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EXPERT REVIEW

# Management Options in Triple-Negative Breast Cancer

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**Abstract:** Notorious for its poor prognosis and aggressive nature, triple-negative breast cancer (TNBC) is a heterogeneous disease entity. The nature of its biological specificity, which is similar to basal-like cancers, tumors arising in BRCA1 mutation carriers, and claudin-low cancers, is currently being explored in hopes of finding the targets for novel biologics and chemotherapeutic agents. In this review, we aim to give a broad overview of the disease's nomenclature and epidemiology, as well as the basic mechanisms of emerging targeted therapies and their performance in clinical trials to date.

**Keywords:** triple-negative breast cancer, basal-like, targeted therapy

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## Overview

Breast cancer classification is in constant evolution, as advances in DNA and RNA microarrays as well as immunohistochemical (IHC) staining allow researchers to define the molecular heterogeneity of different disease subtypes and to guide the selection of appropriate treatment. With routine clinical testing for the expression of HER-2/neu in all breast cancer cases and a significantly improved survival rate by trastuzumab in women with HER-2/neu positive disease,[1–5] a subtype—triple-negative breast cancer (TNBC)—has been recognized and garnered recent attention. The lack of HER-2/neu coupled with the absence of estrogen-receptors (ER) and progesterone-receptors (PR) defines triple-negative breast cancer. Without these targets, women with TNBC do not benefit from hormonal therapy or trastuzumab, and are left with chemotherapy as their only option. TNBC is a disease that accounts for approximately 7%–20% of all breast cancers[6–12] and is known for its aggressive nature and poor prognosis. Traditional chemotherapy drugs may benefit some of these patients but the relapse rate is high and the survival rate continues to lag behind other subtypes. The biological specificity of TNBC however, may be exploited in the development of novel targeted therapy.

## Defining TNBC and basal-like breast cancer

One of the difficulties in addressing TNBC is the heterogeneity of the disease entity. As a result, various terminologies have been used to describe the disease and associated biologies. TNBC is a clinical term, characterized by the lack of expression of ER, PR, and HER-2/neu in a subgroup of breast cancer cases. Perou et al defined five molecular subtypes (luminal A and B, HER-2/neu positive, normal breast-tissue like, and basal-like) in their microarray-based expression profiling study.[13] Basal-like breast cancer, which expresses genes usually found in the basal cells of the normal breast, has since become an area of research interest.[14] While TNBC is clearly defined by the absence of three marker expressions, there is no universally accepted profile of basal-like breast cancer.[15] Nielsen et al compared transcriptomic and IHC profiles, concluding that a panel that was negative for ER and HER-2/neu, and positive for CK 5/6, and epidermal growth factor receptor (HER-1 or EGFR) could accurately identify basal-like carcinomas.[16] Korsching et al included the presence of cytokeratins 14 and 17 in the definition.[6] Others have proposed that some basal-like tumors may be positive for ER and/or HER-2/neu amplification.[15,17–22]

Though some studies claim basal-like tumors and TNBC may be considered synonymous,[7,23–25] it has been shown repeatedly that though there is significant overlap between the two, they are not identical.[9,26–28] When examining basal-like breast cancers, Bertucci et al found that 77% were TNBC and 23% were not.[26] Similarly, when Livasy et al and Kandel et al performed IHC testing of a panel of characteristic markers of basal-like tumors on a group of TNBC tumors, they found that only about 85% were basal-like.[27,28] What has become clear is that basal-like carcinoma and TNBC are neither exclusive nor synonymous diseases. Both represent heterogeneous types of breast cancer and further classification studies are underway.

The relationship between basal-like/TNBC, and BRCA-1-related disease is also of great relevance. While probing into the genetic machinery of basal-like disease, it became clear to researchers that the tumors arising preferentially in carriers of the BRCA-1 mutation, especially those diagnosed before the age of 50, bore transcriptomic and IHC profiles that were strikingly similar.[29–31] BRCA-1 mutations lead to derangements in repair pathways of double-stranded DNA breaks and though a patient may lack the BRCA-1 somatic mutation, sporadically arising basal-like cancers often display a dysfunctional BRCA-1 pathway.[32,33] Both share certain histological features (eg, central necrosis, lymphocytic infiltrate, and genomic instability[34] as well as mutations in p53,[22,31,35] which disrupt apoptosis and are associated with a poor prognosis.[36] As high as 75% of tumors in BRCA-1 carriers are reported to be TNBC, basal-like, or both.[15,37] Studies taking a converse approach, looking at patients with TNBC but without a significant familial breast cancer risk, found that 11%–29% of that population under 50 are BRCA-1 mutation carriers.[19,38] It has been suggested recently that for women under the age of 50 who are diagnosed with TNBC, BRCA mutation testing is a cost-effective strategy and should be integrated into genetic testing guidelines.[39]

While distinct from basal-like cancers, claudin-low tumors are triple-negative and are thus considered another subtype of triple-negative disease. This recently discovered claudin-low subtype[40,41] takes its name from its low expression of the claudin genes. It lacks epithelial cell junction proteins including E-cadherin, and is marked by intense immune cell infiltrate, stem-cell-like features, and epithelial-mesenchymal transition features. A study looking at tumor-initiating cells in tumor subtypes suggested that claudin-low tumors are enriched with stem cells, presenting the possibility of linking tumor initiating cells with stem cells.[42] Tumors arresting at various points in differentiation would have different characteristics and it is thought that claudin-low tumors arrest at the step preceding that of basal-like phenotypes, making it the most primitive cell of cancer cells.[43]

At the other end of the spectrum lies the normal breast-like group, which can often be mistaken for normal breast tissue. Some studies have questioned the existence of this subtype, though it may be a question of pathological rigor.[44] It is a heterogeneous subgroup that includes tumors with high stromal content, those with high lymphocytic infiltration, and those with tumors of low malignant cell content.[45] From breast tumors that resemble primitive stem cells to those that closely mimic normal tissue, attempts at characterizing TNBC have only reaffirmed a true heterogeneity exists within the subtype.

## Epidemiology and risk

It has been well-documented that African-American women are overrepresented in the TNBC group.[8,10,11,46–48] A population based study of the California Cancer Registry reported by Bauer et al[10] showed that non-Hispanic black women accounted for 10% of all TNBC patients diagnosed and treated in California. They were twice as likely to be diagnosed with TNBC when compared with whites and the incidence of black women with TNBC was more than twice the incidence of black women with other types of breast cancer. Studies by Bauer et al and Carey et al[8] also showed a worse 5-year survival rate for black women with late stage TNBC than for other ethnicities.

While most breast cancer cases are associated with increasing age, TNBC has a preferential occurrence in younger/pre-menopausal women.[7,8,10,25,49–51] Phipps et al[52] and Freedman et al[47] found age and menopausal status trended to affect recurrence and survival but neither reached statistical significance in women with TNBC. Demographics, while useful in targeting at-risk populations, may not be particularly prognostic in women already diagnosed with TNBC.

Other clinical associations with TNBC patients have been ventured as well, such as increased parity, young age at first full-term pregnancy (AFFTP), elevated waist-to-hip ratio (WHR), gain of adiposity since childhood, and obesity. Though several studies[52,53] found that increased parity did not correlate with TNBC, Millikan et al[48] found that women with basal-like carcinoma were more likely to display increased parity in combination with a lack of breast-feeding when compared to women with luminal A disease. The data is also split on the significance of AFFTP: Millikan et al found an association between basal-like disease and younger AFFTP while Phipps et al did not.

Women with TNBC, if premenopausal, were also more likely to be obese when compared to women with other disease subtypes.[54–56] Other studies have looked at more specific measurements like WHR and adiposity gain since childhood. Millikan et al[48] found positive associations between basal-like breast cancer and an elevated WHR and a gain of adiposity since childhood. Slattery et al[57] similarly found that weight gain since age 15 and an elevated WHR were both associated with an increased risk of ER-negative breast cancer. Metabolic syndrome has also been noted to be more prevalent in TNBC patients than those with non-TNBC disease.[58] Whether or not any of these clinical associations have a causal effect on developing TNBC has yet to be elucidated.

