The Breast Journal

ORIGINAL ARTICLE

The Paradox of Triple Negative Breast Cancer: Novel Approaches to Treatment

Monica Fornier, MD,* and Pierre Fumoleau, MD†

Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York City, New York; and †Centre Georges-François Leclerc, Dijon, France, 1 rue Professeur Marion, BP 77980 Dijon Cedex France

■ **Abstract:** Breast cancer that lacks expression of estrogen/progesterone receptors and overexpression of the human epidermal growth factor receptor2 (HER2), i.e. triple-negative breast cancer (TNBC), is not amenable to current targeted therapies and carries a poor prognosis. This review discusses the natural history of TNBC and published literature in the relevant treatment landscape, with a focus on newer therapies. Compared with other subtypes of breast cancer, TN tumors have higher response rates to neoadjuvant chemotherapy; however, this advantage is not clearly translated into the metastatic setting and has not improved these patients' overall survival. Numerous cytotoxic and targeted strategies have demonstrated efficacy or are under investigation. Strategies showing promise in this difficult-to-treat group of patients include cytotoxic therapy with platinum-containing agents, ixabepilone, and novel targeted approaches such as poly(ADP-ribose) polymerase inhibitors. ■

Key Words: ixabepilone, novel agents, poly(ADP-ribose) polymerase, platinum agents, triple-negative breast cancer

Breast cancer that lacks expression of estrogen receptor/progesterone receptor, and overexpression of the human epidermal growth factor receptor 2 (HER2), or triple-negative breast cancer (TNBC), accounts for around 15–20% of breast cancers in the US. It typically carries a poorer prognosis than other breast cancer subgroups, with shorter periods of disease-free and overall survival (OS) (Fig. 1) (1–3). TNBC also has a propensity for visceral or central nervous system metastases (4–7).

A retrospective analysis of 1601 breast cancer patients showed that compared with other breast cancer subgroups, those with TNBC have a significantly higher risk of distant recurrence and death within 5 years of diagnosis (5). In this analysis, the risk of recurrence rose sharply from date of diagnosis, peaked at 1–3 years after surgery, and dropped quickly thereafter. This pattern was distinct from the steady risk of recurrence characteristic of other breast tumor subtypes (Fig. 2).

Address correspondence and reprints request to: Monica Fornier, MD, Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA, or e-mail: fornierm@mskcc.org.

DOI: 10.1111/j.1524-4741.2011.01175.x

Patients with TNBC tend to have a worse prognosis than patients with hormone receptor-positive disease, but a better prognosis than patients who have disease, which is hormone receptor-negative, but HER2-overexpressed and not treated with trastuzumab (8).

Triple-negative breast cancer continues to be the focus of intense clinical research, and this article seeks to review what is currently known about treating this enigmatic subtype, focusing on newer therapies that have shown promise in recent clinical trials. It is hoped that the current work will aid oncologists in evaluating the ever-changing treatment landscape of this challenging disease.

METHODS

For this review, clinical data with relevance to the molecular biology or treatment of TNBC were compiled through searches within PubMed and congress abstract databases, with no date limits, specific inclusion, or specific exclusion criteria applied. These searches were current as of December 2010. Bibliographies of publications were also scanned by eye for additional relevant studies not captured in the initial searches, and ongoing clinical trials in TNBC patients were identified from the National Institutes of Health

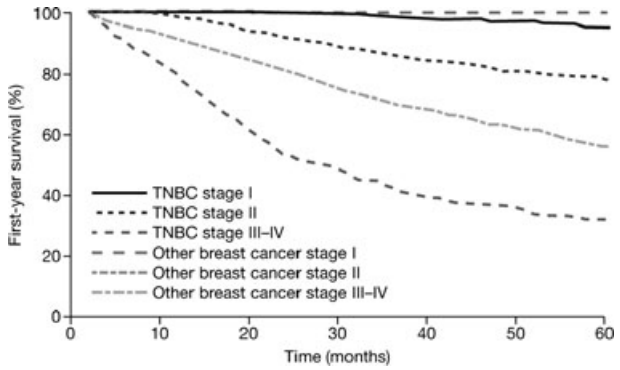

Figure 1. California cancer registry: survival of triple-negative breast cancer (TNBC) (1).

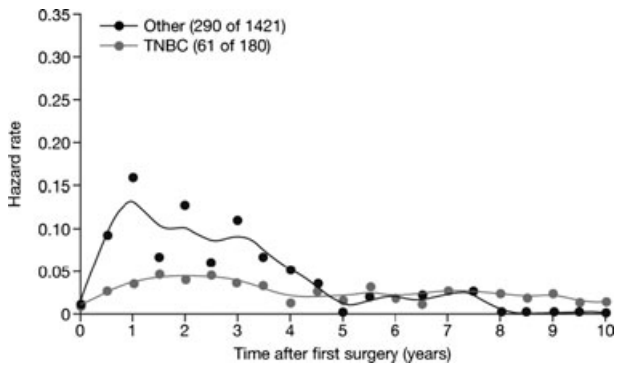

Figure 2. Rates of distant recurrences following surgery in triple-negative breast cancer (TNBC) and other breast cancers (5).

clinical trial registry. Preference for inclusion was given to more recent phase II or III studies, although older studies were included if they contained data that were deemed relevant to current clinical practice. Ongoing clinical trials were included if designed to focus on the efficacy or safety of therapeutic agent(s) in TNBC patients. Relevant preclinical molecular biology, biomarker, and statistical references were also included to provide sufficient background on the disease state.

INCIDENCE AND RISK FACTORS

Studies in the United States report that TNBC accounts for 15–20% of breast cancers in the general population (1,9), but TNBC has a higher prevalence among premenopausal women and women with the *BRCA1* mutation (10–12). The incidence and prevalence of TNBC also varies with race. The prevalence of TNBC in Asian women ranges from 12% to 19% (13–17), and in a population of Hispanic women, the prevalence was 24% (18). Reported incidences in black women are particularly high, ranging from 26% in all ages to as high as 39% in premenopausal black women (10). In a retrospective analysis of 471 TNBC patients diagnosed between 1996 and 2005 and treated with primary systemic therapy, investigators found no significant difference in relapse-free or OS between non-black and black patients, after controlling for patient and tumor characteristics (19).

Although black women in the US and UK have a higher breast cancer mortality rate than white women (20,21), race does not appear to be predictive of treatment efficacy in patients with TNBC.

