs 11%; p = 0.034) [30]. Three-year survival for women achieving pCR was comparable for TNBC and non-TNBC cases (94 vs 98%; p = 0.24). However, for those with residual disease, 3-year survival was significantly poorer in the TNBC subset (68 vs 88%; p < 0.0001; Figure 3). Comparable data were reported with neoadjuvant doxorubicin/cyclophosphamide with or without sequential taxane therapy in a cohort of 107 women [36]. Higher pCR rates were achieved among basal-like and HER2-overexpressing patients compared with those having luminal subtypes (p = 0.01). Early relapse was rare after pCR regardless of breast cancer subtype, whereas with residual disease, outcome was poorer for the basal-like and HER2-overexpressing subset compared with the luminal subsets. The addition of capcitabine to anthracycline/taxane regimens has also proven effective in studies of patients with early breast cancer. Data
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from the Phase III ABCSG-24 trial demonstrated significant improvements in pCR with the addition of capecitabine to a neoadjuvant regimen of epirubicin plus docetaxel (24.3 vs 16.0%; p = 0.02) [37]. Furthermore, a review of subgroup analyses from ABCSG-24 showed that patients with TNBC (n = 122) had a significantly greater chance of achieving a pCR than non-TNBC (n = 348; odds ratio = 5.29; 95% CI: 3.22–8.68; p < 0.0001), independent of the regimen. And in the total study population, the highest pCR rates were achieved in patients with TNBC who received epirubicin, docetaxel and capecitabine compared with those who only received epirubicin and docetaxel (47.5 vs 31.2%; p = NS) [38]. Taken together, these studies highlight the importance of achieving pCR with neoadjuvant therapy in patients with early-stage TNBC. In two recent studies, sequential anthracycline/taxane regimens produced pCR rates of 29 and 36% in patients with TNBC [39,40]. This underscores the need for more effective therapies capable of producing much higher pCR rates.

In the adjuvant setting, a meta-analysis of four Phase III clinical trials suggested that adjuvant anthracycline-based therapy was more effective than classical cyclophosphamide, methotrexate and fluorouracil in prolonging disease-free survival (DFS) in TNBC (hazard ratio [HR]=0.77; 95% CI: 0.54–1.09) [41]. The magnitude of benefit of anthracycline-based therapy was comparable to that of patients whose cancers overexpress HER2. In comparison, there was no difference in DFS among patients with HER2 or TNBC with regard to the two regimens. Results from the Phase III FinXX trial have also demonstrated the effectiveness of adjuvant anthracycline – as part of sequential therapy – with significant improvements in 3-year recurrence-free survival (RFS) observed with the incorporation of capecitabine to a sequential taxane-anthracycline adjuvant regimen (92.5 vs 88.9% control; HR = 0.66; 95% CI: 0.47–0.94; p = 0.020) [42]. A subsequent review of subgroup analyses from FinXX demonstrated that patients with TNBC (n = 202) had significantly shorter RFS than patients without TNBC (n = 1294; 81.7 vs 92.2%; HR = 0.43; 95% CI: 0.29–0.63; p < 0.001). Moreover, 3-year RFS was significantly longer in the capecitabine-containing treatment arm (n = 93) than in the control arm (n = 109; 87.7 vs 76.6%, respectively; HR = 0.43; 95% CI: 0.21–0.90; p = 0.024) [38]. These promising data for capecitabine in early breast cancer have provided the foundation for an ongoing randomized Phase III study conducted by the CIBOMA collaborative group. This trial is prospectively investigating capecitabine-maintenance therapy after adjuvant anthracycline/taxane treatment in patients with early TNBC (NCT00130533).
Triple-negative breast cancer & new treatment developments

Use of anthracyclines and taxanes in early-stage disease limits their value in the metastatic disease setting, directed in part by emergence of drug resistance, as well as limitations on the maximum cumulative dose due to cardiotoxicity (anthracyclines) or neurotoxicity (taxanes). Nevertheless, patients with metastatic TNBC remain sensitive to cytotoxic chemotherapy. In a cohort of 111 patients with metastatic TNBC, many of whom were treated with neoadjuvant or adjuvant chemotherapy, the median duration of first-, second- and third-line treatment was approximately 12, 9 and 4 weeks, respectively [48]. Median survival for the entire cohort with metastatic TNBC was 13.3 months. The short durations of treatment indicate a need for more effective interventions that can be administered over longer intervals once metastatic TNBC occurs.