## Histological tendencies and subtypes

Basal-like carcinomas and TNBC are most likely to be infiltrating ductal carcinoma of no special type (IDC-NST)[7,13] but metaplastic, atypical or typical medullary, and adenoid cystic cancer, histologies that are usually quite rare, are prevalent in TNBCs.[24,28,59] Medullary cancer in particular has been observed to be a subtype that occurs with notable frequency within basal-like populations.[11,26,60] Both typical medullary cancer and basal-like carcinomas have an increased rate of p53 mutations[35] and share certain genomic alterations

(eg, 1q, 8q and X losses), though other alterations are specific to medullary cancer. It may be appropriate to consider medullary breast cancers as an entity within the basal-like spectrum.[60]

Large tumor size,[8,10,26] high histological grade (75%–100% are grade 3),[18,28,61] and poor differentiation[10] also mark basal-like tumors. EGFR overexpression, though technically not a basal-like breast carcinoma-specific marker, has been found to be present in 44%– 50% of samples[16,26,62] and, as Nielsen et al suggested, has a strong enough correlation with basal-like disease to aid in its identification. It has been shown that most tumors that do express c-KIT also express basal-like cytokeratins.[16] They often have a high Ki-67, a marker of poor prognosis even though it is associated with a greater chance of chemotherapy response,[63] high mitotic index, and marked nuclear pleomorphism.[8] High proliferative rate, central necrosis, a pushing border, frequent apoptotic cells, scant stromal content, and stromal lymphocytic response are also often noted.[11,19,28,64] As Rakha et al suggested, histological characteristics such as tumor grade, histological subtype, and tumor architecture, in combination with other features such as patient age and tumor size, may aid in the understanding of clinically-identified TNBC.[61]

## Clinical outcomes

As a group, TNBC and basal-like disease is frequently thought of as having poor outcomes (eg, development of distant metastasis, shorter survival, and higher mortality rate) than other disease subtypes.[8,10,16,22,31,35,51,65–67] There are, however, data suggesting that prognostic outcome should be discussed in terms of specific subgroups. For instance, lymph-node status may be one qualifier, though its significance has yet to be clearly defined. Carey et al's study[8] found the basal-like subgroup had the poorest breast-cancer specific survival amongst all tumor subtypes in both lymph node-negative and lymph node-positive patients. Van de Rijn et al however, found that in node-negative breast cancer, the expression of CK 15 and/or CK 5/6 was a negative prognostic factor independent of tumor size and tumor grade, though they had no predictive value in node-positive disease.[65] Nielsen et al found the presence of basal cytokeratin was associated with poor outcome only in the node-positive group.[16]

The importance of specificity in terms of TNBC vs. basal-like discussion was highlighted with Liu et al's study which found that tumors that simultaneously over-express HER-2/neu and basal markers had a significantly worse 5-year overall survival rate than basal-like breast tumors and might require different treatment strategy, suggesting that the poor outcomes associated with basal-like disease may be a function of a variety of factors.[68]

Subdivisions within the TNBC category by additional marker profiling exist as well. While some studies have shown that the poor prognosis of TNBC is conferred almost entirely by tumors with basal markers,[66] Choi et al[69] subdivided TNBC into basal-like (ER, PR, HER-2/neu negative, and EGFR and CK 5/6 positive) and quintuple-negative breast cancer (QNBC) (negative for ER, PR, HER-2-neu, CK 5/6, and EGFR). Within the TNBC group, the QNBC group had a worse overall survival (OS) than the basal-like tumors, emphasizing that definition and specificity of nomenclature is important when discussing survival data.

The markers that each study uses to define "basal-like" are also of critical importance. A study by Fulford et al used only CK14 staining to identify basal-like tumors among a sample set of grade III IDC-NST tumors. The authors found that in the five years following diagnosis, those grade III IDC-NST tumors had similar relapse-free survival and OS regardless of CK14 expression, but those expressing CK14 had a better prognosis after 5 years. They suggested that two subgroups may exist within basal carcinomas: one exhibiting early relapse and aggressive clinical course and a separate group that despite the traditionally poor prognostic indicators do not relapse.[64] Banerjee et al's study, which also looked at grade III carcinomas, screened for CK 5/6, CK 14, and CK 17, qualifying a case as basal-like if any one of these markers was found positive. Here, though women with basal-like disease had shorter disease-free survival (DFS) and OS, basal-like status, as an independent prognostic variable, did not reach significance in multivariable analysis.[70]

A unique pattern of relapse has been observed amongst TNBC: in the first two years following diagnosis, there is a rapid rise in rate of relapse, with a peak within three years, followed by a rapid decline over the next five, and a very low risk of subsequent recurrence.[25] The location of relapse also requires some discussion. Whether specifically local-regional relapse

(LRR) is higher for basal-like disease than other subtypes is of some debate, with some studies reporting high rates of LRR[71] and others failing to find a significantly increased risk of isolated LRR after breast-conserving surgery.[47] The pattern of metastatic relapse has been examined in a number of studies, and lung and soft-tissue relapse has been found to be more common than bone relapse or lymph-node metastases.[64,71–74] There is also a greater risk of brain metastases, which, along with lung metastases, has been associated with a poorer prognosis.[64,73,75,76] Because many studies did not find a relationship between an increase in tumor size and an increase in node-positivity in TNBC disease and because this phenomenon has also been shown to be present in BRCA-associated cancers, it has been hypothesized that basal-like disease may have a hematogenous pattern of spread.[72,77]

## Loco-Regional Treatment of Triple-Negative Breast Cancer

When triple-negative breast cancer is diagnosed in young women, African-American women, women of Jewish descent, and women with a high-risk family history of breast and/or ovarian cancer, BRCA testing should be included as part of the pretreatment assessment. For those who test positive for the BRCA1 and BRCA2 mutation are frequently advised to undergo bilateral mastectomy, especially if they are young. Other than this subset of patients, the considerations for choosing loco-regional treatment for TNBC are the same as for other infiltrating ductal cancers. Breast conservation surgery with postoperative radiation remains to be the choice of local therapy for women with T1 and some T2 TNBCs. Mastectomy is reserved for women with multicentric disease or with persistently involved margins after re-excision. Women with large TNBC may still be candidates for breast conservation surgery as studies such as ours[78] have demonstrated the extreme sensitivity of TNBC to neoadjuvant chemotherapy and the significant size reduction of the tumor following neoadjuvant treatment. Mastectomy in general renders radiation unnecessary unless the tumor is 5 cm or larger, margins are involved, or there is nodal metastasis, but Tseng et al suggested that adjuvant radiation in all patients with metaplastic breast cancer may lead to improved overall survival.[79]

Voduc et al[80] suggested that basal-like breast cancer and HER-2 positive breast cancer have the worst 10 year loco-regional survival rate when compared with other molecular subtypes of breast cancer after breast conservation surgery. This finding raises concerns about breast conserving surgery for women with TNBC. However, the same study showed that the 10-year loco-regional recurrence rate after mastectomy was also the highest among basal-like TNBC and HER-2 positive breast cancer. Therefore, the poor relapse-free survival rate observed in these women is more likely to be the result of the biology of TNBC and less likely to be dictated by the type of surgery. In our own analysis of TNBC treatment at UCLA, we found that treatment factors such as lumpectomy, radiation, and negative surgical margins were associated with significantly better relapse-free survival in women with TNBC. Though LRR rate may be higher[7,81] and time to recurrence may be shorter in TNBC patients,[25] we believe that lumpectomy followed by postoperative adjuvant radiation is an excellent local treatment for many with this disease subtype,[82] and we put a strong emphasis on clean surgical margins regardless of the type of surgery chosen.

## Mechanisms of Therapeutic Agents in TNBC Treatment

### Chemotherapy

Though new targeted biologic therapies show promise in many other subtypes of breast cancer, chemotherapy remains the only therapeutic option for patients with TNBC. TNBC's superior sensitivity and responsiveness to chemotherapy has been well documented and while doxorubicin and taxanes are the classic choices, the most efficacious chemotherapeutic regimen has not yet been clearly established. Recent interest has focused on several classes of chemotherapeutic agents whose mechanisms of action target the unique molecular defects of TNBC.