Aside from premenopausal status and African descent, other possible risk factors for TNBC include younger age at menarche, higher parity, younger age at first term birth, choosing not to breastfeed, pharmacological lactation suppression, and elevated waist-to-hip ratio (22,23). Recent evidence suggests that metabolic syndrome may also increase the risk of TNBC (24).

MOLECULAR FEATURES OF TRIPLE-NEGATIVE BREAST CANCER

Breast cancer may be subdivided into five molecular subtypes using complementary deoxyribonucleic acid (cDNA) microarray profiling: luminal subtype A (estrogen receptor and/or progesterone receptor positive, and HER2 normal), luminal subtype B (estrogen receptor and/or progesterone receptor positive and HER2 overexpression), HER2-overexpressed/gene-amplified basal-like, and normal breast-like (Table 1) (10,25,26). Approximately 85% of TNBCs fall within the basal-like subtype, the remaining 15% being termed ''non-basal-like'' and consisting largely of luminal-B tumors (a subtype that typically has lower estrogen receptor expression than the luminal-A subtype) (27). As the majority of TNBC lesions are basal-like, the terms ''basal-like'' and ''TN'' are often used

Table 1. Summary of Breast Cancer Molecular Subtypes (10,25,26)

Molecular subtype	Luminal subtype A	Luminal subtype B	ERBB2+	Basal-like	Normal breast-like
Breast cancer (%)	~50	~15	~7	~20	~6
Prognosis	Good	Intermediate	Poor	Poor	Poor
ER expression	✔	✔	x	x	✔/x
HER2 overexpression	x	✔	✔	x	✔/x

✔, ER expressed / HER2 overexpressed; x, ER not expressed/normal expression of HER2; ER, estrogen receptor

interchangeably; however, distinct similarities and differences exist for these two tumor types (28). Like TN tumors, tumors with *BRCA1* mutations are strongly associated with the basal-like phenotype (26), and TN tumors tend to share characteristics with *BRCA1*-associated tumors. Basal-like and TN tumors have important differences in terms of messenger RNA (mRNA) expression patterns: basal-like tumors tend to express c-kit, epidermal growth factor receptor (EGFR) or HER1, and mutant forms of p53 (26,29), while TNBCs have exhibited a more heterogeneous mRNA expression pattern in gene profiling studies (30). Furthermore, basal-like tumors specifically express one or more of the cytokeratins, CK5/6, CK17, and CK14, whereas, some TN tumors do not express any of these markers (28). These expression patterns have important implications for treatment that will be discussed later in this article. Interestingly, non-basal-like TNBC may carry a better prognosis than basal-like TNBC. In a study of 958 women, the 16 women with non-basal TNBC experienced rates of distant recurrence comparable to those with hormone receptor-positive disease (31). A recent retrospective analysis showed that patients with recurrent and/or metastatic TNBC may be classified into two subgroups by relapse-free survival (RFS). Furthermore, TNBC patients with RFS $\geq$ 3 years had a better disease control rate (DCR), progression-free survival (PFS) to first-line palliative chemotherapy, and OS than those with RFS < 3 years (DCR 55% versus 77%, p = 0.022; median PFS 3.6 versus 7.7 months, p = 0.0001; median OS 17.4 versus 42.0 months, p = 0.0003) (32). Given these differences, it may be wise to consider different treatment strategies for these subgroups.

CLINICAL FEATURES OF TRIPLE-NEGATIVE BREAST CANCER: THE TRIPLE-NEGATIVE PARADOX

No formal guidelines exist regarding which specific systemic regimens are most appropriate for TNBC. Lack of estrogen receptor, progesterone receptor, or HER2 overexpression rules out tailored therapeutic approaches with endocrine and HER2-directed therapies. Conventional cytotoxic therapy is the only treatment recommended by the National Comprehensive Cancer Network (33). The paradox of TNBC lies in that it seems to be particularly responsive to cytotoxic chemotherapy, but this responsiveness frequently has little bearing on patient survival.

Neoadjuvant/Adjuvant Setting

Triple-negative breast cancer is sensitive to chemotherapy, and patients who achieve a pathological complete response (pCR) with neoadjuvant treatment have good OS. In fact, recent clinical trial data indicate that patients with hormone receptor-negative tumors (basal-like or ERBB2-positive) show better responses to adjuvant and neoadjuvant chemotherapy regimens than patients with luminal A and B tumors (34–37). Patients with TNBC treated with platinum-based chemotherapy in the neoadjuvant setting have demonstrated a higher pCR rate than those with non-TN disease, although this topic is controversial (38). In a study of anthracycline- and taxane-based neoadjuvant therapy, Rouzier and colleagues reported a significantly higher pCR rate for basal-like and ERBB2-positive tumor types than for luminal tumors (45% versus 7%) (36). In a subsequent analysis, Carey and colleagues reported pCR rates of 36% and 27%, respectively, for patients with the ERBB2-positive and basal-like subtypes, compared with 7% for luminal tumors (p = 0.01) (35). Patients who achieved a pCR had good prognosis regardless of tumor subtype; however, patients with basal-like or ERBB2-positive tumors who did not achieve pCR had a higher risk of relapse and poorer prognosis than other subgroups.

Similar results were found in an analysis of a prospectively collected clinical database of 1118 patients who received neoadjuvant chemotherapy for stage I–III breast cancer between 1985 and 2004. The study showed that patients with TNBC had significantly higher pCR rates than non-TNBC patients (22% versus 11%, p = 0.034) (6). As before, TNBC patients who achieved a pCR had similar OS to patients with non-TNBC, but among those with residual disease (RD), TNBC patients had significantly decreased OS compared with those with non-TNBC (hazard ratio [HR], 1.5; 95% confidence interval [CI], 1.3–1.8; p < 0.0001) (Fig. 3) (6). Furthermore, recent data indicate that TNBC patients who respond to treatment and remain disease-free for at least 3 years tend to survive without recurrence. In contrast, it is not uncommon for non-TNBC to relapse over a decade (5,39).

