research article

*Annals of Oncology* 23 (Supplement 6): vi46–vi51, 2012
doi:10.1093/annonc/mds195

# Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents

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Triple-negative breast cancer (TNBC) is an aggressive histological subtype with limited treatment options and very poor prognosis following progression after standard chemotherapeutic regimens. Resistance to current standard therapies such as anthracyclines or taxanes limits the available options for previously treated patients with metastatic TNBC to a small number of non-cross-resistant regimens, and there is currently no preferred standard chemotherapy. Duration of response is usually short, with rapid relapse very common and median survival of just 13 months. The newly approved agent eribulin has shown a survival benefit in patients who had previously been treated with anthracycline- or taxane-containing regimens, including in patients with TNBC. Platinum-based regimens are an emerging option for patients with *BRCA1* mutation, and newer targeted agents such as anti-angiogenic treatment with bevacizumab or anti-epidermal growth factor receptor treatment with cetuximab, have shown some benefit in combination therapy. However, there remains an urgent unmet need for improved targeted agents for this patient population. Improved treatment may be facilitated by biomarker-led understanding of subgroup molecular targets, which may predict benefit from currently approved agents, as well as newer targeted drugs.

**Key words:** approved, metastatic, treatment, triple-negative breast cancer



## introduction

Triple-negative breast cancer (TNBC) is clearly defined based upon immunohistological criteria, but it remains a heterogeneous disease that encompasses a number of intrinsic molecular subtypes, most frequently basal-like and claudin-low [1]. TNBC has a highly aggressive nature, accounting for a disproportionate number of metastatic disease cases and breast cancer deaths [2–4]. Nevertheless, studies of neoadjuvant chemotherapy suggest that women with TNBC who have a pathological complete response (pCR) to treatment achieve excellent outcomes [5, 6]. Unfortunately, the majority of patients with TNBC have residual disease after treatment of early breast cancer, and for these patients, there is a high risk of relapse and a sharp decrease in survival in the first 3–5 years after treatment [2, 7–9]. The peak risk of disease recurrence is at ~3 years after treatment, and late relapse is rare [7]. A high proportion of patients therefore eventually present with metastatic TNBC, and the majority of these patients have relapsed shortly following prior treatment. The focus of this review will be the currently available treatment options and their optimal use in this pretreated patient population.

## currently approved therapies and treatment strategies

### efficacy of established approved treatments

There is currently no preferred standard chemotherapy for previously treated patients with TNBC, as previous randomised studies in the metastatic setting have not addressed the predictive values of the molecular subtypes of breast cancers. Treatment is therefore selected (as for other subtypes) from a number of current recommended agents that are approved in the general breast cancer population. Conventional treatments for relapsed patients are limited, particularly, because standard chemotherapeutic regimens containing anthracyclines and taxanes have usually already been given in the adjuvant and neoadjuvant settings.

Anthracyclines and taxanes have been suggested as rechallenge regimens in patients with 6–12 months of disease-free survival following completion of adjuvant chemotherapy and recurrence [10]. There are few data on the use of anthracycline- and taxane-containing rechallenge regimens as first- or second-line therapy for metastatic breast cancer, and there is therefore a lack of reliable evidence documenting their efficacy [10]. To date, only one prospective phase III trial examining anthracycline rechallenge has been reported [11]. In this study, 751 patients with advanced breast cancer who had previously been treated with neoadjuvant or adjuvant anthracycline therapy, were randomly assigned to receive either

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docetaxel or pegylated liposomal doxorubicin (PLD) followed by docetaxel [11]. Treatment with PLD–docetaxel significantly improved time to progression (median 10 versus 7 months for docetaxel monotherapy) and overall response rate (ORR; 35% versus 26% for docetaxel monotherapy). However, it should be noted that PLD has a different pharmacological profile than non-pegylated anthracyclines, and the conclusions regarding the validity of the rechallenge concept should be treated with caution. Moreover, cumulative doses of non-pegylated anthracyclines should be monitored closely in view of the potential for cardiac adverse events such as congestive heart failure. Further studies will be required to confirm whether anthracycline- and taxane-containing rechallenge regimens are appropriate treatment of patients with metastatic breast cancer. Importantly, there is no evidence investigating the use of anthracycline- and taxane-containing rechallenge regimens in patients who have previously been treated with both types of agent.