#### Platinum salts

It is well established that TNBC is prevalent among carriers of BRCA1 and BRCA2 mutations.[83–85] The cancers of these women frequently have a defect in homologous recombinant DNA repair, which prevents the repair of double-stranded DNA breaks. A similar derangement has also been seen in sporadic TNBC. It is thought that DNA damaging agents, such as the platinum salts, which bind directly to and cross-link DNA, are likely to lead to an irreversible collapse of DNA

repair and achieve the desirable therapeutic result.[86] The expression of p63/p73 proteins expressed in about 33% of TNBC patients, might be a potential biomarker indicating platinum sensitivity of the tumor.[87]

### Anti-tubulin agents

Antitubulin agents can be divided into taxanes (paclitaxel and docetaxel) and non-taxane (vinca alkaloids, ixabepilone, eribulin) drugs. Both work through the stabilization of microtubules; by acting on the spindle, they block the metaphase-anaphase transition and ultimately lead to cell-cycle arrest and apoptosis.

Ixabepilone, a semi-synthetic antineoplastic agent derived from the natural epithilones,[88] was designed to have a low susceptibility to mechanisms causing drug resistance,[89] holding a theoretical advantage over taxanes by bypassing drug efflux pumps and binding to beta-tubulin in a different manner than taxanes.[89–93] Ixabepilone-sensitivity may be correlated with the tumor expression of high beta-III tubulin (a type of tubulin highly expressed in TNBC, basal-like, and HER2+ tumors, and a marker of taxane-resistance)[93] and inversely related to ER expression levels.[89] Both ixabepilone and eribulin, new non-taxane microtubule dynamics inhibitors, may also have an important role in the treatment of metastatic disease, especially in patients with anthracycline/taxane-resistant metastatic disease.[94,95]

## Targeted Therapy

### Poly-adenosine-diphosphate ribose-polymerase (PARP) inhibitors

Agents of this class are a promising targeted therapeutic for TNBC. PARP is an enzyme recruited by either single-stranded or double-stranded DNA breaks (SSB or DSB) for base-excisional repair. Its zinc finger domain binds to the SSB and cleaves off NAD+, which in turn causes the attachment of multiple ADP-ribose units and unwinding of the damaged DNA for repair. Because of the depletion of NAD+, tumor necrosis is frequently seen in tumors with PARP overaction such as TNBC/basal-like breast cancers. The overactive PARP can also increase the release of apoptosis-inducing factor from mitochondria and cause cell death and necrosis.[96] Most PARP inhibitors mimic NAD+, thus blocking the binding of NAD+ to the PARP enzyme and inhibiting base-excision repair.

In tumor cells with BRCA1 and BRCA2 deficiencies, the repair of DSB is impaired through deranged homologous recombination repair pathways. Further blockage by PARP1 inhibitors induce SSBs, stalled replication forks, and persistent DSBs ultimately lead to cell-cycle arrest and apoptosis.[97] Augmented cell death caused by the repair block of both SSB and DSB is known as synthetic lethality.

Beyond its role in base-excision repair of DNA damage, PARP has also been implicated in other vital functions for cancer growth, such as tumor angiogenesis through the modulation of tumor-released hypoxia-inducible factor and vascular endothelial growth factor.[98,99]

Given the BRCA1 pathway dysfunction also seen in sporadic TNBC, PARP inhibitors should theoretically be effective not only in the tumors of carriers with BRCA mutations but also in sporadic TNBC as well. Currently, clinical studies are investigating the efficacy of PARP inhibitors in both patient populations while bench research is delving into the mechanisms of tumor growth suppression and predictive markers of response to PARP-inhibitor treatment.

### Anti-angiogenic agents

#### Anti-VEGF

Shown to be elevated in TNBC, vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, may play an important role in the progression of TNBC given this disease subtype's penchant for high proliferation.[100] VEGF stimulated the proliferation and migration of epithelial cells, inhibits apoptosis of endothelial tissue, increases vascular permeability and vasodilation. Bevacizumab (Avastin), the best known anti-angiogenic agent, is a humanized monoclonal antibody (mAb) that binds to VEGF and prevents it from interacting with vascular endothelial cells.[101,102] Bevacizumab was shown to have added value when combined with chemotherapy in patients with hormone receptor (HR) negative breast cancer, although as a group the benefits and toxicities of anti-angiogenesis drugs in breast cancer treatment has not been clearly established.

#### Anti-EGFR

Although EGFR/HER1 is not a specific marker for basal-like breast cancer, its over-expression has been found in 44%–78%[16,62] of these tumors and may be an important prognostic marker in long-term survival.[51]

Similarly, over-expression of EGFR is also found in TNBC[23,26,103] and there may be an inverse relationship between estrogen receptor expression and EGFR amplification.[62] TNBC cell growth and survival may be supported by signaling via EGFR over-expression and increased ligand levels.

Expression of TIMP-2, an endogenous inhibitor for several ADAM (a disintegrin and metalloproteinase) and matrix metalloproteinase (MMP) family members, inhibits Erb-B ligand and receptor shedding by the tumor and tumor suppression in vivo. In many human tumors, reduced TIMP-3 expression correlated with disease suppression.[104] These results suggest ADAM inhibitors INCB7839 (an inhibitor of ADAM 10 and ADAM 17) and TMI-002, an inhibitor specific for ADAM 17, may suppress the downstream signaling from all EGFR family members. Drugs have been developed to target both the extra-cellular domain of EGFR (monoclonal antibodies) and the intracellular domain (tyrosine kinase inhibitors). Clinical trials evaluating cetuximab, a humanized anti-EGFR IgG1 antibody, panitunumab, a full human anti-EGFR antibody, gefitinib and erlotinib, both small molecule tyrosine kinase inhibitors in TNBC are encouraging.

### Multi-tyrosine kinase inhibitors

C-src, the cellular homolog of the viral oncogene v-src, is a non-receptor signaling kinase that works downstream of multiple growth factors including platelet-derived growth factor receptor (PDGFR), EGFR, IGF–1. It plays an important role in cancer cell proliferation and invasion through multiple pathways.

Dasatinib is an orally active small molecule inhibitor of both scr and abl proteins. In vitro studies show that dasatinib inhibits growth of "basal-like/triple-negative" breast cancer cell lines both as a single-agent, and also in combination with chemotherapy (namely 5'-5'-DFU or cisplatin).[105]

## Other targeted therapies

### mTOR inhibitors

The serine-threonine kinase mammalian target of rapamycin (mTOR) promotes protein translation, angiogenesis, proliferation, migration, and metabolism.[106] mTOR has two complexes, mTOR complexes 1 and 2 (mTORC1 and mTORC2). The mTORC1 consists of mTOR, mammalian LST8 (mLST8), proline-rich Akt substrate 40 (PRAS 40) and raptor.[107] Release of PRAS 40 leads to mTORC1 activation and phosphorylation of eukaryotic initiation factor 4E-binding protein (4E-BP1) and S6 kinase 1 (S6K1). Activation of 4E-BP1 enhances cell proliferation, survival and angiogenesis.[108] Phosphorylation of S6K1 leads to many important cellular functions including activation of insulin receptor substrate 1 (IRS-1), eukaryotic initiation factor 4B, cellular apoptosis, eukaryotic elongation factor-2/kinase/mTOR, and glycogen synthase kinase 3.[109] Both 4E-BP1 and S6K1 have been associated with cellular transformation and poor prognosis of cancer patients.[108,110] The other mTOR complex, mTORC2, consists of mTOR, SIN1, and mLST8, PRR, and rector.[111–115] This complex has been shown to activate Akt phosphorylation and has been implicated in cellular migration and apoptosis.[111,116]

Inhibiting mTOR's mediated PI3K/Akt signaling pathway abolishes cellular proliferative responses and causes cell cycle arrest. As PI3K/Akt overactivity has been identified in a number of breast cancers,[117] rapamycin and its analogs temsirolimus, everolimus, and deforolimus, are undergoing clinical evaluation in TNBC treatment.

### IGF-1R

Insulin-like growth factor I receptor belongs to a class of tyrosine kinase receptors that contribute to proliferative control, apoptosis, angiogenesis and tumor invasion.[118] Expressed in 29%–36% of all TNBC tumors[119] has been implicated in the activation of the PI3 K/Akt proliferative pathway in breast cancer.[120,122] Preclinical studies in TNBC tumor grafts treated with anti-IGF-IR/InsR dual TKI and chemotherapy have demonstrated complete tumor regression.[123] Drugs targeting IGF-1R are of two types: monoclonal antibodies specific for IGF-1R (eg, cixutumumab, ganitumab, figitumumab) and TKIs (linsitinib, XL-228). Drugs of both types are being investigated in treating TNBC.