Metastatic Disease

Patients with TNBC that metastasizes typically have poor survival (7). A retrospective analysis of the CALGB 9342 study found that among patients treated with paclitaxel, OS was significantly shorter in those

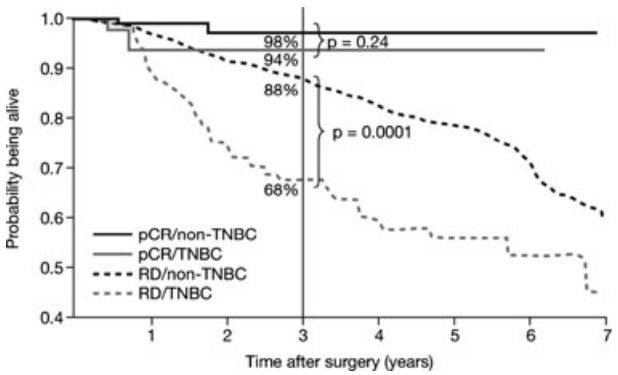

Figure 3. Overall survival (OS) as a function of response to chemotherapy (pathological complete response [pCR] versus residual disease [RD]) and triple-negative [TN] status (triple-negative breast cancer [TNBC] versus non-TNBC) (6).

with TNBC compared with those with non-TNBC (8.7 versus 12.9 months; p = 0.008), despite similar objective response rates (ORRs) and times-to-treatment failure (40). Furthermore, a retrospective multicenter review of patients with metastatic TNBC (n = 111) noted rapid progression through multiple lines of chemotherapy: median durations of response for first-, second-, and third-line palliative treatments were 12 weeks (range, 0–73.1 weeks), 9 weeks (range, 0–120.9 weeks), and 4 weeks (range, 0–59 weeks), respectively (41).

Such high relapse rates and short OS highlight a clear need for more effective treatment options. As TNBC has increased chemosensitivity in the neoadjuvant setting compared with luminal tumors, and as patients achieving a pCR seem to have similar outcomes to patients with other genotypic profiles, optimizing early chemotherapy might improve the outcomes for this patient group. Moreover, distinguishing subtypes of TNBC may be of great importance in developing targeted regimens for this disease. In addition, because these patients are at increased risk of visceral or brain metastases—early brain metastases in particular (associated with poor survival)—they may be candidates for preventive strategies that target brain metastases (4,6).

NOVEL APPROACHES TO TREATMENT OF TRIPLE-NEGATIVE BREAST CANCER

Improved understanding of the molecular biology of TNBC has led to the evaluation of newer agents, including those that cause aberrant DNA repair (such as newer platinum agents and trabectedin) or microtubule stabilization (such as ixabepilone). In addition, given the chemosensitivity of TNBC, ''dose-dense'' and metronomic schedules of chemotherapy are being investigated in these patients (42,43). Also under study are novel receptor-targeted approaches, including inhibitors of angiogenesis (e.g., bevacizumab, sunitinib), growth-promoting proteins such as EGFR (e.g., cetuximab), poly(ADP-ribose) polymerase (PARP) inhibitors (e.g., BSI-201, AZD2281), and SRC (e.g., dasatinib, bosutinib). Table 2 presents a summary of early phase I/II trials with novel investigative agents.

Aberrant Deoxyribonucleic Acid Repair

Platinum Agents Triple-negative breast cancer cells exhibit an abundance of DNA aberrations, suggesting that their DNA repair mechanisms are defective. Consequently, these tumors may have an increased sensitivity to agents that cause inter-strand DNA breaks (e.g., platinum agents) (38). In support of this idea, TNBC tends to be phenotypically and molecularly similar to *BRCA1*-associated breast cancer, for which defects in DNA repair confer sensitivity to agents that cause inter-strand cross-links (55,56). Therefore, the sensitivity of TNBC to platinum-based chemotherapy has been the focus of several recent clinical trials in the neoadjuvant/adjuvant and advanced disease settings.

In the neoadjuvant setting, TNBC patients might have a higher pCR rate to platinum-based chemotherapy than those with non-TN disease (38). In other neoadjuvant studies of platinum-containing regimens, investigators reported respective pCR rates of 34% and 46% in TNBC patients with locally advanced and large operable disease (57,58). A recent study assessed the efficacy of platinum-based combination chemotherapy (carboplatin plus docetaxel) in patients with early TNBC who were unsuitable for standard anthracycline-based chemotherapy. Preliminary results suggest that this regimen is active and well tolerated in these patients, with 4/10 patients achieving pCR remission (59). Higher sensitivity to platinum-based therapy may or may not hold true in the advanced disease setting. The overall response rate (RR) to platinum-based chemotherapy was reported higher in patients with TNBC than non-TNBC patients in one study (38), but similar RRs have also been reported (60). A recent comparison of platinum-containing chemotherapy in patients with TN and non-TN metastatic breast cancer (MBC) determined that similar benefits were obtained in terms of RR, DCR, PFS, and

Table 2. Clinical Trials of Novel Agents in Patients with Triple-Negative Breast Cancer (TNBC)