Newer therapies under investigation for TNBC
Numerous agents are currently being explored for use in TNBC – both in neoadjuvant/adjuvant therapy, as well as in treatment of metastatic disease (Table 1).

Agents targeting aberrant DNA repair
Patients with mutated *BRCA1* have defects in homologous recombination mechanisms that repair DNA double-strand breaks [44]. The overlap of TNBC with *BRCA1* breast cancer raises the possibility that the pathogenesis of TNBC may also involve defective DNA repair. This has led to reconsideration of alkylating agents, such as cisplatin and carboplatin, that interfere with DNA repair, as well as the development of PARP-1 inhibitors that target the key enzyme involved in base excision repair of single-strand DNA. The latter pathway is important in repairing DNA damage in cells with defective homologous recombination.

In a retrospective analysis of patients treated at the Royal Marsden in London, neoadjuvant platinum-based chemotherapy produced higher clinical complete response rates in TNBC than in non-TNBC (88 vs 51%; p = 0.005), although DFS tended to favor the non-TNBC subset [45]. In a Phase II neoadjuvant study, 74 patients received eight cycles of cisplatin, epirubicin and paclitaxel with granulocyte-colony stimulating factor support. This regimen produced a pCR in 46 patients (62%) with large, operable TNBC [46]. 5-year DFS was 90 and 56% among patients who did and did not achieve pCR, respectively. In a similar population, neoadjuvant cisplatin, epirubicin and infusional fluorouracil followed by weekly paclitaxel produced pCR in 12 of 30 patients with TNBC (40%) and 2-year DFS of 87.5% [47]. In comparison, four cycles of single-agent cisplatin (75 mg/m² every 21 days) resulted in pCR in only six of 28 patients with TNBC (22%). Interestingly, decreased *BRCA1* mRNA expression was associated with good response to cisplatin therapy [48].

Platinum-based chemotherapy has also been suggested to produce favorable results in patients with advanced TNBC compared with patients without TNBC. In a retrospective cohort from the Royal Marsden, the TNBC subset had a numerically higher response rate (41 vs 31%), significantly longer progression-free survival (PFS; 6 vs 4 months; p = 0.05), and a trend for longer overall survival (OS; 11 vs 7 months; p = 0.10) [48]. In a retrospective study of 36 patients, cisplatin/gemcitabine showed a trend for longer PFS in metastatic TNBC compared with non-TNBC (5.3 vs 1.7 months; p = 0.058) [49]. However, in another retrospective study of 143 patients with metastatic breast cancer, platinum-based therapy was not associated with improvement in PFS or OS in TNBC compared with non-TNBC, despite a higher response rate (33 vs 22%) [50].

Brostallicin (PNU-166196A) is a new synthetic α-bromoacrylic derivative that belongs to the pharmacological class of DNA minor groove binding anticancer agents. In preclinical human and murine tumor models, brostallicin is a potent inducer of apoptosis, which retains activity in cancer cells resistant to alkylating agents, topoisomerase I inhibitors, and is fully active against DNA mismatch repair-deficient tumor cells [51–53]. The North Central Cancer Treatment Group is conducting a Phase II trial (N0937) of cisplatin followed by brostallicin in patients with advanced TNBC who have received up to four prior lines of therapy in the metastatic setting (NCT01091454). The rationale for this study is based on preclinical observations that cisplatin increases