### Androgen receptor (AR) inhibition

Preclinical in-vitro studies demonstrated that androgens can induce proliferative changes in breast cancer cell lines and promote tumorigenesis in animal models by androgen receptor stimulation.[124] Doane and colleagues examined MDA-MB-453, a cell line with the same biomarker phenotype as TNBC and found that androgen enhanced growth of this cells line was ER-independent and AR-dependent.[125]

10%–35% of TNBC express androgen receptors,[126,127] and it has been suggested that a subset of TNBC cases may benefit from the addition of androgen blockade to their therapy.[128] Bicalutamide, a nonsteroidal competitive androgen inhibitor, is used in the treatment of advanced prostate cancer, but until recently, its anticancer effects were not tested in women.

### Heat shock protein (Hsp) 90 inhibition

Hsp 90 is a chaperone protein that is widely expressed in breast cancer. It stabilizes client oncogenic proteins and contributes to the survival of tumor cells. In a preclinical study, Caldas-Lopes and colleagues demonstrated that the Hsp 90 inhibitor PU-HTI suppressed TNBC xenograft growth in vivo, showing both partial tumor regression and complete response.[129] In vitro, Hsp 90 inhibition has been shown to 1) down-regulate members of the Ras/Raf/MAPK pathway and G 2-M phase to suppress Hsp 90 dependent tumor proliferation, 2) degrade the activated Akt and Bcl-XL, thus inducing apoptosis, and 3) inhibit the activated NF-KB, Akt, ERK2, Tyk2, and PKC, therefore reducing the invasive potential of TNBC. Their findings suggest that Hsp 90 may be an effective and pluripotent target for TNBC therapy.

## Clinical Studies in TNBC Management Options

### Chemotherapy

Until recently, due to a lack of a specific target, systemic treatment options for TNBC were limited to cytotoxic chemotherapy. TNBC, when compared with other phenotypes, were found to have a more favorable outcome after chemotherapy.[14] Shorter OS and disease-free intervals have been seen in patients who did not receive adjuvant chemotherapy.[9] In addition, TNBC patients are known to have a greater pathologic complete response (pCR) rate when compared with non-TNBC patients.[130] But does chemoresponsiveness lead to better overall survival? The NSABP B-18 and B-27 trials, which looked at a combination of neoadjuvant and adjuvant regimens of doxorubicin and cyclophosphamide (AC) with or without docetaxel, found that patients who achieved a pCR continued to have superior DFS and OS when compared with patients who did not.[131] However, there exists what is known as the "triple-negative paradox": while TNBC may be more chemosensitive, the poor prognosis associated with the disease can be explained by the high relapse rate in those patients who are unable to achieve a pCR.[132]

Many studies examining the timing of chemotherapy in the treatment of breast cancer have found that neoadjuvant therapy is equivalent to adjuvant therapy in OS and disease-free survival. A meta-analysis of nine randomized studies by Mauri et al however, found that neoadjuvant therapy was associated with an increased risk of loco-regional recurrence in patients treated with radiation therapy without surgery.[133] As this meta-analysis lacked a subset for TNBC patients, further investigation into the issue of neoadjuvant versus adjuvant therapy for TNBC patients is warranted.

The specific scheduling of chemotherapy may also be important in treating TNBC.[130,134] Dose-dense (in which intertreatment intervals are shortened) and/or metronomic scheduling (chronic, low-dose administration of therapy) have been shown not only to improve progression-free survival (PFS), but also increase pCR;[135–137] this in turn could mean significantly greater OS, whereby weekly or bi-weekly AC and paclitaxel may greatly benefit TNBC patients. Dose intensification may also improve event-free survival and overall survival in TNBC patients with multiple positive nodes.[138]

Though trials have yet to demonstrate a clear increase in DFS and OS with neoadjuvant chemotherapy, there is still a clinical advantage given the availability of tissue and the ability to correlate potential biomarkers with pathologic response. More experimental neoadjuvant regimens including platinum salts paired with a taxane and excluding the use of anthracyclines, have shown to achieve high pCR rates in TNBC but choice of drug in this setting has yet to be established.[139,140]

In the adjuvant setting, anthracyclines and taxanes remain the standard of care for TNBC patients with operable, node-positive breast cancer.[141–143] Relative anthracycline sensitivity and taxane-resistance among TNBC patients may hinge on BRCA-1 function. The loss of BRCA-1 is associated with sensitivity to DNA-damaging chemotherapy as well as resistance to spindle poisons, such as taxanes and vinca alkaloids.[144] This is relevant not only for carriers of the BRCA-1 mutation but for patients with sporadically-occurring TNBC whose tumors have DNA repair defects similar to BRCA-1 associated tumors; in this population, it has been demonstrated that anthracycline sensitivity and taxane-resistance may be predicted by a BRCA-1

associated expression signature.[145] A recent study showed that the classical regimen of cyclophosphamide, methotrexate, and fluorouracil (CMF) had a greater benefit in node-negative TNBC patients than in patients with hormone-receptor positive or HER-2 positive/hormone-receptor negative disease, suggesting CMF may be a good choice for adjuvant therapy in certain populations.[146] Currently, there is no standard first line agent to recommend for use in metastatic disease.

### Platinum salts

The use of platinum salts in the neoadjuvant setting is promising, as TNBC patients undergoing regimens containing platinum salts with or without other agents showed pathological complete response rates ranging from 15%–83%.[78,83,84,132] The best partner agents for platinum salts in the adjuvant setting has yet to be determined; regimens combining platinum salts with epirubicin, adriamycin, taxol, and taxotere all showed high pCR rates in TNBC patients.[78,147,148] Pairing neoadjuvant cisplatin with bevacizumab did show 15% complete pathologic response in TNBC patients, though toxicity limited completion of therapy in about 10% of patients.[149] The tumor response to platinum-based drugs in metastatic TNBC is also being evaluated.[85] Mature data from prospective randomized controlled trials, such as NCT00532727, a phase III randomized trial comparing carboplatin and docetaxel as first-line treatment in metastatic and recurrent TNBC, and CALGB 40603, which is testing neoadjuvant carboplatin and taxane therapy in stage II and III TNBC, are not yet available (CALGB NCT00861705). While the role of this class of drug in treating patients with TNBC is being actively pursued, routine use of platinum-containing regimens in patients with early-stage TNBC is not recommended.

## Anti-tubulin drugs

### Taxanes

The taxanes include paclitaxel and docetaxel and has proven effective in all breast cancer types in both the neoadjuvant and adjuvant setting.[78,85] TNBC has shown to have a better response to taxane-containing regimens than to chemotherapy without taxanes[142] and to have a significantly better response rate to neoadjuvant taxane treatment.[85,150,151] Whether they prove more effective in TNBC patients in the adjuvant setting than other breast cancer subtypes is questionable. Subset analysis from the BCIRG001 trial (docetaxel, doxorubicin, and cyclophosphamide vs. fluorouracil, doxorubicin and cyclophosphamide) found that the benefits of the docetaxel-containing regimen were independent of hormone receptor status.[142] Similarly equivocal results between hormone-receptor subgroups were obtained in the NSABP B28 trial, which looked at doxorubicin and cyclophosphamide with or without paclitaxel.[152]

### Ixabepilone

Its antitumor activity in TNBC has been demonstrated both when used as monotherapy or in combination with capecitabine. When administered as monotherapy, ixabepilone induced a higher pCR in TNBC groups (26%–28%) when compared to non-TNBC patients or to the overall study patient population (15%–18%).[89,153–155]

Several phase II and III trials have also looked at ixabepilone's efficacy when paired with capecitabine, a second-line therapy widely used in anthracycline and taxane-resistant disease. Analysis of pooled data from these trials found that overall response rate (ORR) (31 vs. 15%) and PFS (4.2 vs. 1.7 months) were improved in TNBC patients who received combination therapy as opposed to those who received single-agent capecitabine.[156]

Ongoing trials are examining ixabepilone activity in combination with sunitinib (as first-line therapy in TNBC patients), cetuximab (in metastatic TNBC patients), and in direct comparison to docetaxel and paclitaxel-containing regimens.[153] Ixabepilone has been shown to have a manageable safety profile, with neutropenia, sensory neuropathy, fatigue, arthralgias, myalgias, and stomatitis as its main side effects.[157]

# Targeted Therapy

## PARP inhibitors

Preclinical data on the mechanisms of PARP inhibitors have led to early phase clinical trials in the targeted treatment of BRCA-deficient breast cancer and TNBC. This class of drug includes olaparib (AZD2281, KU-0059436), iniparib (BSI-201), and veliparib (ABT888). The following PARP inhibitors are being studied in various phases of clinical trials (Table 1).