Agent	Patients	Outcomes
Aberrant deoxyribonucleic acid (DNA) repair		
Trabectedin (44)	Metastatic TNBC, pretreated and progressive (n = 43)	PR in two of 43 TNBC patients, prompting closure of this study arm
BSI-201 + gemcitabine + carboplatin (BGC) or gemcitabine + carboplatin alone (GC) (45)	Metastatic TNBC with ≤2 prior chemotherapies (clinical benefit rate [CBR] and progression-free survival [PFS]: BGC n = 57, and GC n = 59; OS: BGC n = 61, and GC n = 62)	CBR: 62% BGC versus 21% GC Median PFS: 6.9 BGC versus 3.3 months GC Median OS: 12.2 BGC versus 7.7 months GC
Olaparib (46)	Recurrent, chemorefractory, BRCA-deficient BC (n = 27)	Objective response rate (ORR): 38% (based on unconfirmed responses)
Microtubule stabilization		
Ixabepilone (47)	Untreated BC (n = 164)	pCR: 19%
	Taxane-naïve MBC (n = 23)	ORR: 57%; median PFS: 5.5 months
	Anthracycline-pretreated MBC (n = 65)	ORR: 41.5%, median PFS: 4.8 months; median OS 22 months
	Taxane-pretreated MBC (n = 37)	ORR: 22%; median PFS 2.6 months
	Taxane-resistant MBC (n = 49)	ORR: 12%; median PFS 2.2 months; median OS 7.9 months
	Anthracycline- / taxane-pretreated MBC (n = 50)	ORR: 30%; median PFS 3.8 months
	Anthracycline- / taxane- / capecitabine-resistant MBC (n = 126)	ORR: 11.5%; median PFS 3.1 months; median OS 8.6 months
Ixabepilone + capecitabine (Arm 1) versus capecitabine (Arm 2) (48)	Anthracycline- / taxane-pretreated or -resistant (n = 752)	ORR: 31% (Arm 1) versus 15% (Arm 2); median PFS: 4.2 (Arm 1) versus 1.7 months (Arm 2); median OS: 10.3 (Arm 1) versus 9.0 months (Arm 2)
Angiogenesis inhibition		
Bevacizumab + paclitaxel (Arm 1) or paclitaxel alone (Arm 2) (49)	Metastatic hormone receptor-negative (n = 233; subgroup data), majority also HER2- due to inclusion criteria; first-line treatment	PFS: 8.8 (Arm 1) versus 4.6 months (Arm 2)
Sunitinib (50)	MBC previously treated with anthracyclines/ taxanes (TNBC, n = 20; non-TNBC, n = 44)	RR: 15% in TNBC and 11% in non-TNBC
Epidermal growth factor receptor (EGFR) inhibition		
Cetuximab (+ carboplatin at progression; Arm 1) or cetuximab + carboplatin from day 1 (Arm 2) (51)	Metastatic TNBC, ≤3 prior chemotherapies, no prior platinum or EGFR inhibitor (Arm 1, n = 31; Arm 2, n = 71)	Arm 1: PR: 6%, CBR 10% Arm 2: RR: 18%, CBR 27% Median PFS: 2 months
Cetuximab + paclitaxel or cetuximab + docetaxel (52)	Metastatic TNBC with ≤2 prior chemotherapies (n = 12)	Clinical response 82% (assessed by tumor marker↓ or metastasis size↓)
Irinotecan + carboplatin (Arm 1) or Irinotecan + carboplatin + cetuximab (Arm 2) (53)	Metastatic TNBC (Arm 1: n = 33, Arm 2: n = 39)	ORR: 30% in Arm 1, 49% in Arm 2 PFS 5.1 (Arm 1) versus 4.7 months (Arm 2) OS 12.3 (Arm 1) versus 15.5 months (Arm 2)
Src kinase inhibition		
Dasatinib (54)	Metastatic TNBC previously treated with anthracyclines and taxanes (n = 36)	RR: 4.7% CBR: 9.3%

MBC, metastatic breast cancer; PR, partial response.

OS since the time of initiation of therapy in both groups (61). Furthermore, a combination of gemcitabine plus carboplatin showed only modest activity in a recent prospective randomized phase II study of patients with metastatic TNBC (45).

A phase II study of cisplatin or carboplatin as first- or second-line therapy is currently ongoing in patients with TN-MBC. The primary objectives are to determine ORR and to evaluate p63/p73 as a biomarker of response to cisplatin.

Platinum compounds might be a good treatment option for patients with TNBC; however, no controlled randomized data are available, and platinum agents are not in current adjuvant or neoadjuvant guidelines.

Trabectedin Trabectedin is a naturally derived compound that binds to the minor groove of DNA. Its cytotoxicity is conveyed by synergistic action between two DNA repair mechanisms, the efficient nucleotide excision repair and deficient homologous recombination repair machinery (62). In a phase II clinical trial, only two of 43 patients with metastatic TN disease who received trabectedin (1.3 mg/m^2 every 3 weeks) achieved a partial response. As such, the trabectedin arm of the study was closed due to poor response

(44). This agent has limited potential for use in TNBC.

Poly(ADP-Ribose) Polymerase Inhibitors The PARP enzyme has a well-established role in DNA repair processes, and PARP inhibitors have been recently shown to selectively target cells with defects in double-strand DNA repair (63). Furthermore, breast tumor cells that are deficient in *BRCA1* or *BRCA2* (including the basal-like phenotype) have increased sensitivity to PARP inhibition. The apparent molecular overlap between basal-like and TN disease suggests that PARP inhibition may be an effective approach for TNBC (64), especially considering that TNBC may be prone to high expression of PARP1 (45).

Results (n = 123) of a phase II trial in patients with metastatic TNBC showed that adding the PARP inhibitor BSI-201 (6 mg/kg; intravenously on days 1, 4, 8, and 11 every 21 days) to gemcitabine and carboplatin in combination significantly improved the clinical benefit rate (CBR) (56% versus 34% p = 0.01) and PFS (5.9 versus 3.6 months; HR 0.59, p = 0.01) over chemotherapy alone (45). The median OS was also significantly improved in the arm containing BSI-201 (12.3 versus 7.7 months; HR 0.57, p = 0.01) (45). BSI-201 is also undergoing evaluation in combination with gemcitabine and carboplatin in a randomized phase III trial in patients with metastatic TNBC and in a single-arm study in neoadjuvant TNBC (NCT00938652 and NCT00813956). Another PARP inhibitor, olaparib (AZD2281; KU-0059436), has shown anti-tumor efficacy against *BRCA1*-deficient breast cancer cells, both alone and in combination with chemotherapy (65). Phase I data of olaparib demonstrate its anti-tumor activity in patients who were carriers of the *BRCA1* or BRCA2 mutation (66). In a single-arm, phase II trial, ORR (currently based on unconfirmed responses) was 38% (9/24) with oral olaparib 400 mg bd. The majority of reported toxicities were mild (grade 1–2); however, five patients (19%) had grade 3 or greater toxicities (46). This agent is currently undergoing clinical evaluation in combination with paclitaxel in a phase I/II single-arm trial (NCT00707707) and in combination with carboplatin in a phase I study (NCT00516724), both in metastatic TNBC. Olaparib is also undergoing investigation in combination with cisplatin in a phase I/II single-arm trial in neoadjuvant TNBC (NCT00782574). The PARP inhibitors show promising activity in patients with TNBC. Further data are awaited to confirm their potential in this setting.

Microtubule Stabilization

Ixabepilone Ixabepilone, a member of the epothilone class of macrolide antibiotics, possesses high microtubule stabilizing activity and low susceptibility to drug resistance mechanisms, including multidrug-resistant protein and P-glycoprotein (67). In the US, ixabepilone is approved for use in combination with capecitabine for the treatment of metastatic or locally advanced breast cancer after failure of an anthracycline and a taxane. It is also approved in the US as a monotherapy in the same setting after failure of an anthracycline, a taxane, and capecitabine.

A retrospective analysis of phase II studies (including patients in the neoadjuvant and metastatic setting) showed activity for ixabepilone in TNBC patients, including patients who had previously received or were resistant to anthracyclines, taxanes, and capecitabine (47). Notably, in a neoadjuvant study, pCR rates in patients with TNBC were 26% in the breast and 19% in the breast plus lymph nodes (68). In the total population, pCR rates were 18% in the breast and 11% in the breast plus lymph nodes (68).

