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The Management of Early Stage and Metastatic Triple Negative Breast Cancer: A Review

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Abstract

Triple negative breast cancer (TNBC) defined as lacking expression of the estrogen receptor, progesterone receptor and HER2, comprises approximately 15% of incident breast cancers and is over-represented among those with metastatic disease. It is increasingly clear that TNBC is heterogeneous and that there are several biologically distinct subtypes within TNBC, in particular the basal-like subtype but also the claudin-low, among others. While the incidence of *BRCA* mutations across all subsets of breast cancer is quite low (~5%), *BRCA* mutations are more common among those with TNBC (~20%) and may have therapeutic implications. The general principles guiding the use of chemotherapy and radiation therapy do not differ dramatically between early stage TNBC and non-TNBC. There is a trend, however, to treat TNBC at a lower stage with chemotherapy as this is the only way to systemically reduce recurrence risk. In the metastatic setting, while cytotoxic chemotherapy is the mainstay of treatment for advanced TNBC, there are many promising targeted therapies in development in both the preclinical and early phase clinical trial settings. While the treatment of TNBC remains a challenge, coordinated efforts between clinician/scientist partnerships providing a comprehensive understanding of TNBC genomic, proteomic and other biologic processes may result in individualized therapy for TNBC faster than other subtypes -- driven by both the heterogeneity we know exists within this clinical entity and the intense need for improved treatment.

Keywords

breast cancer; triple negative; chemotherapy; targeted agents; radiation; BRCA mutation

Introduction: Overview and Scope of the Problem

The management of triple negative breast cancer (TNBC), a disease that affects approximately 180,000 women world-wide, is challenging[1]. Clinically defined as lacking expression of the estrogen receptor (ER), the progesterone receptor (PR) and expression of HER2 by immunohistochemistry (IHC), TNBC comprised approximately 15% of incident

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breast cancers and is over-represented among those with metastatic disease[2–4]. TNBC is usually high grade, more often an "interval" breast cancer (ie. diagnosed between screening mammograms) and, when recurrent, preferentially relapses in visceral sites such as lungs, liver and brain[4–6]. Given the higher rates of recurrence and lack of traditional targets (such as ER and HER2), treating those with TNBC evokes anxiety on the part of both the patient and provider. In this review article, we will address the unique biology of TNBC, followed by a detailed discussion of state-of-the-art local and systemic treatments in the early stage setting. We will then discuss approved cytotoxics to treat advanced TNBC and the many emerging targeted agents in development to treat this aggressive disease.

Unique Biology of Triple Negative Breast Cancer

As above, TNBC is defined clinically as lack of ER, PR and HER2 expression by IHC (with confirmation of HER2 status by fluorescence in-situ hybridization [FISH] if indeterminate [2+] by IHC). As per the most recent ASCO/CAP guidelines, ER and PR negativity is strictly defined as <1% expression, as opposed to older definitions allowing up to 1 –10% "borderline" ER/PR expression[7]. Interestingly and in an analysis of > 1,700 breast tumors, while the majority of TNBC's (as strictly defined by IHC as <1% ER/PR expression) fall into the basal-like subtype by gene expression analysis (207/283, 73%), borderline cases (n = 48) were more commonly luminal (46%) or HER2-enriched (29%)[8] Based on this observation, it is recommended that clinical trials aimed at enrolling women patients with TNBC/basal-like breast cancer should adhere to the ASCO/CAP guideline recommended definition of ER/PR < 1% when developing inclusion/exclusion criteria.

While the basal-like breast cancer subtype has been associated with TNBC for nearly a decade, newer subtypes within TNBC are emerging[9,10]. More recently, a novel molecular subtype identified as Claudin-low has been characterized via gene expression of human breast tumors, a panel of breast cancer cell lines, and mouse models of breast cancer[11] ENREF 11. Clinically, Claudin-low breast tumors are commonly ER, PR and HER2 negative via immunohistochemistry, show a high frequency of metaplastic and medullary differentiation, and an intermediate response to cytotoxic chemotherapy (between that of Basal-like and Luminal breast tumors). Moreover, Claudin-low breast tumors have been shown to exhibit stem-cell characteristics, low expression of cell-cell adhesion proteins (i.e. Claudin 3, 4 and 7), high enrichment for epithelial-to-mesenchymal transition (EMT) markers, and low luminal/epithelial differentiation.

