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Breast Cancer

Biology and Management of Patients With Triple-Negative Breast Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

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ABSTRACT

Triple-negative breast cancer (TNBC) accounts for 15% of all breast cancers and is associated with poor long-term outcomes compared with other breast cancer subtypes. Because of the lack of approved targeted therapy, at present chemotherapy remains the mainstay of treatment for early and advanced disease. TNBC is enriched for germline *BRCA* mutation, providing a foundation for the use of this as a biomarker to identify patients suitable for treatment with DNA-damaging agents. Inherited and acquired defects in homologous recombination DNA repair, a phenotype termed "BRCAness," may be present in a large proportion of TNBC cases, making it an attractive selection and response biomarker for DNA-damaging therapy. Triple-negative breast cancer is a diverse entity for which additional subclassifications are needed. Increasing understanding of biologic heterogeneity of TNBC has provided insight into identifying potentially effective systemic therapies, including cytotoxic and targeted agents. Numerous experimental approaches are under way, and several encouraging drug classes, such as immune checkpoint inhibitors, poly(ADP-ribose) polymerase inhibitors, platinum agents, phosphatidylinositol-3-kinase pathway inhibitors, and androgen receptor inhibitors, are being investigated in TNBC. Molecular biomarker-based patient selection in early-phase trials has the potential to accelerate development of effective therapies for this aggressive breast cancer subtype. TNBC is a complex disease, and it is likely that several different targeted approaches will be needed to make meaningful strides in improving the outcomes. ***The Oncologist*** 2016;21:1050–1062

Implications for Practice: Triple-negative breast cancer (TNBC) is an aggressive subtype that is associated with poor outcomes. This article reviews clinical features and discusses the molecular diversity of this unique subtype. Current treatment paradigms, the role of germline testing, and platinum agents in TNBC are reviewed. Results and observations from pertinent clinical trials with potential implications for patient management are summarized. This article also discusses the clinical development and ongoing clinical trials of novel promising therapeutic agents in TNBC.

INTRODUCTION

Triple-negative breast cancer (TNBC), which is defined by the lack of expression of estrogen receptor (ER) and progesterone receptor (PgR) and absence of *ERBB2* (*HER2*) overexpression and/or gene amplification, accounts for 15% of all breast cancers in the U.S. [1–4]. TNBC is the most fatal subtype of breast cancer and is associated with poor long-term outcomes compared with other breast cancer subtypes [5–7]. TNBC demonstrates some unique clinical and molecular characteristics, which are summarized in Table 1. Compared with other breast cancer subtypes, TNBC usually demonstrates high pathologic grade, more frequently affects younger women, is more prevalent in black women, and shows a higher prevalence of germline *BRCA* mutation [8–12]. During the past two decades, institution and/or enhancement of targeted therapies has improved the outcomes of *HER2*-amplified and hormone-positive breast cancers. However, these recent advances in targeted therapies have bypassed triple-negative breast cancer because of its tremendous heterogeneity and the lack of defined molecular targets. This article reviews molecular characterization, current treatment paradigms, and the emerging role of newer agents in TNBC.

MOLECULAR CHARACTERIZATION OF TNBC

In recent years, significant progress has been made in unraveling the biological diversity of TNBC and linking gene expression patterns to distinct molecular subtypes with potential therapeutic associations [13–16].

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Table 1. Clinical and molecular characteristics of triple-negative breast cancer

Clinical and pathological
Accounts for 15% of all breast cancers in the U.S.
Younger age at presentation compared with other breast cancer subtypes
More common in black and/or Hispanic women
Usually high-grade
Tumor infiltrating lymphocyte infiltration more common than other subtypes
Higher prevalence of germline *BRCA* mutations compared with other breast cancer subtypes (15% of unselected TNBC patients demonstrate germline *BRCA* mutation).
Shorter time to relapse
Higher risk for visceral metastases, including brain metastasis
Molecular
Basal-like subtype the most common intrinsic subtype by gene expression analysis
Heterogeneous: Several subtypes within TNBC identified by gene expression analysis
Demonstrates significant similarities with serous ovarian cancer at the molecular level (TCGA)
BRCA mutation-associated TNBC demonstrates defective DNA repair and thus sensitivity to DNA-damaging agents, such as platinum compounds and poly(ADP ribose)polymerase inhibitors
Homologous recombination deficiency can result from diverse factors and may be present in significant proportion of *BRCA* wild-type TNBC
Somatic *p53* mutations common (60%–80%), but "clinically actionable" aberrations occur in $<$20%
PI3K pathway activation, despite the low PI3K mutation rate, due to *PTEN* and *INPP4B* loss and/or amplification of *PIK3CA*, is common
Androgen receptor-positive subtype within TNBC manifests luminal molecular features and may be targeted with antiandrogen therapy