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<td><strong>Approach</strong></td>
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expression of glutathione S-transferase in tumor cells, and that brostallicin has greater cytotoxicity in tumor cells with elevated levels of glutathione and glutathione S-transferase. The PARP-1 inhibitors are novel targeted agents designed to inhibit single-strand DNA repair mechanisms that may be important to the survival of TNBC cells, especially those harboring a BRCA mutation. Multiple studies of PARP-1 inhibitors in TNBC are currently in progress. The furthest advanced of the PARP-1 inhibitors is iniparib (also known as BSI-201). It was evaluated in a randomized Phase II trial involving 116 patients with TNBC who had received up to two prior chemotherapy regimens for metastatic disease [54]. Patients were allocated to carboplatin/gemcitabine with or without iniparib, with the PARP-1 inhibitor administered at a dose of 5.6 mg/kg intravenous twice-weekly for the first 2 weeks of a 3-week cycle. When added to carboplatin/gemcitabine, iniparib significantly improved the response rate (52.5 vs 32.3%; \( p = 0.023 \)), PFS (5.9 vs 3.6 months; \( p = 0.0012 \)), and OS (12.3 vs 7.7 months; \( p = 0.014 \)) compared with carboplatin/gemcitabine alone. Chemotherapy-related adverse events were not increased by the addition of iniparib to carboplatin/gemcitabine. The encouraging data from this trial have led to a randomized Phase III study using the same treatment arms. This trial is now complete and awaits final assessment (NCT00938652). Notably, on 28 January 2011, a press release from Sanofi-Aventis and its subsidiary, BiPar Sciences, stated that this Phase III trial did not meet the specified criteria for significance for co-primary end points of OS and PFS. Conversely, data from the prespecified analysis in patients treated in the second- and third-line setting do support the findings reported in the Phase II trial – improvement in OS and PFS.

The PARP-1 inhibitor olaparib (AZD2281) was evaluated in advanced breast cancer patients with BRCA1 or BRCA2 mutations in a multicenter, proof-of-concept, Phase II trial [59]. The study cohort had received a median of three previous chemotherapy regimens. Olaparib produced objective responses in a dose-related manner (41% at 400 mg twice daily [b.i.d.] and 22% at 100 mg b.i.d.) and was well tolerated with mainly grade 1/2 toxicities. Importantly, at an end-of-year discussion, AstraZeneca decided to discontinue the Phase III trial of olaparib in TNBC with BRCA mutations and instead, focus on development in serous ovarian cancer – a decision apparently based on iniparib not meeting its end points in the Phase III trial.

Other studies of PARP-1 inhibitors in TNBC are currently in progress, including a Phase II trial of iniparib plus carboplatin/gemcitabine as neoadjuvant therapy (NCT00813956), and Phase I trials of olaparib with either carboplatin, paclitaxel, or both in metastatic disease (NCT00516724; NCT00647062; NCT00707707). Another PARP-1 inhibitor, veliparib, is being investigated with and without carboplatin in a Phase II trial in patients with BRCA1/2 mutations (NCT01149083) and in combination with cisplatin/vinorelbine in a Phase I study in patients with metastatic TNBC (NCT0104259). Additional studies are also in development and will likely be activated by the time of this publication.