In two phase III trials with large TNBC subpopulations, combination therapy with ixabepilone and capecitabine significantly improved overall RR and prolonged PFS over single-agent capecitabine in TNBC disease that had already progressed following anthracyclines and taxanes. A prospective analysis of the pooled data for TNBC patients from the two studies yielded median overall RR of 31% and 15% for combination and single-agent capecitabine arms. PFS times were 4.2 months in patients receiving combination therapy and 1.7 months in capecitabine monotherapy recipients (HR 0.63; 95% CI 0.52–0.77) (48). Median OS in these arms were 10.3 months and 9.0 months, respectively, a difference that was not statistically significant (HR 0.87; 95% CI 0.71–1.07).

Ixabepilone, alone or in combination with capecitabine, has demonstrated efficacy in a broad spectrum of patients with TNBC. Further studies will help define its use and value in these patients.

Eribulin The halichondrin B analog, eribulin, was approved by the Food and Drug Administration (FDA) on 15 November 2010 for the treatment of patients with MBC who have received at least two prior chemotherapy regimens for late-stage disease. In an open-label, randomized, phase III study of 762 patients with

anthracycline and taxane-pretreated locally recurrent or MBC, eribulin significantly improved median OS compared with treatment of physician choice (13.1 versus 10.7 months; HR = 0.81, 95% CI 0.66–0.99; p = 0.041) (EMBRACE; 69). In this study, eribulin also improved RR versus the control arm (12% versus 5%; p = 0.005 by independent radiology review [IRR]), and there was a trend for improved IRR-assessed PFS (3.7 versus 2.2 months; HR = 0.87; 95% CI: 0.71–1.05; p = 0.14).The survival benefit was maintained in different prespecified patients' subsets, including hormone receptor expression and HER2 status, number of organs involved, sites of disease and prior treatment with capecitabine (70). Another phase III trial is still ongoing and will compare eribulin versus capecitabine in locally advanced or MBC patients who had received up to three prior chemotherapy regimens (but no more than two regimens for advanced or MBC) including an anthracycline and a taxane (71).

Angiogenesis Inhibition

Bevacizumab The angiogenesis inhibitor bevacizumab in combination with paclitaxel demonstrated improvements in RR and PFS for patients with metastatic TNBC (49). In a large phase III study, PFS was 8.8 months in TNBC patients receiving bevacizumab plus paclitaxel versus 4.6 months in those receiving paclitaxel alone (HR 0.53; 95% CI 0.40–0.70) (49). OS, however, was not significantly improved in the overall population (72).

A number of phase II studies are currently evaluating how patients with metastatic TNBC respond to the addition of bevacizumab to standard chemotherapy, both in the first-line (NCT00691379; NCT00733408; NCT00608972) and later-line settings (NCT00479674; NCT00472693). In a first-line MBC study in which over one-third of the population had TNBC, RRs for the overall patient population were, however, comparable when adding bevacizumab to either weekly ixabepilone or weekly paclitaxel. When ixabepilone and bevacizumab were given on a 3-weekly schedule, the RR was higher (73).

A large phase III study (BEATRICE; NCT00528567) is evaluating the benefits of adjuvant bevacizumab when added to standard chemotherapy in patients with TNBC. This study has completed accrual and results should be available in 2014. Bevacizumab is also being evaluated in the neoadjuvant setting in patients with TNBC: a randomized neoadjuvant phase II trial of paclitaxel with or without carboplatin and/or bevacizumab followed by doxorubicin and cyclophosphamide is currently recruiting patients with hormone receptor-poor/HER2-negative resectable breast cancer. The primary outcome measure is pCR (NCT00861705).

Sunitinib Sunitinib, a dual inhibitor of the receptors for platelet-derived growth factor and vascular endothelial growth factor, has been investigated in a preliminary phase II trial in TNBC patients with metastatic disease who had received prior anthracycline and taxane therapy (50). Objective responses to single-agent sunitinib were reported in three of 20 (15%) patients with TNBC and seven of 64 patients (11%) in the total population. Ongoing phase I/II studies are also evaluating sunitinib in patients with metastatic TNBC previously treated with an anthracycline and taxane (NCT00246571), and in the neoadjuvant setting in combination with carboplatin plus paclitaxel (NCT00887575). Recent phase II and phase III studies of sunitinib have shown that there is limited potential for this agent in MBC (74,75). Combination of sunitinib plus docetaxel and sunitinib plus capecitabine improved ORR, but did not prolong PFS or OS compared with single agent docetaxel or capecitabine in first-line MBC.

Epidermal Growth Factor Receptor Inhibition

Recent studies have indicated that EGFR is frequently overexpressed in TNBC and is a negative prognostic factor when present (76,77), suggesting a potential role for EGFR-targeted therapies in this indication.

Cetuximab Monotherapy with the EGFR inhibitor cetuximab (with carboplatin added at progression) demonstrated limited activity in a largely pretreated metastatic TNBC population (87% had received prior adjuvant chemotherapy; 54% had received prior chemotherapy in the metastatic setting) (51). Most patients progressed rapidly, and overall median PFS was 2.0 months. Preliminary data in patients with pretreated TNBC indicate that adding cetuximab to irinotecan and carboplatin may improve anti-tumor activity over chemotherapy alone (53). The triple-therapy regimen achieved a higher overall RR (49% versus 30%) and longer median survival (15.5 months versus 12.3 months) than chemotherapy alone, although PFS appeared to be shorter (4.7 months

versus 5.1 months). Interestingly, the overall RR with the triple-therapy regimen was higher in TNBC than in the overall study population (49% versus 38%, respectively) (53).

Cetuximab, used in combination with other agents, may have potential for use in TNBC; however, further studies are warranted to investigate the benefit/risk profile of these combinations. Other EGFR inhibitors that are being investigated as potential treatments for TNBC include panitumumab (NCT00894504), gefitinib (76), and erlotinib (NCT00491816 and NCT00739063).

SRC Kinase Inhibition In vitro studies have indicated that TNBC cell lines display greater sensitivity to growth inhibition by the multitarget kinase inhibitor, dasatinib, than luminal or HER2-overexpressed breast cancer cell lines (78). In a phase II study in patients with metastatic TNBC previously treated with anthracyclines and taxanes, dasatinib was associated with modest single-agent activity, with a CBR of 9.3% (4/43) (54).