Olaparib, an oral PARP 1 and PARP2 inhibitor, is active in BRCA-deficient ovarian and breast cancers. In phase I and II studies, single agent olaparib has

shown antitumor activity in BRCA-mutation carriers with refractory and/or advanced disease. A greater partial response rate to olaparib has been demonstrated in TNBC patients than in non-TNBC patients (54% vs. 29% respectively).[158] Toxicities observed were primarily grade 1 and 2 and were similar to those observed with conventional chemotherapy (fatigue, nausea, vomiting, anemia).[159]

Encouraging as these results are, it still remains unclear if olaparib is effective outside the BRCA-associated cancer. Canadian study 20, a phase II trial looking at four cohorts of patients with advanced breast or ovarian disease, closed the arm of sporadic TNBC patients as no response to olaparib treatment was seen.[160]

The efficacy of olaparib in combination with conventional chemotherapy agents has yet to be determined. Concerning toxicity patterns (mainly grade 2–4 neutropenia) resulted when the drug was paired with paclitaxel in the treatment of metastatic TNBC.[161] Given pre-clinical data that PARP1 inhibition may potentiate the effects of platinum compounds,[162] olaparib is now being tested in combination with carboplatin and cisplatin in TNBC. Safety data from these trials will be important in determining olaparib's therapeutic place in TNBC.

Iniparib (BSI 201) is a PARP 1 inhibitor administered intravenously. The addition of iniparib to gemcitabine and carboplatin in a phase II study in metastatic TNBC prolonged the median overall survival from 7.7 months to 12.3 month, translating to a 43% reduction in the risk of death (HR = 0.57, $P = 0.01$). Median PFS in the iniparib group was 5.9 months compared to 3.6 months for the chemotherapy group (HR = 0.59, $P = 0.01$). No significant difference in adverse events was seen between the groups.[163]

These promising results paved the way for a phase III study to evaluate OS and PFS in metastatic TNBC (NCT00938652). 519 women with metastatic TNBC were randomized to receive chemotherapy (gemcitabine and carboplatin) with or without iniparib. The study admittedly failed to meet the pre-specified criteria for significance for its co-primary endpoints of OS and PFS. There was, however, an improvement in OS and PFS for patients treated in the second and third-line. The safety analysis indicated that the addition of iniparib did not add to the toxicity profile of gemcitabine and carboplatin [JC, Sanofi-Aventis press release, January 2011]. The use of iniparib in TNBC is currently being tested in the neoadjuvant setting (NCT00813956, NCT01204125), and in the treatment of brain metastases (NCT01173497).

Veliparib (ABT888), an oral PARP 1 and PARP 2 inhibitor, is also being investigated. It has shown to be well tolerated in combination with metronomic cyclophosphamide and to have activity in TNBC.[164] Veliparib with temozolomide, an agent found to be synergistic in breast cancer xenograft models, was shown to have activity in patients with metastatic breast cancer.[165] Though the preliminary data from this phase II trial did not include a TNBC subgroup analysis, full accrual and final efficacy results are pending.

Whether all TNBC patients will benefit from PARP-inhibitors or if only a portion of TNBC patients, such as BRCA-deficient tumors, will have clinical improvement beyond chemotherapy alone remains to be seen.[166] The clinical utility of PARP inhibitors may become better realized if predictive biomarkers can be identified.[158]

## Anti-angiogenic agents

### Anti-VEGF

Numerous studies have examined bevacizumab as treatment for metastatic disease and subset analyses suggest that TNBC may have an increased sensitivity to anti-angiogenic agents. Multiple studies looking at the addition of bevacizumab to different chemotherapy agents have shown an increase in PFS in TNBC patients.[167,168] Several multicenter randomized trials, including the Cancer and Leukemia Group B (CALGB) 40503 and National Surgical Adjuvant Breast and Bowel Project (NSABP)-B40 studies, hope to gather more data on the effect of bevacizumab on TNBC. However, as Greenberg and Rugo pointed out, all trials to date have used PFS as an endpoint and an improvement in OS has yet to be shown.[100] In late 2010, the FDA began the process to remove breast cancer as an indication from the Avastin label not only due to a lack of efficacy, but safety. A 2011 meta-analysis in JAMA highlighted the dangers of the drug, finding that compared with chemotherapy alone, the addition of bevacizumab was associated with an increase risk of fatal adverse events (FAEs), the most common

being hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal tract perforation (7.1%).[169] While there were differences in relative risk across tumors types and between drug doses and combinations, it warned of the possible increased risk of FAEs, especially when pairing bevacizumab with taxanes or platinum drugs.

### EGFR inhibitors

Cetuximab as a single agent appears to have low activity in metastatic TNBC and so recent research has focused on finding the right therapeutic partner for this monoclonal antibody. Cetuximab combined with the platinum salts has seen encouraging results. Carey et al's study showed little response in the cetuximab alone-group, but patients who received cetuximab with carboplatin had an 18% response rate (CR and PR) and 27% saw clinical benefit (PR or SD $>$ 6 months).[170] The BALI-I trial demonstrated a response rate of 20% in the cetuximab plus cisplatin arm, nearly doubled the response rate of cisplatin alone. Overall survival data is still forthcoming and though it failed to reach its primary endpoint (a response rate of more than 20% in the combination arm), the findings reinforce the idea that anti-EGFR agents may have an important role to play in TNBC.[171]

Adding cetuximab to irinotecan and carboplatin resulted in an increased in ORR in the TNBC subset of O'Shaughnessy's phase II trial conducted in patients with metastatic disease. A drawback, however, was that the primary toxicity of the irinotecan/carboplatin combination (diarrhea) was exacerbated in patients who received cetuximab.[172]

Preliminary results of a phase I/II trial of cetuximab in combination with either paclitaxel or docetaxel demonstrated a response (defined as a clinical response, decreased tumor markers, or a decrease in size of metastases) in 9 of 11 patients. The observed toxicity in this combination was the cumulative expected toxicity of each individual agent.[173]

Patients who suffer infusion reactions (bronchospasm, stridor, urticaria, hypotension, and cardiac arrest) to cetuximab, a chimeric monoclonal antibody, may be treated by panitumumab, a fully human anti-EGFR monoclonal antibody.[174] This new agent is currently under clinical investigation in the setting of metastatic TNBC (NCT01009983).

### Anti-EGFR tyrosine kinase inhibitors

TKIs showed early promise in pre-clinical studies, demonstrating efficacy in treating anti-hormone resistant breast cancer.[175] In theory these drugs should be very effective in TNBC, given that the proliferation of these tumors seemed to be EGFR-dependent.[176] But clinical studies have not supported the hypothesis; single-agent TKI studies were not impressive in the heavily pre-treated metastatic population nor in the ER(−), EGFR-overexpressing population.[177] Instead, the TKIs seemed to be more effective in ER(+), tamoxifen-resistant patients even though the EGFR expression in their tumors tends to be low-to-moderate.[178]

However, like cetuximab, the key to effective TKI use probably lies in treatment combinations. Gefitinib paired with carboplatin and docetaxel has been shown to be synergistic and enhance response in TNBC cells.[179] Inhibitors of ADAM (enzymes involved in the activation of EGFR ligands) may also be potential partners for TKIs in TNBC treatment. Studies testing gefitinib with TMI-002 (a compound that specifically inhibits ADAM-17 in breast cancer cell lines), did not see any additional benefit when the two agents were administered simultaneously; gefitinib treatment administered 72 hours after the ADAM inhibitor, however, was more effective, though the difference did not reach statistical significance. An un-named inhibitor of both ADAM 10 and ADAM 17 has been found to reduce cell growth by 91% in pre-clinical studies and has also been shown to reduce TNBC's migratory ability [EM, EORTC-NCI-AACR press release, November 2010].

### Multi-Tyrosine kinase inhibitors

Dasatinib and sunitinib have been tested mostly in patient populations that have been heavily pre-treated. A Phase II trial of single-agent dasatinib in patients with locally advanced or metastatic TNBC and prior anthracycline and/or taxane therapy found only modest activity (clinical benefit rate of 9.3%).[180] Candidate genomic markers for dasatinib therapy selection have been identified in breast cancer patients[181] and are currently being tested for clinical utility (NCT00780676).