### Angiogenesis inhibitors

VEGF is a major angiogenic factor in human malignancies. Patients with TNBC have been shown to have higher intratumoral levels of VEGF compared with patients without TNBC [31]. When added to first-line paclitaxel, the anti-VEGF monoclonal antibody bevacizumab significantly improved PFS compared with paclitaxel alone in the Phase III E2100 trial, with subset analyses showing comparable benefits among hormone receptor-negative patients (which is a TNBC cohort given the HER2-negative status of the study population) as in hormone receptor-positive patients [56]. A meta-analysis of patients with TNBC treated in the first-line setting in the Phase III E2100, AVADO, and RIBBON-1 trials assessed the difference in PFS and OS between treatment groups (chemotherapy [taxane-, anthracycline-, or capecitabine-based] plus bevacizumab compared with chemotherapy alone). Although median PFS was significantly longer in the chemotherapy plus bevacizumab cohort compared with chemotherapy alone (8.1 vs 5.4 months; unstratified HR = 0.65; 95% CI: 0.54–0.78, log-rank \( p < 0.0001 \); stratified HR = 0.68; 95% CI: 0.56–0.83, log-rank \( p = 0.0002 \)), there was no significant difference in OS (18.9 vs 17.5 months, respectively; unstratified HR = 0.96; 95% CI: 0.79–1.16, log-rank \( p = 0.673 \); stratified HR = 0.99; 95% CI: 0.81–1.21, log-rank \( p = 0.930 \) [57]). In a separate study, bevacizumab added to first-line nab-paclitaxel/gemcitabine produced a clinical benefit rate of 85% in a small subgroup of patients with metastatic TNBC, which was comparable to the benefit seen in hormone receptor-positive, HER2-negative patients in a single-arm Phase II study [58]. Bevacizumab is currently being evaluated in numerous trials in patients with TNBC, including the Phase III BEATRICE trial comparing bevacizumab plus chemotherapy versus chemotherapy alone in the adjuvant setting (NCT00528567). Notable Phase II studies in first-line treatment of metastatic TNBC include bevacizumab plus carboplatin/gemcitabine (NCT01201265) and bevacizumab plus bevacizumab/docetaxel (NCT01208480) and bevacizumab in combination with sequential nab-paclitaxel/
Sunitinib is a tyrosine kinase inhibitor that targets the VEGF receptor, PDGF receptor, and c-kit. Sunitinib administered at a dose of 50 mg/day for 4 weeks of a 6-week cycle produced objective responses in three of 20 (15%) patients with metastatic TNBC previously treated with an anthracycline and a taxane [59]. In another Phase II trial, first-line treatment with sunitinib 25 mg/day in combination with weekly paclitaxel produced responses in three of nine (33%) patients with TNBC [60]. Other outcome data for the TNBC subsets in these trials were not reported. Sunitinib is currently being evaluated in a randomized Phase II trial against standard-of-care chemotherapy in patients with advanced TNBC who had been treated previously, with up to two prior chemotherapy regimens (NCT00246571). Results based on an independent central review showed no significant improvement in median PFS in patients treated with sunitinib compared with those treated with standard-of-care chemotherapy (2.0 vs 2.7 months, respectively; HR = 1.20; 95% CI: 0.89–1.63; 1-sided p = 0.889). Similarly, sunitinib did not prolong median OS (9.4 vs 10.5 months, respectively; HR = 1.22; 95% CI: 0.89–1.68; 1-sided p = 0.892) [61]. Sunitinib is also being investigated in a Phase I/II trial as neoadjuvant therapy in combination with paclitaxel/carboplatin for TNBC (NCT00887575). However, it is unlikely that sunitinib will play any significant role in breast cancer management. SUN 1107, a Phase III trial of sunitinib versus capecitabine in a broad range of advanced breast cancer patients with metastatic TNBC who had been treated previously, with up to two prior chemotherapy regimens (NCT00633464). Results from a trial comparing cetuximab plus cisplatin with cisplatin alone in patients with metastatic TNBC treated with up to one prior regimen (NCT00463788) demonstrated that the addition of cetuximab to cisplatin nearly doubled the overall response rate (ORR): 20.0% (95% CI: 13.1–28.5) versus 10.3% (95% CI: 3.9–21.2; p = 0.05 for testing ORR against 20.0%). Moreover, cetuximab in combination with cisplatin was associated with a significantly lower risk of disease progression compared with cisplatin alone (HR = 0.675; 95% CI: 0.470–0.969; p = 0.032), with a manageable safety and toxicity profile [65].