The major cause of metastatic treatment failure is multidrug resistance to standard therapies, which can be either primary (preceding drug exposure) or acquired resistance (induced by treatment) [12, 13]. Patients with progression or resistance may be given non-cross-resistant agents such as capecitabine, gemcitabine, vinorelbine or albumin-bound paclitaxel, and combination regimens with these agents have demonstrated efficacy in studies in patients with anthracycline-pretreated advanced breast cancer [14, 15]. Superior survival has been demonstrated with capecitabine plus docetaxel combination therapy compared with docetaxel alone in anthracycline-pretreated patients with advanced breast cancer [16], and until the recent approval of ixabepilone, capecitabine was the only additional agent that was US Food and Drug Administration (FDA)-approved following failure of anthracycline/taxane therapy [17]. In a recent randomised phase II study, comparable efficacy and toxicity data were obtained with three gemcitabine-based regimens in pretreated patients, with ORR of 39% (gemcitabine/vinorelbine), 48% (gemcitabine/cisplatin) and 35% (gemcitabine/capecitabine). Corresponding median survival times were 17.5, 13.0 and 19.4 months, respectively [18]. The use of multidrug regimens in the treatment of patients with metastatic breast cancer is controversial, particularly when first-line trials of combination regimens have not always addressed the questions directly relevant to daily clinical practice. The 2009 European School of Oncology Metastatic Breast Cancer Task Force (6th European Breast Cancer Conference) recommended sequential monotherapy for advanced breast cancer, and patient- and disease-related factors to be used in determining which patients would benefit from combination regimens, who remain poorly defined [19]. Other consensus groups have arrived at a recommendation to administer polychemotherapy for aggressive disease with associated risks to inner organ function [20]. Therefore, given the aggressive nature of TNBC and the need for tumour shrinkage in most cases, the authors would recommend a multidrug regimen rather than a single-drug regimen for this subtype.

Despite the available treatment regimens, an analysis of prospectively collected data from 1118 patients (including 255 patients with TNBC), showed that TNBC patients with residual disease after neoadjuvant therapy had significantly worse survival outcomes than non-TNBC patients in the first 3 years following treatment [6]. Duration of response for metastatic TNBC patients is thus usually short, with rapid relapse very common. A recent retrospective multicentre analysis ($N = 111$) of patients with metastatic TNBC receiving various forms of single-agent or multi-agent palliative therapy (67% and 33% of patients, respectively) showed that median duration of first-line palliative therapy was just 12 weeks (range 0–73 weeks). Eighty-seven patients (78%) went on to receive second-line therapy with a median duration of 9 weeks (range 0–121 weeks), and 55 patients (49%) received third-line therapy with a median duration of 4 weeks (range 0–59 weeks). Median overall survival (OS) for patients with metastatic TNBC was 13 months (range 1–100 months) [21], which compares unfavourably with median OS for the general metastatic breast cancer population (median OS 2.0–3.5 years) [22, 23].

Platinum-based regimens have attracted some attention as potential TNBC therapies, and their use has been supported by the strong association of TNBC tumours with germline mutations in the *BRCA1* gene, with ~10% of TNBC tumours having *BRCA1* mutation (90% of *BRCA1*-mutated tumours are TNBC, and 80–90% of *BRCA1*-associated breast cancers display a basal-like phenotype) [24, 25]. *BRCA1* mutation compromises the ability of the tumour to recover from DNA-damaging agents by reducing their capacity for DNA repair by homologous recombination [26]. pCR rates of 72–83% have been reported for *BRCA1* mutation-positive patients, although first-line pCR rates are typically much lower (16–32%) if *BRCA1* mutation is not considered [27–31]. Platinum agents have shown limited benefit in the general metastatic breast cancer patient population, but some randomised trials have addressed the efficacy of platinum-based regimens in metastatic TNBC. A retrospective analysis of platinum–taxane regimens indicated similar response rates (39%) to non-TNBC but worse OS [32]. There has been recent early evidence of activity for platinum doublets, and in another retrospective study, the cisplatin/gemcitabine combination was reported to improve outcomes in TNBC patients [33]. However, overall outcomes remain poor in the general TNBC population. For example, in a recent randomised phase II study of iniparib, a novel investigational anticancer agent, in patients with metastatic TNBC, the gemcitabine/carboplatin arm ($n = 62$) had a progression-free survival (PFS) of 3.6 months, and a median OS of only 7.7 months [34].