A second group of investigators has further dissected the biology of TNBC, identifying 6 unique subsets of TNBC through gene expression analysis of over 500 breast tumors from over 20 independent datasets[12]. This analysis classified TNBC into the following clusters: 2 basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem–like (MSL), and a luminal androgen receptor (LAR) subtype. Approximately 30 TNBC cell lines were then classified into each of the aforementioned categories and pharmacologically inhibited to illustrate that classification may inform therapeutic strategies. Results showed that the BL1 and BL2 subtypes, both with higher expression of DNA damage response genes, responded to cisplatin. Response to PI3K/mTOR (phosphatidylinositide 3-kinase/mammalian target of rapamycin) and SRC inhibition was observed among the M and MSL subtypes, which are enriched for epithelial-mesenchymal transition (EMT) and growth factor pathways. Finally, cell lines within the LAR subtype were preferentially responsive to the androgen receptor (AR) antagonist, bicalutamide – a concept that has borne out to a degree in the clinical arena[13]. Given the apparent heterogeneity within TNBC, a "one-size-fits-all" approach is no longer appropriate as we design clinical trials for patients with TNBC. Consideration of the distinct subsets within TNBC will be paramount as we aim to improve outcomes for this aggressive disease.

Association with BRCA mutations

In addition to advances in understanding the underlying biology of TNBC, several studies have illustrated the association of TNBC with germline *BRCA* mutations. A recent observational study aimed to determine the incidence of germline *BRCA1* and *BRCA2* mutations among 77 patients with TNBC[14]. *BRCA* mutations were detected in 19.5% of patients: 15.6% *BRCA1* and 3.9% *BRCA2*. Interestingly, in this cohort of patients, outcomes were superior among *BRCA* mutation carriers as compared to wild-type patients, including 5-yr recurrence free survival [RFS, 51.7% vs. 86.2%, p = 0.031] and 5-yr overall survival [OS, 52.8% vs. 73.3%, p = 0.225]. Further confirming these findings, an integrated molecular analysis of breast carcinomas in The Cancer Genome Atlas (TCGA), reports ~20% of Basal-like breast tumors harbored a *BRCA1* or *BRCA2* mutation, of which ~2/3 were germline and 1/3 somatic[15]. *BRCA1* inactivation was found to be common among both Basal-like breast cancer and serous ovarian cancer. This finding suggests shared driving events for both diseases and that therapeutic approaches (i.e. use of platinums, taxanes and inhibitors of PARP [Poly-ADP-Ribose Polymerase]) may be guided more by molecular profile, and less by tissue of origin.

Therapeutic Options for Early Stage Triple Negative Breast Cancer

While the basic principles, including the surgical management, radiation therapy techniques, and decisions regarding systemic therapies, are similar between stage I – III TNBC (as defined by the TNM staging system) compared to endocrine and/or HER2+ counterparts, there are some nuances specific to TNBC that should be considered. In addition, there have been several provocative studies in the field of radiation therapy specific to patients with TNBC that are worthy of review.

Local Therapy/Radiation Therapy

Given conflicting retrospective studies regarding whether women with TNBC are at a higher risk of local recurrence following breast-conserving therapy (BCT) and whether they might be better served by a modified radical mastectomy (MRM)[16–18], it has become accepted that either treatment paradigm is reasonable in the management of early stage TNBC. However, recent studies suggested that early-stage TNBC patients may be at a higher risk for local recurrence when treated with MRM alone, omitting post-mastectomy radiotherapy (RT) (i.e. in T1-T2N0 patients lacking classic indications for post-mastectomy RT), which warrants discussion.

In a large single institution retrospective review of 768 women with T1-T2N0 TNBC, investigators from McGill University found a significant difference in locoregional recurrence rates (LRR) between patients treated with BCT, MRM or MRM plus RT[19]. Five-year LRR-free survival was 96% and 90% among BCT and MRM patients, respectively ($p<0.03$), and MRM was the only independent prognostic factor associated with LRR (HR 2.5), suggesting that MRM alone may not be “enough” local therapy in these patients. A prospective trial performed in Shanghai randomized 681 women with stage I-II TNBC after MRM to chemotherapy +/− RT[20]. While not their primary endpoint(s), the investigators found a statistically significant difference in relapse free survival (RFS) and overall survival (OS), favoring the group who received both adjuvant chemotherapy and post-MRM RT. Five-year RFS improved from 75% to 88% with the addition of RT, and adding RT improved 5 year OS impressively from 79% to 90%. Although retrospective and thus subject to unintended bias, these are intriguing but hypothesis-generating data, warranting further study in a rigorous randomized controlled trial, but do not warrant a change in clinical practice.