The EGFR tyrosine kinase inhibitor erlotinib is also being evaluated in Phase II clinical trials in TNBC. In one study, patients with advanced breast cancer are given first-line nab-paclitaxel plus bevacizumab over a 24-week period, and those without disease progression receive maintenance therapy with bevacizumab plus erlotinib until disease progression (NCT00733408). Other trials are evaluating erlotinib in combination with neoadjuvant chemotherapy (NCT00491816) and in combination with bendamustine in women with advanced breast cancer (NCT00834678). However,
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a Phase II trial of erlotinib in patients with EGFR-overexpressing TNBC was recently terminated due to poor accrual (NCT00739063). Although, as previously noted, up to 60% of TNBC may express EGFR, the results of some of the above trials raise serious questions as to whether EGFR is an appropriate target in this malignancy.

- **Src inhibitors**

Src tyrosine kinase is an important messenger in numerous steps of oncogenesis, including tumor cell proliferation, invasion and metastasis [66]. Preclinical studies suggest that basal-like/TNBC cell lines are more likely to respond to src inhibitors, such as dasatinib, than other breast cancer subtypes [67]. Moreover, breast cancer cells that have undergone an epithelial-to-mesenchymal transition – which correlates with the basal-like phenotype – are also highly sensitive to src kinase inhibition [68]. Dasatinib exhibited modest single-agent activity in a Phase II trial involving women with advanced TNBC who had received prior anthracycline and/or taxane therapy and up to two previous regimens in the advanced disease setting [69]. Dasatinib was initially given at a dose of 100 mg b.i.d. but it caused toxicity necessitating dose interruption or delay. The starting dose was subsequently lowered to 70 mg b.i.d., and the drug was generally well tolerated with fatigue (9%) as the most common grade 3 event. Because both of the starting doses resulted in similar exposure, the efficacy analysis was combined. Overall, patients responded to dasatinib unfavorably, with partial responses observed in only two of 43 evaluable patients (5%) lasting 54 and 8 weeks, respectively. The disease control rate was 9.3% and median PFS was 8.3 weeks. Dasatinib is still being evaluated in multiple clinical trials in breast cancer, but only one trial is specifically evaluating the role of dasatinib in the adjuvant setting: the TTIAN trial is comparing sequential adjuvant therapy with doxorubicin plus cyclophosphamide followed by either ixabepilone or paclitaxel in patients with TNBC (NCT00789581), and the PACS-08 trial is comparing sequential adjuvant therapy with 5-fluorouracil, epirubicin and cyclophosphamide, followed by either ixabepilone or docetaxel (NCT00630032) in patients with TNBC or ER positive – but PR/HER2-negative with poor prognosis – patients. In addition, the Phase II ECLIPSE study is evaluating ixabepilone plus carboplatin in patients with metastatic breast cancer treated with up to two lines of prior therapy and includes a predefined analysis of the TNBC subgroup (NCT01075100).

- **PI3K-Akt pathway inhibitors**

The PI3K/Akt pathway utilizes signals from the cell surface to drive a variety of cellular functions including proliferation, survival and apoptosis. Approximately 70% of breast cancers have mutations in components of the PI3K/Akt pathway [75]. Loss of the phosphatase and tensin homolog is common in TNBC and results in activation of the mTOR, a downstream kinase in the PI3K/Akt pathway that regulates G1 cell-cycle protein synthesis prior to cell replication [76,77]. Blocking mTOR suppresses proliferative signals causing cell-cycle arrest. The mTOR inhibitor everolimus was evaluated in first- or second-line treatment of advanced breast cancer in a Phase II trial [77]. When administered at a dose of 10 mg/day, everolimus produced objective responses in 12% of patients, with HER2-negative status being predictive of clinical benefit. However, the activity of
everolimus in patients with TNBC in this trial was not specified. Of patients receiving daily everolimus, 16% discontinued due to pneumonitis. Everolimus is currently being evaluated in several Phase II trials specifically targeting TNBC: as single-agent therapy (NCT00827567), in combination with carboplatin for metastatic disease (NCT01127763), and in combination with cisplatin/paclitaxel in the neoadjuvant setting (NCT00930930). Another mTOR inhibitor, temsirolimus, is also being evaluated in breast cancer. However, none of the ongoing trials is specifically targeting the TNBC population.