In vitro studies have shown that dasatinib in combination with certain chemotherapy agents has a synergistic effect on TNBC tumor growth, suggesting further evaluation of this agent in combination with chemotherapy (79). Further to this idea, two recent phase I trials for patients with MBC reported that dasatinib plus capecitabine and dasatinib plus paclitaxel had good tolerability and promising activity (80,81). Two ongoing phase I/II trials are investigating the combinations of dasatinib plus paclitaxel (NCT00820170) and dasatinib plus ixabepilone (NCT00717704).

Other Approaches to Treatment of Triple-Negative Breast Cancer

Several other approaches may be worthy of investigation in patients with TNBC. For example, the androgen receptor may be a valid target, given that it is frequently expressed on TNBC tumors (82). Heat shock proteins (HSPs) may also be good choices for targets; an in vitro study found that TNBC cells respond to retreatment with the HSP90 inhibitor PU-H71 for several cycles (extending over 5 months) without evidence of resistance (83). Other potential approaches include the histone deacetylase inhibitor entinostat, which has demonstrated cytotoxicity in TNBC cells (84); and the somatostatin analog AN-162, which produced greater growth inhibition than doxorubicin in TNBC cells (85). In addition, the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus may have potential for the treatment of TNBC and are currently being investigated in phase I/II trials of TNBC. Ongoing clinical studies of these agents in breast cancer patients will determine the validity of these targets against TNBC.

CONCLUSIONS

There is a clear need to broaden the pool of effective treatments for TNBC. In this regard, recent studies have suggested that cytotoxic therapy with platinum-containing agents or ixabepilone, as well as novel targeted approaches such as PARP inhibition, may be effective in this difficult-to-treat indication.

In addition, a significant body of preclinical and clinical breast cancer research is aimed at addressing the many unanswered questions regarding the biology of TNBC. In the future, the resulting data may yield risk prediction models that will allow us to further subclassify and diagnose TNBC tumors based on individual gene expression profiles. Such personalized approaches are expected to become valuable tools for more accurately defining prognosis for TNBC patients and predicting the likelihood of response to the various treatment options. This information should in turn help to overcome the enigma associated with TNBC.

Acknowledgments

The authors take full responsibility for the content of this publication and confirm that it reflects their viewpoint and medical expertise. The authors also wish to acknowledge StemScientific, funded by Bristol-Myers Squibb, for providing writing and editing support. Neither Bristol-Myers Squibb nor StemScientific influenced the content of the manuscript, nor did the authors receive financial compensation for authoring the manuscript.

REFERENCES

1. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. *Cancer* 2007;109:1721–8.

2. Mersin H, Yildirim E, Berberoglu U, Gulben K. The prognostic importance of triple negative breast carcinoma. *Breast* 2008;17:341–6.

3. Nishimura R, Arima N. Is triple negative a prognostic factor in breast cancer? *Breast Cancer* 2008;15:303–8.

4. Dawood S, Broglio K, Esteva FJ, *et al.* Survival among women with triple receptor-negative breast cancer and brain metastases. *Ann Oncol* 2009;20:621–7.

5. Dent R, Trudeau M, Pritchard KI, *et al.* Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res* 2007;13:4429–34.

6. Liedtke C, Mazouni C, Hess KR, *et al.* Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol* 2008;26:1275–81.

7. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. *Cancer* 2008;113:2638–45.

8. Kaplan HG, Malmgren JA. Impact of triple negative phenotype on breast cancer prognosis. *Breast J* 2008;14:456–63.

9. Morris GJ, Naidu S, Topham AK, *et al.* Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. *Cancer* 2007;110:876–84.

10. Carey LA, Perou CM, Livasy CA, *et al.* Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA* 2006;295:2492–502.

11. Lund MJ, Butler EN, Bumpers HL, *et al.* High prevalence of triple-negative tumors in an urban cancer center. *Cancer* 2008;113:608–15.

12. 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* 2009;11:R18.

13. Iwase H, Yamamoto Y, Kurebayashi J, *et al.* Clinicopathologic and prognostic features of triple-negative breast cancer analyzed in registration data of the Japanese Breast Cancer Society, 11705 cases. *J Clin Oncol* 2009;27. Abstract e22122.

14. Kim MJ, Ro JY, Ahn SH, Kim HH, Kim SB, Gong G. Clinicopathologic significance of the basal-like subtype of breast cancer: a comparison with hormone receptor and Her2/neu-overexpressing phenotypes. *Hum Pathol* 2006;37:1217–26.

15. Liu ZB, Liu GY, Yang WT, *et al.* Triple-negative breast cancer types exhibit a distinct poor clinical characteristic in lymph node-negative Chinese patients. *Oncol Rep* 2008;20:987–94.

16. Tian XS, Cong MH, Zhou WH, Zhu J, Chen YZ, Liu Q. Clinicopathologic and prognostic characteristics of triple-negative breast cancer. *Onkologie* 2008;31:610–4.

17. Tsang J, Lai TL, Lau DH, Au GK, Chua DT. Triple-negative breast cancer in Hong Kong Chinese patients. *J Clin Oncol* 2009;27. Abstract e22127.

18. Khan A, Tovar YE, Rodriguez C, *et al.* Incidence of triple negative breast cancer phenotype in a predominantly Hispanic cohort. *J Clin Oncol* 2009;27. Abstract e22188.

19. Dawood S, Broglio K, Kau SW, *et al.* Triple receptor-negative breast cancer: the effect of race on response to primary systemic treatment and survival outcomes. *J Clin Oncol* 2009;27:220–6.

20. Ries LAG. *SEER Cancer Statistics Review, 1974–2004.* Bethesda, MD: National Cancer Institute, 2009.

21. Bowen RL, Duffy SW, Ryan DA, Hart IR, Jones JL. Early onset of breast cancer in a group of British black women. *Br J Cancer* 2008;98:277–81.

22. Dolle JM, Daling JR, White E, *et al.* Risk factors for triple-negative breast cancer in women under the age of 45 years. *Cancer Epidemiol Biomarkers Prev* 2009;18:1157–66.

23. Millikan RC, Newman B, Tse CK, *et al.* Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat* 2008;109:123–39.

24. Maiti B, Kundranda MN, Jin T, Spiro TP, Daw HA. The association of metabolic syndrome with triple-negative breast cancer. *J Clin Oncol* 2009;27. Abstract 1038.