Many TNBC patients receive neoadjuvant chemotherapy in the hopes of becoming BCT candidates or as a means to assess *in vivo* response to systemic therapy. There has been a growing discussion about whether or not to omit post-MRM RT in patients with significant down-staging secondary to chemotherapy, or even to modify RT field design based on response to chemotherapy. This issue is not unique to women with TNBC. Unfortunately, there are no prospective data to support this practice. Retrospective data from MD Anderson suggests that patients with residual nodal disease benefit from post-MRM RT, but those left with stage I/II disease after chemotherapy do not derive such a benefit[21,22], however interpretation of these findings must acknowledge the limitations of subgroup analyses of patients in whom the use of RT was left to the discretion of the physician, and the absence of prospective or controlled studies. In the absence of prospective data, it remains standard of care to irradiate the same fields (i.e chest wall, supraclavicular fossa with or without irradiation of the internal mammary chain if cT3 or node positive) after neoadjuvant chemotherapy as one would do if patients had up-front surgery.

Systemic Therapy – Neoadjuvant and Adjuvant Treatments and Ongoing Clinical Trials

The only opportunity for recurrence risk reduction to treat TNBC with curative intent is systemic chemotherapy, as there are currently no approved targeted treatments, like endocrine or HER2-directed therapy, to ameliorate baseline risk. As such and in compliance with guidelines as put forth by the National Cancer Comprehensive Network (www.NCCN.org), it is common and appropriate for oncologists to prescribe anthracycline/taxane-based chemotherapy at a lower stage for TNBC compared with hormone receptor positive counterparts. While use of a more aggressive regimen (i.e. anthracycline/taxane as opposed to a taxane-based regimen) may be reasonable in many TNBC, it is also true that "biology does not trump anatomy." A small node-negative TNBC carries a low (15% or less) 5-year risk of recurrence[23] and a proportionally lower benefit of treatment. Using tools such as AdjuvantOnLine, the mortality risk at 10 years for a T1a/bN0 tumors is <10%. An observational study of over 1,000 T1a/bN0 TNBC found excellent prognosis, with 95% remaining free of distant metastasis at 5 years and without a notable difference between those that did and those that did not receive chemotherapy[24]. Taking this into account, a reasonable algorithm for adjuvant chemotherapy in node-negative TNBC is to offer it if tumor size is > 1cm (T1c) and otherwise medically-appropriate, a balanced discussion in 0.6–1.0 cm (T1b) tumors, and no adjuvant chemotherapy in breast tumors 0.5cm or less (T1a). As with other subtypes of breast cancer, adjuvant anthracycline/taxane-based chemotherapy is recommended in patients with lymph node positive disease (N1 or greater), regardless of primary tumor size (Figure 1).

The principles that govern the decision to proceed with neoadjuvant versus adjuvant chemotherapy are similar between TNBC and other subtypes of breast cancer. These principles are largely driven by (1) resectability of the primary tumor and lymph nodes to achieve negative margins and (2) the ability to cytoreduce a breast cancer to facilitate breast conservation, as opposed to a mastectomy. Historically and as guided by the landmark study National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27[25], chemotherapy sequenced prior to (as opposed to after) surgery does not appear to improve survival. However, response to chemotherapy, particularly achievement of pathologic complete response (pCR), can help identify those patients with better prognosis. Basal-like/TNBC has consistently been shown to be more sensitive to neoadjuvant chemotherapy (i.e. higher pCR rates) than Luminal breast cancers. Collectively, however, TNBC patients experience poorer overall outcomes as compared to other breast cancer subtypes. The poorer prognosis of Basal-like/TNBC has been explained by a higher likelihood of relapse in those patients in whom pCR was not achieved and has been termed the "triple negative paradox. [26,27]