**Future perspective**

Although multiple targeted therapy approaches are being explored in clinical trials, cytotoxic chemotherapy continues to be the mainstay of treatment for TNBC. Understanding the role of BRCA1 in DNA repair and its overlap with TNBC has led to reconsideration of platinum agents and development of PARP-1 inhibitors. Similarly, identification of EGFR overexpression as a common marker in basal-like tumors and recognition of common mutations in downstream effector pathways has led to multiple targeted approaches. As a greater understanding is obtained about the mechanisms driving this aggressive phenotype, new targeted strategies for TNBC should continue to evolve over the next 5–10 years. Those therapies with proven benefit will be integrated into current treatment paradigms. Apart from targeted therapy, newer cytotoxic agents with low susceptibility to common resistance mechanisms will provide additional treatment options for patients with TNBC.

Triple-negative breast cancer is a heterogeneous subtype and consequently, a ‘one-size-fits-all’ treatment strategy is unlikely to be optimal. It is anticipated that predictive biomarkers identified in the coming years can be used to select patients with TNBC who are most likely to respond to a specific treatment. The development of targeted therapies and identification of predictive biomarkers are expected to have a substantial impact on TNBC. Such an impact would be analogous to the benefit of hormone therapy in hormone receptor-positive breast cancer and HER2-targeted therapies in HER2-positive disease. As a result, it is anticipated that outcomes for patients with TNBC will improve over the next 10 years.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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**Executive summary**

- Triple-negative breast cancer (TNBC) is an aggressive phenotype identified by immunohistochemical analysis. However, TNBC is actually a heterogeneous classification that overlaps with the basal-like subtype identified by gene expression analysis, as well as with BRCA1-related breast cancer.
- Cytotoxic chemotherapy is the mainstay of treatment for TNBC. Despite high chemosensitivity, TNBC is associated with poor patient outcomes underscoring the need for new treatments.
- Newer treatment approaches – both in terms of chemotherapy and targeted agents – are currently being evaluated in ongoing clinical trials. Initial results with several agents appear promising both in early-stage and metastatic disease.
- Predictive biomarkers need to be identified to select those patients with TNBC who are most likely to benefit from various treatments.

**Bibliography**

Papers of special note have been highlighted as:

- of interest
- of considerable interest


This seminal study classifies breast tumors in different subtypes based on their gene expression.


The retrospective study shows that outcomes differ between TNBC and non-TNBC for those with residual disease after neoadjuvant chemotherapy but not for those achieving pathologic complete response.


Demonstrates that patients with basal-like tumors have higher sensitivity to anthracycline-based neoadjuvant chemotherapy than those with luminal tumors. Despite the initial chemosensitivity, patients with luminal tumors have poorer outcomes.


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17 Choi YL, Bocanegra M, Kwon MJ et al. ILYN is a mediator of epithelial-mesenchymal transition and a target of dasatinib in breast cancer. Cancer Res. 70, 2296–2306 (2010).

18 Linterman M, Bocanegra M, Kwon MJ et al. ILYN is a mediator of epithelial-mesenchymal transition and a target of dasatinib in breast cancer. Cancer Res. 70, 2296–2306 (2010).


22 Stead LA, Lash TL, Sobieraj JE et al. Triple-negative breast cancers are increased in black women regardless of age or body mass index. Breast Cancer Res. 11, R18 (2009).


30 The retrospective study shows that outcomes differ between TNBC and non-TNBC for those with residual disease after neoadjuvant chemotherapy but not for those achieving pathologic complete response.


37 Demonstrates that patients with basal-like tumors have higher sensitivity to anthracycline-based neoadjuvant chemotherapy than those with luminal tumors. Despite the initial chemosensitivity, patients with luminal tumors have poorer outcomes.


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45 Reviews the role of BRCA1 in the repair of DNA double-strand damage and provides the basis for treatment strategies targeting aberrant DNA repair.


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Saal LH, Holm K, Maurer M et al. PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. *Cancer Res.* 65, 2554–2559 (2005).