Sunitinib, a TKI that targets the VEGF-associated TK, has been found to elicit response in TNBC

**Table 1.** TNBC clinical trial summary.

| Trial | Total patients | Pt popul | Regimen | Primary endpoint | Secondary endpoint | Results | Conclusions | Reference |
|---|---|---|---|---|---|---|---|---|
| **PARP inhibitors** | | | | | | | | |
| Phase II **Iniparib (BSI-201)** O'Shaughnessy J. NCT00540358 *NEJM* 2011; 364:205–14. | 123 | Met TNBC breast CA, ≥18 years old, ECOG performance status = 0–1, ≤2 prior treatments | Gemcitabine + Carboplatin +/– Iniparib. Gemcitabine 1000 mg/m$^2$ IV days 1,8, Carboplatin AUC 2 IV days 1,8, Iniparib 5.6 mg/kg IV days1,4,8,11 (init dose = 4 mg/kg prior to Jan 2008), Cycle = 21 days | Rate of clinical benefit (% pts w/complete response (CR), partial response (PR) or stable disease (SD) for 6 months) and safety of iniparib. | Secondary endpt: ORR, PFS | Rate of clinical benefit was 56% in iniparib group (grp) and 34% in chemotherapy only grp ($P = 0.01$). ORR = 52% in iniparib group and 32% in chemo only grp ($P = 0.02$). PFS = 3.6 months (mo) in chemo alone and 5.9 mo in iniparib grp (HR for progression, 0.59; 95% CI, 0.39–0.9; $P = 0.01$) Median OS = 7.7 mo for chemo alone and 12.3 mo for iniparib grp (hazard ratio (HR) for death, 0.57; $P = 0.01$). No sig. difference seen between the 2 grps in rate of adverse events (AE). | Addition of iniparib to gemcit + carboplat improved clinical benefit and survival of pts with metastatic TNBC | 159 |
| Phase III **Iniparib (BSI-201)** O'Shaughnessy J. NCT00938652 Press Release Jan 27, 2011. | 519 | Metastatic (met) TNBC breast CA, ≤2 prior treatments | Gemcitabine + Carboplatin +/– Iniparib, Gemcit 1000 mg/m$^2$ IV days 1,8, Carboplatin AUC 2 IV days 1,8, Iniparib 5.6 mg/kg IV days 1,4,8,11, Cycle = 21 days | Overall survival (OS) and progression-free survival (PFS) | | Did not meet pre-specified criteria for significance for co-primary endpts of OS and PFS. In pre-specified analysis in pts treated in 2nd and 3rd line setting demonstrate an improvement in OS and PFS. Overall safety analysis indicates addit of iniparib to gemcitabine + carbplatin did not add signif to toxicity profile of gemcitabine + carbplatin | Ongoing | JC, Sanofi-Aventis press release, January 2011 |

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|---|---|---|---|---|---|---|---|---|
| Phase I **Olaparib (AZD2281; KU-0059436)** Fong P. NCT00516373 *NEJM* 2009; 361:123–34. | 60 | Solid tumors, refractory to standard therapy or there was no suitable effective standard therapy ≥18 y/o, ECOG PS ≤ 2 | Olaparib (dose accelerated-titration design) | Phase I objectives: determine safety, dose-limiting toxicity, max tolerated dose, dose associated w/max PARP inhibition, pharmacokinetic (PK) profile | | Objective antitumor activity was reported only in BRCA1 or BRCA2 mutation carriers. | Olaparib has antitumor activity in cancer assoc w/ BRCA1 or BRCA 2 mutation. "Predictive biomarkers of homologous-recombinant DNA repair deficiency in tumor cells should be used to evaluate usefulness of PARP inhibitors". | 154 |
| Phase II **Olaparib (AZD2281; KU-0059436)** Tutt A. NCT00494234 *Lancet* 2010; 376:235–44. | 54 | Stage IIIB/ IIIC or IV Breast cancer, ≥18 y/o, ECOG PS = 0–2, confirmed BRCA mutation, ≥1 prior treatment | Non-randomized assignment Cohort 1 (n = 27): Olaparib 400 mg PO BID Cohort 2 (n = 27): Olaparib 100 mg PO BID | Objective response rate (ORR) | Secondary endpoint: rate of clinical benefit (% pts w/CR, PR, and SD for ≥23 wks), PFS, duration of response | ORR was 41% in cohort 1 and 22% in cohort 2. In Cohort 1, 54% (7/13) TNBC pts had PR vs. 29% (4/14) non-TBC pts. In Cohort 2, 25% (4/16) TNBC pts had PR vs. 18% (2/11) non-TNBC pts. One CR observed in Cohort 1 (pt with BRCA1 mutation). | Results provide positive proof of concept for PARP inhibition in BRCA-deficient breast cancers. Toxicity in BRCA carriers was similar to that observed previously in non-carriers in Fong et al's study. | 155 |
| Phase II **Veliparib (ABT888)** Isakoff SA. NCT *JCO* 2010; 28:1019 (abstract) | 41 | Met breast, >1 prior met breast Tx, PS ≤ 2, previously Tx'd stable brain mets allowed | Veliparib 40 mg PO BID, days 1–7 Temozolomide (TMZ) 150 mg/m$^2$ PO QD, days 1–5, Cycle = 28 days | ORR | Secondary endpoint: PFS, OS, safety, toxicity | Best response for 24 evaluable pts at time of abstract submission include 1CR, 2PR, 7SD (all unconfirmed), and 14 PD; 17 pts not yet evaluable for response. Most common grade 3/4 AE's: thrombocytopenia, neutropenia. | Combined veliparib + TMZ was active in met breast CA. | 161 |
| Phase I **Veliparib (ABT888)** Kummar S. NCT00810966 *JCO* 2010; 28:2605. | 18 | Refrac solid tumors and lymphomas, ≥ 18 y/o, KPS > 70% | Veliparib + Metronomic cyclophosphamide (C), Cycle = 21 days | Phase I objectives: establish safety, tolerability, max tolerated dose of combination of Veliparib + metronomic (C), PK profile | | Confirmed PR's in 3 pts (2 BRCA + ovar CA, 1 TNBC), stable disease in 2 pts (BRCA2 + male breast CA, BRCA + ovarian CA) | Regimen of veliparib + metronomic C showed activity in BRCA+ ovarian and TNBC | 160 |

(*Continued*)

**Table 1.** (*Continued*)

| Trial | Total patients | Pt popul | Regimen | Primary endpoint | Secondary endpoint | Results | Conclusions | Reference |
|---|---|---|---|---|---|---|---|---|
| Phase I/II **Olaparib (AZD2281)** Dent R. *JCO* 2010; 28:1018. | 19 | Met TNBC breast CA, ≤1 prior met breast Tx | Olaparib 200 mg PO BID + paclitaxel qweek for 3 of 4 wks | Phase I objectives: determine safety and tolerability, followed by phase II trial | | 12/19 patients had Grade 1–4 neutropenia. 2/10 pts in second cohort (w/GCSF prophylaxis) had recurrent grade 2 neutropenia despite GCSF. 37% had confirmed PR, 10 pts had confirmed + unconfirmed PR. | Combination of olaparib and weekly paclitaxel well-tolerated but acceptable dose intensive not achieved due to neutropenia. Preliminary analysis demonstrated promising efficacy. Alternative schedules and dosing of olaparib should be considered. | 157 |
| **Anti-tubulin agents** | | | | | | | | |
| Phase II **Ixabepilone** Baselga J. *JCO* 2009; 27:526–34. | 161 | Invasive BC ≥ 3 cm, patients not amenable to BCS | Neoadjuvant ixabepilone 40 mg/m$^2$, day 1. Cycle = 21 days | Analysis of pretreatment mRNA expression for potential response predictors | pCR rate, clinical and radiologic responses, proportion of patients able to have post-treatment BCS, drug safety | pCR 26% in TNBC subgroup analysis vs. 18% in overall study population | Inverse relationship between ER expression levels and ixabepilone sensitivity. Neoadjuvant ixabepilone has manageable safety profile and promising activity in invasive breast tumors. | 84 |
| Phase I/II **Ixbepilone** Bunnell C. *Clin Breast Cancer*. 2008; 8:234–41. | 106 | Locally advanced or MBC previously treated with an anthracycline and taxane | Schedule A: ixabepilone 40 mg/m$^2$, day 1 + capecitabine 1650–2000 mg/m$^2$, day 1–14. Schedule B: ixabepilone 8–10 mg/m$^2$ on days 1–3 + capcitabine 1650 mg/m$^2$ on days 1–14. Cycle = 21 days | ORR | time to response, duration of response, PFS | Objective response rate = 30%, median time-to-response = 6 weeks, mediation duration of response = 6.9 months, median PFS = 3.8 months. | Ixabepilone + capecitabine has an acceptable safety profile and clinical activity in this patient population. | 150 |