Using pCR rates for patients with TNBC as an endpoint, investigators are evaluating additional chemotherapies and targeted agents in the neoadjuvant setting. A trial of interest, Cancer and Leukemia Group B, (CALGB) 40603 (NCT00861705), is evaluating the addition of a platinum (i.e. carboplatin) and/or an anti-angiogenesis agent (i.e. bevacizumab) to standard anthracycline/taxane-based neoadjuvant chemotherapy in the setting of locally-advanced TNBC. Importantly, all patients in this trial are required to undergo dedicated biopsies in order to identify predictive markers of response. Platinum agents have been an area of investigation in TNBC based upon the hypothesis of augmented sensitivity to DNA-damaging agents in dysfunctional *BRCA*. Although small studies have suggested high clinical responses to cisplatin in germline *BRCA* mutation carriers[28,29], whether this holds true in sporadic TNBC is uncertain; prospective data await the results of CALGB 40603. Results of neoadjuvant bevacizumab studies in TNBC have previously been mixed[30,31], and the addition of one year of bevacizumab to adjuvant chemotherapy in TNBC failed to improve invasive disease-free survival in a recently-reported, large (n > 2,500 patients), open-label, randomized, multi-national phase III trial[32]. Anticipated results of CALGB 40603 will continue to add our understanding of the role of bevacizumab, if any, in the curative treatment of TNBC and to identify those patients who may benefit from these approaches.

Another area of active research pertains to those with “residual disease” – specifically, the group of patients with TNBC who do not achieve a pCR following neoadjuvant chemotherapy – in an effort to improve outcome for those at greatest risk for local and/or distant recurrence. While scientists are actively analyzing the molecular changes in residual breast tumor following pre-operative cytotoxic therapy[33], an ongoing randomized, phase III trial is also evaluating the benefits of an intensive diet/exercise intervention or without adjuvant metronomic chemotherapy (6 months of cyclophosphamide/methotrexate, CM) plus bevacizumab (12 months) in patients with residual disease to determine if this strategy will reduce recurrence among this high-risk group.

At this point, the choice of chemotherapy regimen does not differ between TNBC and non-TNBC. Retrospective studies have suggested that much of the benefit of adjuvant anthracyclines is in the HER2-overexpressing subset of tumors, however this finding is not universal or definitive. More recently, molecular studies suggest that the HER2-enriched molecular subtype derived the primary benefit of an anthracycline regimen (CEF, cyclophosphamide, epirubicin, 5-fluoruracil) over classic CMF (cyclophosphamide, methotrexate, 5-fluoruracil); in that retrospective analysis, the basal-like subtype appeared to benefit equally from both regimens[34]. While intriguing, intrinsic subtyping for this purpose is not yet clinically available, nor is it sufficiently validated for decision-making. While TNBC behaves differently than other subtypes of breast cancer with higher local and distant metastasis rates and earlier pattern of relapse, breast conservation and multimodality options for care in the early breast cancer setting remain similar to other subtypes.

Advanced Triple Negative Breast Cancer

Principles of Systemic Therapy

In spite of great excitement in the recent past, with potential novel drugs like PARP inhibitors and bevacizumab offering a “targeted” option in TNBC, we remain with multiple cytotoxic choices, but no targeted therapy in the metastatic setting at this time. Conventional treatment of metastatic TNBC begins with cytotoxic chemotherapy, of which there are ~14 single agents and ~8 doublets listed in the treatment of HER2-negative, recurrent or metastatic breast cancer as per NCCN (www.NCCN.org). Choice of palliative cytotoxic regimen is no different in TNBC than other subtypes, with options of poly-chemotherapy

generally reserved for symptomatic or rapid visceral progression, and sequential single agents for relatively asymptomatic, stage IV disease.

A recent randomized phase III study, CALGB 40502, confirms that weekly paclitaxel is the optimal first-line regimen compared with the more modern microtubule-directed agents nab-paclitaxel or ixabepilone, including in the TNBC subset[35]. A similar subset analysis in TNBC of eribulin compared with capecitabine in the first to third line setting found no difference between the two drugs overall, although the TNBC subset had improved progression-free survival with eribulin compared with capecitabine. This subset analysis, however, should be considered exploratory rather than definitive[36]. The decision of which drug to use, in this case eribulin versus capecitabine, may reasonably be made on the basis of their very different toxicity profiles. Many of our patients with advanced TNBC receive a variety of cytotoxics while still medically well enough to do so; individualizing care and selection of cytotoxic should be made on the basis of side effects, convenience, and personal choice as opposed to strictly based on subtype.