In a systematic review of six trials employing high-dose chemotherapy, an overall event-free survival benefit was seen in metastatic breast cancer patients but without substantial OS benefit. Nevertheless, metronomic, dose-dense or high-dose regimens with existing chemotherapeutic agents have shown benefit in adjuvant studies in patients with TNBC, and in the metastatic setting ($n = 850$), event-free survival benefit from high dose chemotherapy (HDC) at 1 year (hazard ratio [HR] = 1.8, $P < 0.00001$) and at 5 years (HR = 2.8, $P = 0.04$) was reported [35]. HDC may therefore be an effective method of optimising currently available chemotherapy for the treatment of patients with metastatic TNBC [36, 37]. However, overall, the prognosis for patients with relapsed TNBC

is very poor when treated with conventional cytotoxic therapies.

### efficacy of recently approved therapies

Eribulin has recently been European Medicines Agency (EMA) approved for advanced or metastatic breast cancer in patients who have progressed after at least two chemotherapeutic regimens for advanced disease and who received prior anthracycline and taxane regimens where suitable. Approval was based on the results of the global phase III EMBRACE study ($N = 762$) assessing treatment of the physician's choice (TPC) versus eribulin, which demonstrated a statistically significant increase in OS compared with TPC (median OS 13 versus 11 months, HR 0.81; $P = 0.041$) [38]. The majority of these patients (74%) were human epidermal growth factor receptor (EGFR)-2-negative, and 19% had TNBC. Of note, eribulin was most effective in hormone receptor-negative patients who had a 34% decreased risk of death compared with TPC chemotherapy, and in TNBC patients, who had a 29% risk reduction, whereas it was least effective in patients who received eribulin without a treatment history that included capecitabine [39].

Ixabepilone is an epothilone antimicrotubule agent, which was FDA approved in 2007 for locally advanced or metastatic breast cancer in combination with capecitabine after failure of anthracycline/taxane therapy. FDA approval was based on the results of two pivotal trials. In a phase II trial ($N = 113$), patients with metastatic breast cancer that had progressed on prior anthracycline, taxane and/or capecitabine therapy received ixabepilone as monotherapy [40]. An ORR of 18% was observed, with 14% of patients achieving stable disease of ≥6 months. The median duration of response, PFS and OS were 5.7, 3.1 and 8.6 months, respectively. This preliminary study was followed by an open-label phase III trial ($N = 752$), which compared ixabepilone plus capecitabine with capecitabine alone in patients with anthracycline-pretreated or -resistant, and taxane-resistant locally advanced or metastatic breast cancer [41]. Patients treated with ixabepilone plus capecitabine demonstrated a 25% reduction in the estimated risk of disease progression (HR = 0.75, 95% CI 0.64–0.88) compared with patients who received capecitabine only [41]. The ORR of patients was also greater for the ixabepilone-treated group (35% versus 14% for capecitabine). However, grade 3/4 treatment-related adverse events were more frequent in the ixabepilone treatment group than in those receiving capecitabine only, with a greater rate of neuropathy (21% versus 0%), fatigue (9% versus 3%) and neutropenia (68% versus 11%) [41].

Despite being approved for use in the United States, ixabepilone has not been approved by the EMA for the treatment of breast cancer, following concerns that the risks associated with the agent (in particular neuropathy [42]) may outweigh its benefits. Nevertheless, the response to ixabepilone plus capecitabine in phase III study subsets has been reported as being superior in TNBC patients, with improved PFS (4.2 versus 1.7 months for capecitabine alone; HR = 0.63, 95% CI 0.52–0.77, $P < 0.0001$); however, no increase in OS was reported [43]. A single partial response to single-agent ixabepilone was reported in a small study in patients with taxane-resistant TNBC [44].