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|---|---|---|---|---|---|---|---|---|
| Phase III **Ixabepilone** Thomas ES. *J Clin Oncol.* 2007;25: 5210–17. | 752 | Pts with measurable locally advanced or MBC pretreated with or resistant to anthracyclines and resistant to taxanes | Ixabepilone 40 mg/m$^2$, day 1 + capecitabine 2000 mg/m$^2$ days 1–14 or capecitabine alone 2500 mg/m$^2$, days 1–14, cycle = 21 days | PFS | Tumor response rate, time to response, duration of overall response, overall survival | PFS in ixabepilone + capcitabine vs. capecitabine alone = 5.8 months vs. 4.2 months. Objective RR = 35% vs. 14%. | Ixabepilone + capecitabine demonstrates superior efficacy to capecitabine alone in this patient population | 151 |
| **ANTI-VEGF agents** | | | | | | | | |
| Phase III **Bevacizumab** Miller K. *N Engl J Med*. 2007;357: 2666–76. | 722 | MBC previously untreated with cytotoxic therapy | Paclitaxel 90 mg/m$^2$, days 1, 8, 15 or bevacizumab 10 mg/kg, days 1 and 15 + Paclitaxel, cycle = 28 days | PFS | OS | In TNBC pts, medial PFS increased from 4.7 mo to 10.2 mo with the addition of bevacizumab. | Initial therapy of MBC w/paclitaxel plus bevacizumab prolongs PFS but not OS, as compared with paclitaxel alone | 97 |
| Phase III **Bevacizumab** Miles DW. *J Clin Oncol*. 2010;28: 3238–47. | 736 | HER2-negative LR or MBC w/outprevious chemotherapy | Docetaxel 100 mg/m$^2$ plus placebo q3weeks or docetaxel 100 mg/m$^2$ + bevacizumab 7.5 or 15 mg/kg q3weeks | PFS | Best overall response, duration of response, time to treatment failure, OS, safety | mPFS increased from 6.0 to 8.1 mo in 15 mg/kg bevacizumab arm | Bevacizumab 15 mg/kg q3weeks significantly increased PFS when combined with docetaxel as first-line therapy for MBC when compared with docetaxel plus placebo. It is equally effective in HR (+) and HR (–) patient populations. | 163 |
| Phase III **Bevacizumab** Robert J. *J Clin Oncol*. 2009;27: abstract 1005. | 1237 | Pts w/LR or MBC previously untreated by chemotherapy | Capecitabine 2000 mg/m$^2$ for 14 days, nab-paclitaxel 260 mg/m$^2$, docetaxel 75–100 mg/m$^2$, or doxorubicin or epirubicin combos q3weeks. BV or placebo administered at 15 mg/kg q3weeks | PFS | OS, 1 year survival rate, objective response rate, duration of objective response, safety | mPFS increased from 4.2 to 6.1 mo in the Cape cohort and from 8.2 to 14.5 mo in taxane/anthracycline cohort. | | 164 |

(*Continued*)

**Table 1.** (*Continued*)

| Trial | Total patients | Pt popul | Regimen | Primary endpoint | Secondary endpoint | Results | Conclusions | Reference |
|---|---|---|---|---|---|---|---|---|
| Phase III **Bevacizumab** von Minckwitz G. SABCS. 2010; abstract S4–6. | 1948 | Early or locally advanced HER2-negative breast cancer | epirubicin 90 mg/m$^2$ + cyclophosphamide 600 mg/m$^2$ with or without bevacizumab 15 mg/kg q3weeks | pCR | Compliance and toxicity | Overall pCR in bevacizumab-containing arm = 17.5% versus pCR in chemotherapy w/ out bevacizumab = 15%. However, 40% increase in pCR in TNBC group w/addition of bevacizumab. | No statistical sig. difference in overall study population with addition of bevacizumab but TNBC sub-group analysis showed greater rates of pCR. | 197 |
| **EGFR inhibitors** | | | | | | | | |
| Phase II **Cetuximab** O'Shaughnessy J. *Breast Canc Res Treat* 2007; 106 (Suppl 1), abstract 308. | 163 | Met breast CA, prior regimen elig | Irinotecan + Carboplatin +/– Cetuximab. Irinotecan 90 mg/m$^2$ followed by Carboplatin AUC 2 days 1, 8 of 21-day cycle. Cetuximab 400 mg/m$^2$ dose 1 then 250 mg/m$^2$ weekly thereafter | Objective response rate | Secondary endpt: PFS, OS, safety | Preliminary analysis: 39% of patients receiving cetuximab had objective response compared to 19% who rec'd chemo only. Patients receiving cetuximab had greater incidence of grade 3–4 toxicities compared to chemo only cohort | Preliminary analysis suggests that addition of cetuximab to irinotecan-carboplatin may improve antitumor activity but is associated with greater incidence of toxicities. | 168 |
| Phase II **Cetuximab (TBCRC 001)** Carey LA. *JCO* 2008;26 (May 20 Suppl), abstract 1009. | 102 | Met TNBC, ≤3 prior regimen | Cetuximab +/– Carboplatin Carboplatin AUC 2 (Qwk × 3, then 1 wk off). Cetuximab 400 mg/m$^2$, then 250 mg/m$^2$ Qwk. Pts randomized to Cetuximab alone had Carboplatin added upon progression | Objective response rate (RR, CR+PR) | | Cetuximab alone (N = 31), Cetuximab + Carboplatin (N = 71). 87% rec'd prior adjuv chemo, 54% rec'd prior chemo for MBC. Cetuximab alone: PR 6%, SD 4%, clinical benefit (CB = PR or SD > 6 mos) = 10%; Cetuximab + Carboplatin: RR 18%, SD 9%, CB 27%. PR did not differ by line of Tx: 15% 1st-line, 31% 2nd-line, 17% 3rd line. Median PFS = 2 months. Regimen was tolerable. Greater incid of grade 3–4 AE's noted in Cetuximab + carboplatin arm | Cetuximab alone is well tolerated but has low activity in met TNBC. Many pts progressed rapidly. | 166 |

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|---|---|---|---|---|---|---|---|---|
| Phase II **Cetuximab (BALI-1)** Baselga J. *Ann Oncol* 2010; 21 (Suppl 8): abstract 2740. | 173 | Met TNBC, ≤1 prior regimen for met disease | Cisplatin (CDDP) +/– Cetuximab | Overall response (ORR) | Secondary endpt: PFS, OS, safety | Cetuximab + CDDP (N = 115), CDDP alone (N = 58). 27% of pts in both arms had prior chemotherapy and were well balanced for PS. ORR was 20% in Cetuximab + CDDP arm vs. 10.33% with CDDP alone. PFS was 3.7 mo with cetuximab+CDDP vs. 1.5 mo with CDDP alone. Grade 3/4 AE's noted in >5% of pts: acne-like rash (Cetuximab + CDDP only), neutropenia, fatigue, dyspnea. | Addition of Cetuximab to CDDP increased ORR and significantly improved PFS without any new safety concerns. | 167 |
| Phase I/II **Cetuximab** Nechushtan H. *JCO* 2009;27 (Suppl), abstract 12018. | 12 | Met TNBC, ≤2 prior regimen for met disease | Taxane (Paclitaxel 80 mg/m$^2$ or Docetaxel 30 mg/m$^2$) + Cetuximab Qwk (dose not specified) | Clinical response | | Preliminary analysis: Response (clinical response, tumor marker decr, decr in met size) noted in 9/11 pts (1 pt non-eval). 3 pts devel brain mets during Tx. 9 pts had prior taxane Tx. | Some impressive clinical responses noted even in taxane pre-treated pts. Toxicity is cumulated expected toxicity of each of the agents. | 169 |
| Phase II **Erlotinib** Dickler MN. *Breast Cancer Res Treat*. 2009; 115:115–21. | 47 | Pts w/locally advanced or MBC w/disease progression during or after therapy with an anthracycline, taxane, and capecitabine (cohort 1), or during or after therapy with one chemo-therapy regimen (cohort 2) | Erlotinib 150 mg PO qday | Response rate | Safety, time to pro-gression, survival | One pt in each cohort had PR. | Erlotinib had minimal activity in unselected previously treated women with advanced BC | 172 |