Incorporation of a Platinum—As discussed in the treatment of early stage TNBC, the question of how and when to sequence direct DNA-damaging agents in the treatment of advanced TNBC remains unknown. Platinum drugs appear to have high single-agent activity in *BRCA1/2*-associated cancers[28,29], but platinum agents in sporadic TNBC demonstrate reasonable, yet not excessively high response rates. As an example, the Translational Breast Cancer Research Consortium (TBCRC) 009 trial found an approximately 30% response rate to cis- or carboplatin in the first- or second-line treatment of advanced TNBC[37]; in the control arm of BALI-1, first-line cisplatin alone produced responses in only 10% of advanced TNBC patients[38]. These agents are appropriate to include in the armamentarium of cytotoxic choices in TNBC but do not need to be preferentially used over other the many other available agents with different mechanisms of action in sporadic, advanced TNBC.

Targeted Agents to Treat Advanced TNBC—Given the relative paucity of available "targeted" agents, ongoing preclinical and clinical efforts are focused on the development of more refined strategies to control advanced TNBC beyond that of cytotoxic chemotherapy (Table 1). In the recently reported TCGA analysis, the most commonly mutated genes and pathways in Basal-like/TNBC were the tumor suppressor gene *TP53* (~80% mutated), loss of *RB1* (tumor suppressor gene) and *BRCA1* (DNA repair gene) function, as well as *PIK3CA* (~9%; as compared to approximately 30% – 49% in luminal A and B breast tumors, respectively). Comprehensive protein analysis illustrated basal-like breast cancers to have the highest relative PI3K pathway activation, likely via alternative mechanisms such as loss of the negative regulators, PTEN and/or INPP4B. Other plausible drug targets identified through this comprehensive analysis included *FGFR1, FGFR2, IGFR1, KIT, MET*, *PDGFRA,* as well as angiogenesis and/or drugs that become activated under hypoxic conditions. Large-scale, coordinated studies such as the TCGA will only continue to foster our understanding of the complex biology underlying TNBC with the goal of translating these findings into rationally-designed clinical trials, of which several historical trials and strategies will be reviewed here.

Anti-angiogenic strategies—Anti-angiogenic strategies appeared promising based upon preclinical data in TNBC models, however a pooled analysis, however, of three randomized first-line metastatic studies of bevacizumab added to chemotherapy (E2100, AVADO, and RIBBON-1) demonstrated improvement in progression-free survival (PFS), but no impact upon overall survival in HER2-negative patients overall or in the TNBC subset[39]. Among approximately 2,500 patients with HER2-negative metastatic breast cancer, median PFS improved from 6.7 to 9.2 months (Hazard Ratio [HR] = 0.64, $p<0.0001$) in the bevacizumab arms, and one-year survival rates were greater in the bevacizumab plus chemotherapy arm

as compared to the control arms (81.6% versus 76.5%; respectively, p = 0.003). In spite of these improvements, there was no difference in overall survival, which was 26.4 months in the control arm and 26.7 months with the addition of bevacizumab. Based on lack of survival benefit and toxicity, bevacizumab's initial FDA accelerated approval in 2008 was revoked in 2011; current use of bevaciuzmab in metastatic breast cancer is essentially restricted to clinical trials. Biomarkers predictive of response to bevacizumab have been difficult to identify; biomarker results from the neoadjuvant study CALBG 40603 are anticipated in hopes of informing future studies in the metastatic setting to augment response to anti-angiogenic strategies.

Inhibitors of Poly-ADP-Ribose Polymerase (PARP)—In those patients with germline *BRCA1* or *BRCA2* mutations, PARP inhibition remains a promising avenue, however this approach remains available only in clinical trials, and reports from small studies have failed to demonstrate a similar outcome in sporadic TNBC. For example, a phase II study of the PARP inhibitor olaparib revealed unconfirmed responses only in BRCA1/2 carriers, with no responses among patients with sporadic TNBC[40]. A phase II study of temozolomide with another PARP 1/2 inhibitor, velparib (ABT-888), enrolled 41 patients with metastatic breast cancer (~50% TNBC); response rate across the entire population was 7%[41], however an exploratory analysis revealed that responses were essentially limited to BRCA1/2 carriers. In those 8 patients, the response rate (complete and partial responses, CR/PR) was 37.5% with a clinical benefit rate (defined as CR, PR, and stable disease [SD] > 16 weeks) of 62.5%. Progression free survival was 5.5 months for *BRCA* mutation carriers and 1.8 months in non-carriers suggesting that the benefit from PARP inhibition was largely derived from those harboring mutations in DNA repair, namely through the *BRCA* pathway. Identifying non-*BRCA* associated TNBC tumors with similar phenotype and DNA damage repair defect with potential to benefit from PARP inhibition, with or without chemotherapy, remains a subject of intense and ongoing research.