The use of anti-angiogenic therapies for TNBC is supported by the highly proliferative nature of TNBC and the importance of vascular endothelial growth factor (VEGF) in the microvascular proliferation of this disease. The anti-VEGF monoclonal antibody bevacizumab has shown benefit in some TNBC subgroups if combined with taxanes and other agents [45–49]. In the RIBBON-1 trial, the addition of bevacizumab to capecitabine increased PFS from 4.2 to 6.1 months (HR = 0.72, 95% CI 0.79–1.06) in the TNBC subgroup ($n = 137$), although benefit was modest when bevacizumab was added to taxane/anthracycline-based therapy (6.5 versus 6.2 months; HR = 0.78, 95% CI 0.53–1.15) in the TNBC subgroup ($n = 142$) [48]. A meta-analysis of all three phase III trials of bevacizumab as first-line therapy investigated the efficacy of the agent in a pooled subset of 621 patients with TNBC [46]. Median PFS was longer in patients treated with bevacizumab plus chemotherapy than in those treated with chemotherapy alone (8.1 versus 5.4 months, respectively), but no difference in OS was observed [46]. Similar observations were made in a subgroup analysis of the RIBBON-2 trial, which investigated various chemotherapies with and without bevacizumab as second-line treatment of metastatic breast cancer [49]. In patients with TNBC ($n = 159$), improvements in PFS with bevacizumab were marked (median 6.0 versus 2.7 months for chemotherapy alone; $P = 0.0006$) and a trend towards improved OS was observed (HR = 0.624), which did not reach statistical significance ($P = 0.0534$), perhaps due to the small sample size [49].

Although larger, prospective, randomised trials of bevacizumab in TNBC are ongoing, the agent is not currently recommended by the FDA for use in metastatic breast cancer, despite having previously been granted approval [50]. An earlier meta-analysis of all three phase III trials of bevacizumab as first-line therapy (corresponding to a pooled analysis of 2447 patients) failed to identify a statistically significant difference in OS when considering the metastatic breast cancer population as a whole—a conclusion that has also been raised by the FDA [50, 51]. In contrast, bevacizumab plus paclitaxel continues to be recommended by the National Comprehensive Cancer Network and has retained its label in a recent EMA decision as first-line treatment of metastatic breast cancer [52, 53].

The anti-VEGFR tyrosine kinase inhibitors sunitinib and sorafenib have shown some activity in breast cancer trials with significant TNBC populations, with a 15% response rate reported for sunitinib in a phase II trial [54, 55]; however, neither agent is currently approved for the treatment of breast cancer. The EGFR-directed monoclonal antibody cetuximab is FDA and EMA approved for the treatment of colorectal and head and neck cancer. EGFR is overexpressed in 60% of basal-like tumours and is a negative prognostic factor in TNBC [56–58]. The BALI-1 trial evaluated cetuximab in combination with cisplatin ($N = 173$) for the treatment of metastatic TNBC, and an ORR of 20% was reported (versus 10% for cisplatin alone); PFS was 3.7 versus 1.5 months (adverse events reported were rash, neutropenia and fatigue) [59]. Activity has also been reported in combination with carboplatin [60] and irinotecan [61]; however, cetuximab is not yet approved for the treatment

**Table 1.** Recent data in metastatic triple-negative breast cancer (TNBC) patients on treatments newly approved for the general breast cancer patient population

| Agent | Phase (trial) | Metastatic TNBC patients | Setting | Results |
|---|---|---|---|---|
| Ixabepilone | III | 433 | +Capecitabine | Superior ORR and PFS for combination: PFS = 4.2 versus 1.7 months; HR = 0.63 (95% CI 0.52–0.77); trend toward improved survival [42] |
| Bevacizumab | III (ECOG2100, AVADO, RIBBON)[a] | 621 | +Chemotherapy | PFS improved upon addition of bevacizumab (8.1 versus 5.4 months for chemotherapy alone; unstratified HR = 0.65 [95% CI 0.54–0.78, $P < 0.0001$]; OS 18.9 versus 17.5 months; unstratified HR = 0.96 [95% CI 0.79–1.16, $P = 0.673$]); grade 3–5 AEs 53% versus 46%; grade 3 hypertension 7.5% versus 1.6% [45] |
| Eribulin | III (EMBRACE)[b] | 144 | Monotherapy versus TPC | OS benefit; HR = 0.71 (95% CI 0.46–1.10) [38] |

[a]Meta-analysis of pooled data from three phase III trials.
[b]Subgroup analysis.
AEs, adverse events; CI, confidence interval; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TPC, treatment of physician's choice.

of metastatic breast cancer. Overall, newer approved agents for the general breast cancer population have resulted in modestly improved outcomes in some TNBC patient subsets (Table 1), but the prognosis for metastatic TNBC patients remains poor.