25. Sorlie T, Perou CM, Tibshirani R, *et al.* Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 2001;98:10869–74.

26. Sorlie T, Tibshirani R, Parker J, *et al.* Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci U S A* 2003;100:8418–23.

27. Bidard FC, Conforti R, Boulet T, Michiels S, Delaloge S, Andre F. Does triple-negative phenotype accurately identify basal-like tumour? An immunohistochemical analysis based on 143 'triple-negative' breast cancers. *Ann Oncol* 2007;18:1285–6.

28. Rakha EA, Elsheikh SE, Aleskandarany MA, *et al.* Triple-negative breast cancer: distinguishing between basal and nonbasal subtypes. *Clin Cancer Res* 2009;15:2302–10.

29. Irvin WJ Jr, Carey LA. What is triple-negative breast cancer? *Eur J Cancer* 2008;44:2799–805.

30. Bertucci F, Finetti P, Cervera N, *et al.* How basal are triple-negative breast cancers? *Int J Cancer* 2008;123:236–40.

31. Nofech-Mozes S, Trudeau M, Kahn HK, *et al.* Patterns of recurrence in the basal and non-basal subtypes of triple-negative breast cancers. *Breast Cancer Res Treat* 2009;118:131–7.

32. Park YH, Chang MH, Lee S, *et al.* Heterogeneity of triple negative breast cancer (TNBC): TNBC might be divided into two or more subgroups by clinicopathologic findings. *Cancer Res* 2009;69(Suppl 24). Abstract 6032.

33. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. *Metastatic Breast Cancer.* 2008;2:BINV19, BINV-N. Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf (accessed September 16, 2009).

34. Berry DA, Cirrincione C, Henderson IC, *et al.* Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. *JAMA* 2006;295:1658–67.

35. Carey LA, Dees EC, Sawyer L, *et al.* The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin Cancer Res* 2007;13:2329–34.

36. Rouzier R, Perou CM, Symmans WF, *et al.* Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 2005;11:5678–85.

37. Sikov WM, Dizon DS, Strenger R, *et al.* Frequent pathologic complete responses in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: a Brown University Oncology Group Study. *J Clin Oncol* 2009;27:4693–700.

38. Sirohi B, Arnedos M, Popat S, *et al.* Platinum-based chemotherapy in triple-negative breast cancer. *Ann Oncol* 2008;19:1847–52.

39. Tomasevic Z, Radosevic-Jelic L, Tomasevic ZM, Jelic S, Milovanovic Z. Late relapse in triple negative breast cancer. *J Clin Oncol* 2009;27. Abstract e12022.

40. Harris LN, Broadwater G, Lin NU, *et al.* Molecular subtypes of breast cancer in relation to paclitaxel response and outcomes in women with metastatic disease: results from CALGB 9342. *Breast Cancer Res* 2006;8:R66.

41. Kassam F, Enright K, Dent R, *et al.* Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. *Clin Breast Cancer* 2009;9:29–33.

42. Mehta RS. Dose-dense and/or metronomic schedules of specific chemotherapies consolidate the chemosensitivity of triple-negative breast cancer: a step toward reversing triple-negative paradox. *J Clin Oncol* 2008;26:3286–8. Author reply 3288.

43. Koya S, Li Y, McDaniel SA, *et al.* Safety and effectiveness of dose dense neoadjuvant chemotherapy in patients with stage II/III breast cancer. *J Clin Oncol* 2009;27. Abstract e11566.

44. Delaloge S, Tedesco KL, Blum J, *et al.* Preliminary safety and activity results of trabectedin in a phase II trial dedicated to triple-negative (ER-, PR-, HER2-), HER2 + ++, or BRCA1/2 germline-mutated metastatic breast cancer (MBC) patients (pts). *J Clin Oncol* 2009;27. Abstract 1010.

45. O'Shaughnessy J, Osborne C, Pippen JE, *et al.* Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med* 2011;364:205–14.

46. Tutt A, Robson M, Garber JE, *et al.* Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer. *J Clin Oncol* 2009;27. Abstract CRA501.

47. Fumoleau P, Llombart-Cussac A, Roche H, *et al.* Clinical activity of ixabepilone, a novel epothilone B analog, across the breast cancer disease continuum. *Eur J Cancer* 2007;5(Suppl). Abstract 2119.

48. Rugo HS, Roche H, Thomas ES, *et al.* Ixabepilone plus capecitabine vs capecitabine in patients with triple negative tumors: a pooled analysis of patients from two large phase III clinical studies. *Cancer Res* 2009;69(Suppl 2). Abstract 3057.

49. Miller K, Wang M, Gralow J, *et al.* Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007;357:2666–76.

50. Burstein HJ, Elias AD, Rugo HS, *et al.* Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol* 2008;26:1810–6.

51. Carey LA, Mayer E, Marcom PK, *et al.* TBCRC 001: EGFR inhibition with cetuximab added to carboplatin in metastatic triple-negative (basal-like) breast cancer. *J Clin Oncol* 2008;26. Abstract 1009.

52. Nechushtan H, Steinberg H, Peretz T. Preliminary results of a phase I/II of a combination of cetuximab and taxane for triple negative breast cancer patients. *J Clin Oncol* 2009;27. Abstract e12018.

53. O'Shaughnessy J, Weckstein DJ, Vukelja S, *et al.* Randomized phase II study of weekly irinotecan/carboplatin with or without cetuximab in patients with metastatic breast cancer. *Breast Cancer Res Treat* 2007;106(Suppl 1). Abstract 308.

54. Finn RS, Bengala C, Ibrahim N, *et al.* Phase II trial of dasatinib in triple-negative breast cancer: results of study CA180059. *Cancer Res* 2009;69(Suppl 2). Abstract 3118.

55. Bhattacharyya A, Ear US, Koller BH, *et al.* The breast cancer susceptibility gene BRCA1 is required for subnuclear assembly of Rad51 and survival following treatment with the DNA cross-linking agent cisplatin. *J Biol Chem* 2000;275:23899–903.

56. Moynahan ME, Cui TY, Jasin M. Homology-directed DNA repair, mitomycin-C resistance, and chromosome stability is restored with correction of a Brca1 mutation. *Cancer Res* 2001;61:4842–50.

57. Leone JP, Guardiola V, Venkatraman A, *et al.* Neoadjuvant platinum-based chemotherapy (CT) for triple-negative locally advanced breast cancer (LABC): retrospective analysis of 125 patients. *J Clin Oncol* 2009;27. Abstract 625.