Inhibition of Epithelial Growth Factor Receptor—While TNBC lacks ER and HER2 expression, expression of EGFR (epithelial growth factor receptor, HER1) has been demonstrated among TNBC at both the gene and protein level[2,6]. Several studies have evaluated the benefit of adding the EGFR-targeted monoclonal antibody, cetuximab, to platinum-based chemotherapy to treat advanced TNBC with modest results. The TBCRC 001 study evaluated treatment with cetuximab as a single agent and/or combined with carboplatin among 102 patients with advanced TNBC. Response rates for cetuximab as a single agent, combined with carboplatin at progression following monotherapy, or with cetuximab/carboplatin from the onset of treatment were 6%, 16% and 17%, respectively.[42] While time to progression was short (2.1 months, 95% CI, 1.8 to 5.5 months), pre- and post-therapy biopsies evaluating dynamic changes EGFR signaling provided further insight into possible compensatory pathways that may have been responsible for the marginal benefit observed from this novel drug combination. Dovetailing the results of TBCRC 001, the BALI-1 study reported a doubling of response rates (RR) by combining cetuximab with cisplatin as compared to cisplatin alone in TNBC (RR: 20% versus 10.3%, respectively)[38]. Despite improvements in response, duration of response was quite short; progression free survival was only 3.7 months following cetuximab/cisplatin versus 1.5 months following cisplatin monotherapy. Although there was initial enthusiasm and strong preclinical rationale for the incorporation of EGFR-based therapy into systemic therapy for advanced TNBC, translation of this approach clinically has resulted in only modest improvements in outcome, possibly due to heterogeneity of disease and compensatory alternate signaling in the cancer cells. Biomarkers predictive of response to this targeted therapy or combinatorial strategies may be needed to enrich for responders if this strategy is to be successful to treat advanced TNBC.

Inhibition of Androgen Receptor Signaling—The luminal androgen receptor (LAR) subtype of TNBC is sensitive to androgen deprivation in preclinical studies[12], making AR signaling in ER-negative breast cancer an intriguing potential target. In the recent TBCRC 011 phase II trial, of > 450 hormone receptor-negative (primarily TNBC) screened, about 10% had AR expression, and single agent bicalutamide in these patients yielded clinical benefit in 19%[13]. Continued study of AR pathway inhibition in advanced TNBC -- albeit the small subset that may be driven by the AR pathway -- is certainly warranted as we move toward the era of personalized medicine.

Inhibition of the PI3K, MEK, CHK and HDAC pathways - Preclinical—A tremendous amount of research is ongoing in search of "targetable" pathways that may be contributing to the aggressive biology of TNBC. As identified in TCGA, activation of the PI3K phosphoinositide-3 kinase pathway (PI3K, either directly via PI3KCA mutations or indirectly via PTEN and/or INPP4B loss) has been identified as important in TNBC/Basal-like breast cancer[15]. Preclinically, inhibition of the PI3K pathway results in TNBC cell growth arrest[43]; several small molecule inhibitors of the PI3K (and downstream mTOR [mammalian target of rapamycin] pathway) are in development. Several studies, including TCGA, have identified high rates of *p53* (tumor suppressor gene) mutations in TNBC/Basal-like breast cancer[15]. In the absence of *p53* function, cells in need of DNA damage repair rely on checkpoint kinase I (*Chk1*) to arrest the cell cycle and push potentially defective cells toward apoptosis; *p53*-deficient mouse models of breast cancer are sensitive to Chk-1 inhibition.[44,45]. Chk-1 inhibitors have therefore become an attractive potential target for the treatment of TNBC harboring *p53* mutations. In addition, inhibition of MEK (mitogen-activated protein–extracellular signal-regulated kinase), in combination with PI3K/mTOR inhibition has shown activity in a TNBC/Claudin-low genetically engineered mouse model; a "window" study of MEK inhibition (GSK1120212) is ongoing to evaluate dynamic reprogramming of the kinome in patients with TNBC to further identify pathways of resistance[46,47]. ENREF_46 (NCT01467310) Finally, epigenetic regulation of gene expression has been a hot topic in TNBC for several years. An inhibitor of the HDAC pathway (panobinostat) has been demonstrated to decrease cell growth in TNBC cell lines, as well as tumorigenesis *in vivo* and may soon make its way into the clinic.[48] This data is in light of the randomized, phase II study, TBCRC 008, where the addition of vorinostat to pre-operative carboplatin and nab-paclitaxel did not appear to improve pCR rates in a TNBC, otherwise unselected, group of n = 62 patients (vorinostat arm pCR = 27.6%; placebo arm pCR = 26.7%)[49]. Biomarkers predictive of those most likely to respond to HDAC inhibition are needed.