## predictive markers of chemosensitivity to current agents

Clearly, there is an urgent need for the introduction of predictive markers, which may lead to ameliorated and targeted management of triple-negative disease. Thus, predictive biomarkers that may identify potential benefit from currently approved breast cancer therapies in TNBC patients may facilitate improved outcomes for these patients. Such predictive markers may include *BRCA1* mutation, p53 and caveolin 1, for which certain data indicate therapeutic potential. BRCA1-deficient tumours show cisplatin sensitivity in animal models, and *BRCA* mutation may predict sensitivity to platinum-based regimens (or other DNA-damaging agents) in TNBC patients. This is exemplified by the greater rates of pCR to neoadjuvant therapy that have been seen in *BRCA1*-mutated patients [27]. Other potential predictive markers include the scaffolding protein caveolin 1, which is overexpressed in TNBC and has been suggested as a predictor of paclitaxel benefit [62]. The tumour suppressor protein family members, p63 and p73 are co-expressed exclusively in the TNBC subset with mutational inactivation of p53, and both mediate and predict platinum sensitivity [63]. In a multivariate analysis of pooled results in patients treated with front line anthracycline-based regimens of various cyclophosphamide dose intensities, a lack of oestrogen receptor (ER) expression and high-dose cyclophosphamide administration were associated with a higher likelihood of pCR and a statistical interaction was detected between p53 status and cyclophosphamide dose intensity [64]. In patients with ER-negative tumours, a mutant *p53* status was associated with anthracycline resistance. However, p53 inactivation was required for response to the dose-intense alkylating regimen and may thus predict high levels of pCR in TNBC patients for this cyclophosphamide dose-intensified regimen [64]. New markers expressed by basal-like, claudin-low, and other TNBC encompassing molecular subgroups may also be useful in optimising current therapies.

Amplification of the *VEGF-A* gene has been reported in 34% of TNBC tumours, and biomarker-driven studies of anti-VEGF-A drugs in patients with TNBC may lead to improved outcomes for these patients, particularly in combination with standard cytotoxic therapies [65]. Standard cytotoxic agents have already been shown to give improved response rates when combined with anti-VEGF-A agents [48, 54]. In the E2100 phase III study comparing paclitaxel with paclitaxel plus bevacizumab as initial chemotherapy for metastatic breast cancer, the VEGF genotype for selected polymorphisms in VEGF and VEGF-2 was found to be predictive of outcome [66]. However, ultimately the heterogeneity of TNBC means that multiple molecular biomarkers may be required to accurately predict benefit from current treatments.

## conclusion

TNBC is an aggressive subtype with limited treatment options and very poor prognosis following progression after standard anthracycline or taxane regimens. Dose-dense and/or metronomic regimens may help to optimise current therapies, but there is an urgent unmet need for new effective therapies for patients with metastatic disease. Platinum-based regimens are an emerging option for patients with *BRCA1* mutation. Although anti-angiogenic treatment with bevacizumab has shown benefit in combination therapy, withdrawal of FDA approval of this agent for metastatic breast cancer (although not withdrawn by the EMA) makes the further development of the drug in TNBC difficult to foresee at the current stage. Investigational anti-angiogenic agents and other potential future targeted treatments such as poly(ADP-ribose) polymerase inhibitors, iniparib and EGFR inhibitors, are reviewed elsewhere in this supplement. In the short term,

improved treatment of TNBC patients may be facilitated by biomarker-led understanding of subgroup molecular targets, which may predict benefit from currently approved agents, as well as newer targeted drugs.

## acknowledgements

Editorial assistance was provided by ArticulateScience Ltd., funded by Sanofi. The authors retain full control of content.

## disclosures

FA has been compensated as a member of a Speakers' Bureau for Sanofi. CCZ has nothing to disclose.

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