(*Continued*)

**Table 1.** (*Continued*)

| Trial | Total patients | Pt Popul | Regimen | Primary endpoint | Secondary endpoint | Results | Conclusions | Reference |
|---|---|---|---|---|---|---|---|---|
| **TYROSINE KINASE inhibitors** | | | | | | | | |
| Phase II **Sunitinib** Burstein HJ. *J Clin Oncol*. 2008;26: 1810–16. | 64 | MBC pts previously treated with anthracycline and taxane | sunitinib 50 mg/d in 6 weeks cycles (4 wks on, 2 wks off) | Objective response rate | | 7 pts achieved PR (3 had TNBC). ORR = 11%. 5% had stable disease >6 months. Median time to progression was 10 wks, overall survival was 38 wks | Sunitinib is active in patients with heavily pretreated MBC. | 178 |
| Phase I **Sunitinib** Bergh J. *J Clin Oncol*. 2010;28: abstract LBA1010. | 533 | Newly dx HER2-metastatic or advanced BC | Arm 1: docetaxel 75 mg/m$^2$, day 1, sunitinib 37.5 mg/day PO, day 2–15, q3weeks. Arm 2: docetaxel 100 mg/m$^2$ q3weeks | PFS | ORR, OS, safety | Prolonged PFS and prolonged OS was not achieved. | Sunitinib and docetaxel is not a recommended treatment option for patients with newly diagnosed advanced BC. | 179 |
| **mTOR inhibitors** | | | | | | | | |
| Phase II **Everolimus** Ellard SL. *J Clin Oncol*. 2009; 27: 4536–41. | 49 | Patients ≤ 1 treatment for MBC | Everolimus 10 mg qday versus 70 mg qweekly | Objective response or lack of early (<8 weeks) progression | | Response rate on daily therapy = 12%, response rate on weekly therapy = 0%. | Oral everolimus has activity in metastatic breast cancer that is schedule dependent. | 112 |
| Phase Ib **Everolimus** Mayer IA. 2009; ASCO: abstract 254. | 14 | MBC | Everolimus in escalating doses (2.5, 5, or 10 mg) with erlotinib 100 or 150 mg daily | Dose-limiting toxicity or disease progression | | Of the 12 pts still on treatment at first assessment, 11 had progression of disease. | Erlotinib + everolimus was well-tolerated but clinically ineffective in heavily pre-treated metastatic breast cancer | 182 |
| **IGF-1R inhibitors** | | | | | | | | |
| Phase I **MK-0646** Atzori F. *J. Clin Oncol*. 2008;26:3519. | 48 | IGF-1R expressing solid tumors | MK-0646 in escalating doses (1.25, 2.5, 5.0, 10, 15 mg/kg qweekly) by cohort | Phase I endpoints: safety and tolerability | | 3 patients had stable disease >3 mo | MK-0646 is safe and tolerable, inhibitirs IGF1R signaling and proliferation in treated tumors and has clinical activity. | 187 |

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| Phase I<br>**IMC-A12**<br>Higano CS. *J Clin Oncol.* 2007;25: abstract 3505. | 15 | Patients with ECOG PS = 2, advanced refractory solid tumors | IMC-A12 in escalating doses by cohort (3, 6, 10, 15, 21, 27 mg/kg q3weekly). | Phase I safety and tolerability | 4/11 had stable disease: 2 >9 mo (3 mg/kg dose), 2 after 1 cycle (6 mg/kg dose). | IMC-A12 appears to be well tolerated. | 188 |
| Phase I<br>**R1507**<br>Rodon J. *J Clin Oncol.* 2007;25: abstract 3590. | 21 | Pts with advanced solid tumors or lymphomas | q3weekly infusions of escalating doses (1–16 mg/kg) of R1507 | Phase I safety and tolerability | 10 pts showed stable disease | R1507 treatment is tolerable at 16 mg/kg q3weeks | 190 |
| **AR inhibitors** | | | | | | | |
| Phase I<br>**Bicalutamide**<br>Traina TA. ASCO. 2009: abstract 251. | 65 | ER-/PR-MBC | AR patients treated with bicalutamide 150 mg PO qday | Complete response + partial response + stable disease >6 months | 4 pts on treatment who were evaluable for response:<br>1 SD for >18 mo,<br>1 SD <6 mo, 2 pt had progression. | Bicalutamide is well tolerated and can stability disease in ER-/PR-/AR + patients | 192 |

**Abbreviations:** TNBC, Triple negative breast cancer; MBC, metastatic breast cancer.

patients. One phase II trial given to patients with metastatic disease who had previously been treated with an anthracycline and taxane, found an overall response rate (ORR) of 15% in the TNBC subset.[182] But, like bevacizumab, this drug is increasingly thought to be ineffective in breast cancer.[183,184] This lack of efficacy may be due to drug's short half-life and the fact that optimal biologic and therapeutic dosing has yet to be defined. Judicious patient selection may also play a key role in maximizing the efficacy of these anti-angiogenic agents.

## Other targeted therapies

### mTOR inhibitors

Preclinical studies demonstrate that mTOR inhibitors used alone are cytostatic in most tumor types and may clinically stabilize disease.[185] Data from clinical studies looking at single-agent everolimus have not been impressive. A phase II study comparing daily dosing with weekly dosing of single-agent everolimus in patients with recurrent/metastatic breast cancer found a low response rate, with no biologic correlates of response despite trends favoring benefit in ER-positive and HER-2 negative breast cancer. However the fairly modest drug-related toxicities encourage drug-combination studies.[117,186] Two trials are currently investigating the use of everolimus in the treatment of TNBC (NCT01272141 is looking at the combination of lapatinib and everolimus in locally advanced or metastatic TNBC, and NCT00827567 is examining the use of single agent everolimus in metastatic TNBC). As with all other targeted therapy, markers of mTOR treatment response will prove paramount in patient selection. Patients with cancer showing decreased PTEN, activated PI3K activation, or high p-mTOR have been reported to benefit the most from this class of drugs[187–190] but work in this area must progress.

### IGF-1R

Multiple phase I studies have found multiple humanized mAbs and TKIs to be safe and tolerable in patients with solid tumors.[191–194] Data from a tissue study by Witkiewicz and colleagues demonstrated that IGF-1R is overexpressed and amplified in 29% of their TNBC samples.[195] High IGF-1R expression was significantly correlated with negative lymph nodes and, in patients younger than 55 years of age,

with longer survival. The IGF-1R/insulin receptor tyrosine kinase domain inhibitor BMS-754807 has demonstrated activity in TNBC[123] and ongoing trials are evaluating the efficacy of this class of targeted treatment in breast cancer.

### Androgen receptor inhibition

NCT00468715 is an ongoing study evaluating the use of bicalutamide, an anti-androgen agent used for treatment of prostate cancer in the treatment of HR-negative, AR-positive breast cancer. Bicalutamide has been well-tolerated in this population and preliminary analysis has demonstrated disease stabilization in ER/PR negative, AR positive with AR inhibition.[196]

### Heat shock protein (Hsp) 90 inhibitor

Clinical studies are evaluating Hsp 90 inhibitor AUY922 and IPI-504, but only in ER and HER2 positive disease (NCT0181613 and NCT01081600). Whether agents of this class will prove effective in vivo and in TNBC specifically, remains to be seen.

## Conclusion

The tumor biology of TNBC, basal-like breast cancer, BRCA-mutated machinery, and claudin-low disease is both specific and diverse. While conventional chemotherapeutic regimens can be successful in treating women with TNBC and basal-like disease, it is clear that this pool of diseases is heterogeneous in nature and must be further sub-categorized. Emerging therapies aimed at damaging DNA, angiogenic players, tubulin structures, mTOR, IGF-1R, AR, and HSP 90 show promise in early stage studies, but their clinical performance has yet to be definitively proven. No doubt much of the work to come must focus on generating more specific terminology in order to identify the optimal patient population for each treatment.

## Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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