Conclusions and Future Directions

In 2013, TNBC is well-recognized as a distinct subset of breast cancer with a unique genomic background and characteristically aggressive clinical behavior in a relative sparse landscape of available, standard-of-care, targeted therapies. Despite this recognition, multimodality options for the care of TNBC in the early and advanced breast cancer settings remain similar (with, of course, the absence of endocrine and HER2-directed strategies) to other breast cancer subtypes. As we look ahead, we must ask ourselves, "What is the way forward?" Based on emerging understanding of the complexity of TNBC, it may be that clinician/scientist partnerships focused on comprehensive understanding of TNBC genomic, proteomic and other biologic processes, will reorient us towards individualized therapy in TNBC faster than other subtypes. This shift in focus will be driven by both the heterogeneity we now know exists within TNBC and the intense need for improved treatment.

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Key Points

1. Triple negative breast cancer (TNBC) lacks expression of the estrogen and progesterone receptors and HER2 by clinical assays.
2. While more commonly associated with the basal-like subtype of breast cancer, research assays have further dissected the biology of TNBC and have identified six subtypes thus far.
3. The incidence of *BRCA* mutations is higher among patients with TNBC (~20%) as compared to those with breast cancer across all subtypes (~5%).
4. Local and systemic therapy approaches to early stage TNBC should be similar to that of non-TNBC; however endocrine and HER2-directed therapies are not prescribed.
5. In the metastatic setting, the mainstay of systemic therapy to treat TNBC is cytotoxic chemotherapy; targetable pathways are currently under investigation in the preclinical setting and early phase clinical trials.
6. A coordinated effort between scientists and clinicians will be required to develop novel therapies to treat TNBC most effectively.

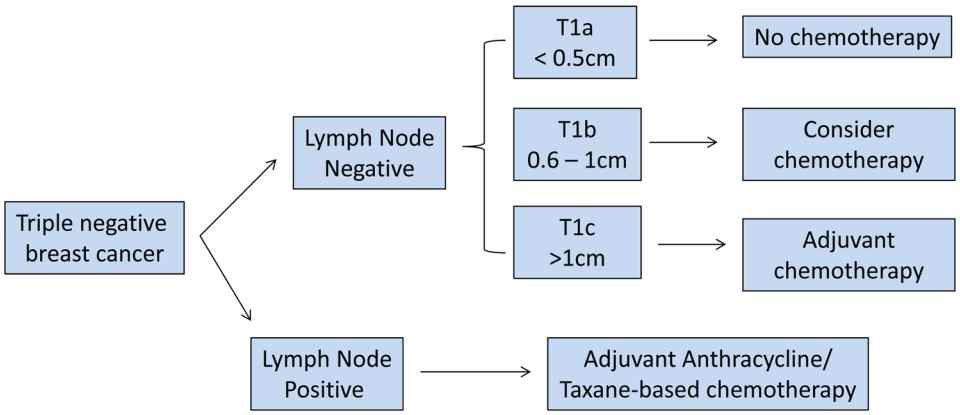

Figure 1.
General Algorithm Guiding Adjuvant Chemotherapy Decisions in the treatment of Early Stage Triple Negative Breast Cancer as adapted by www.NCCN.org, Version 1.2013, Invasive Breast Cancer

Table 1

Overview of Targeted Strategies in Advanced Triple Negative Breast Cancer

Therapeutic Target	Phase of Study	References
Angiogenesis	Phase III	38
PARP inhibition	Phase I/II	39,40
EGFR inhibition	Phase II	41,37
Androgen Receptor signaling	Phase II	13
PI3K inhibition	Preclinical/Phase I	42
MEK inhibition	Preclinical	46, 47
CHK inhibition	Preclinical	43, 44
HDAC inhibition	Preclinical/Phase II	48, 49