58. Frasci G, Comella P, Rinaldo M, *et al.* Preoperative weekly cisplatin-epirubicin-paclitaxel with G-CSF support in triple-negative large operable breast cancer. *Ann Oncol* 2009;20:1185–92.

59. Kern P, Kolberg HC, Stoblen F, *et al.* Primary systemic chemotherapy with carboplatin AUC 6 and docetaxel 75 mg/m2 (q3w) in triple-negative early breast cancer. *J Clin Oncol* 2010;28(Suppl). Abstract e11063.

60. Uhm JE, Park YH, Yi SY, *et al.* Treatment outcomes and clinicopathologic characteristics of triple-negative breast cancer patients who received platinum-containing chemotherapy. *Int J Cancer* 2009;124:1457–62.

61. Kim T, Lee H, Han S, *et al.* The comparison of the benefits obtained from platinum-containing chemotherapy between triple-negative and non-triple-negative metastatic breast cancer. *J Clin Oncol* 2010;28. Abstract 1071.

62. Cassier PA, Dufresne A, Blay JY, Fayette J. Trabectedin and its potential in the treatment of soft tissue sarcoma. *Ther Clin Risk Manag* 2008;4:109–16.

63. Gaymes TJ, Shall S, MacPherson LJ, *et al.* Inhibitors of poly ADP-ribose polymerase (PARP) induce apoptosis of myeloid leukemic cells: potential for therapy of myeloid leukemia and myelodysplastic syndromes. *Haematologica* 2009;94:638–46.

64. Farmer H, McCabe N, Lord CJ, *et al.* Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005;434:917–21.

65. Rottenberg S, Jaspers JE, Kersbergen A, *et al.* High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proc Natl Acad Sci U S A* 2008;105:17079–84.

66. Fong PC, Boss DS, Yap TA, *et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *NEJM* 2009;361:123–34.

67. Rivera E, Lee J, Davies A. Clinical development of ixabepilone and other epothilones in patients with advanced solid tumors. *Oncologist* 2008;13:1207–23.

68. Baselga J, Zambetti M, Llombart-Cussac A, *et al.* Phase II genomics study of ixabepilone as neoadjuvant treatment for breast cancer. *J Clin Oncol* 2009;27:526–34.

69. Twelves C, Loesch D, Blum JL, *et al.* A phase III study (EMBRACE) of eribulin mesylate versus treatment of physician's choice in patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol* 2010;28(Suppl). Abstract CRA1004.

70. Twelves C, Akerele C, Wanders J, *et al.* Eribulin mesylate (E7389) vs treatment of physician's choice (TPC) in patients (pts) with metastatic breast cancer (MBC): subgroup analyses from the EMBRACE study. *Ann Oncol* 2010;21(Suppl 8):viii96. Abstract 275O.

71. Twelves C, Cortes J, Vahdat LT, Wanders J, Akerele C, Kaufman PA. Phase III trials of eribulin mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer. *Clin Breast Cancer* 2010;10:160–3.

72. O'Shaughnessy J, Miles D, Gray RJ, *et al.* A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC). *J Clin Oncol* 2010;28. Abstract 1005.

73. Rugo HS, Campone M, Amadori D, *et al.* Randomized phase II study of weekly vs every-3-week ixabepilone plus bevacizumab (ixa/bev) versus paclitaxel plus bevacizumab (pac/bev) as first-line therapy for metastatic breast cancer. *J Clin Oncol* 2009;27. Abstract 1029.

74. Bergh J, Greil N, Voytko N, *et al.* Sunitinib in combination with docetaxel (D) versus D alone for the first-line treatment of advanced breast cancer (ABC). *J Clin Oncol* 2010;28. Abstract LBA1010.

75. Crown J, Dieras V, Staroslawska E, *et al.* Phase III trial of sunitinib (SU) in combination with capecitabine (C) versus C in previously treated advanced breast cancer (ABC). *J Clin Oncol* 2010;28. Abstract LBA1011.

76. Corkery B, Crown J, Clynes M, O'Donovan N. Epidermal growth factor receptor as a potential therapeutic target in triple-negative breast cancer. *Ann Oncol* 2009;20:862–7.

77. Nogi H, Kobayashi T, Suzuki M, *et al.* EGFR as paradoxical predictor of chemosensitivity and outcome among triple-negative breast cancer. *Oncol Rep* 2009;21:413–7.

78. Finn RS, Dering J, Ginther C, *et al.* Dasatinib, an orally active small molecule inhibitor of both the src and abl kinases, selectively inhibits growth of basal-type/"triple-negative" breast cancer cell lines growing in vitro. *Breast Cancer Res Treat* 2007;105:319–26.

79. Tryfonopoulos D, O'Donovan N, Corkery B, Clynes M, Crown J. Activity of dasatinib with chemotherapy in triple-negative breast cancer cells. *J Clin Oncol* 2009;27. Abstract e14605.

80. Somlo G. Dasatinib plus capecitabine (Cap) for progressive advanced breast cancer (ABC): phase I study CA180004. *J Clin Oncol* 2009;27. Abstract 1012.

81. Fornier MN, Morris PG, Abbruzzi A, *et al.* A phase I-II study of dasatinib (D) in combination with weekly (W) paclitaxel (P) for patients (pts) with metastatic breast carcinoma (MBC). *Ann Oncol* 2011; Mar 15 [epub ahead of print].

82. Ogawa Y, Hai E, Matsumoto K, *et al.* Androgen receptor expression in breast cancer: relationship with clinicopathological factors and biomarkers. *Int J Clin Oncol* 2008;13:431–5.

83. Caldas-Lopes E, Cerchietti L, Ahn JH, *et al.* Hsp90 inhibitor PU-H71, a multimodal inhibitor of malignancy, induces complete responses in triple-negative breast cancer models. *Proc Natl Acad Sci U S A* 2009;106:8368–73.

84. Ordentlich P, Tee L, Huynh Y, Mee S, Mamuszka H, Lee G. Ex-vivo analysis of the isoform selective histone deacetylase inhibitor entinostat in triple-negative breast cancer tumors. *J Clin Oncol* 2009;27. Abstract e14597.

85. Seitz S, Schally AV, Gluck S, *et al.* Effective treatment of triple-negative breast cancer with targeted cytotoxic somatostatin analogue AN-162 (AEZS-124). *J Clin Oncol* 2009;27. Abstract 619.