Abbreviations: *INPP4B*, inositol polyphosphate 4-phosphatase type II; PIK, phosphatidylinositol-3-kinase; *PTEN*, phosphatase and tensin homolog; TCGA, The Cancer Genome Atlas; TNBC, triple-negative breast cancer.

Molecular Subtypes

The seminal work by Perou et al. categorized breast cancer by gene expression profiling into four intrinsic subtypes [13]. The basal-like subtype comprises a group of tumors characterized by the absence or low levels of expression of estrogen receptors, very low prevalence of *HER2* overexpression, and expression of genes usually found in the basal or myoepithelial cells of the human breast [13]. Although most TNBCs fall into the basal-like intrinsic subtype on the PAM50 intrinsic subtyping assay, the overlap between immunohistochemically defined TNBC and basal-like molecular subtype is not complete. Various studies demonstrate that 70%–80% of TNBCs are basal-like on molecular profiling and 20%–30% of non-triple-negative breast cancers are basal-like on molecular profiling [15, 17, 18]. Thus, caution should be used when using the term "basal-like" to refer to TNBCs at large. Further refinement of the original Perou-Sorlie gene expression profiling has identified a claudin-low subset within the basal-like subtype. Claudin-low tumors are characterized by the absence of luminal differentiation markers, enrichment for epithelial-mesenchymal-transition markers, immune response genes, low proliferation, cancer stem cell-like features, and poor prognosis. However, the therapeutic implications of the claudin-low subset are not yet clear [19].

Triple-negative breast cancer is a diverse entity for which additional subclassifications may be needed, and grouping TNBC into basal and nonbasal subtypes may be oversimplifying the molecular heterogeneity of this disease. Using gene expression from publicly available data sets, Lehmann et al. classified TNBC into seven molecular subtypes: basal-like 1, basal-like 2, mesenchymal (M), mesenchymal stem cell-like (MSL), immunomodulatory (IM), luminal androgen receptor (AR)-like (LAR), and unclassified [14]. On the basis of identification of a cell line corresponding to each subtype, they also demonstrated that these subtypes may be responsive to different targeted therapies (Fig. 1). The methods of molecular classification used by Lehmann et al. have recently been simplified to an RNA-seq platform to better fit individual clinical samples (TNBCtype; InsightGenetics, Nashville, TN, http://www.insightgenetics.com) [20]. There is a modest degree of overlap between the subtypes identified by these different gene expression investigations. The MSL and M subtypes closely correspond to the previously described "claudin-low" subtype, the LAR subtype may fit more closely with the "luminal" intrinsic type, and the IM subtype may in fact reflect the tumor microenvironment rather than the tumor itself [15, 18].

It is speculated that heterogeneity of both the tumor and the microenvironment contributes to the transcriptome diversity noted in TNBC. Furthermore, some of this diversity could also stem from the discrete global methylation patterns in TNBC. For example, recent methylome sequencing of The Cancer Genome Atlas (TCGA) samples has identified three prognostically distinct methylation clusters in TNBC [21]. Despite variation in the number/types of subclasses identified by different transcriptome analysis, one common theme has emerged—there are biologically distinct subsets within TNBC. These subclasses respond differently to standard chemotherapy and will likely also display differential responses to novel targeted agents.

Targetable Alterations Are Not Common

Development and refinement of next-generation sequencing have improved our understanding of the prevalence of somatic mutations in various cancers. Mutation or loss of *TP53* occurs at a high frequency in TNBC. In TGCA, 68% of primary TNBC tumors were found to have *TP53* mutation, with an additional 3% demonstrating homozygous deletion of the gene [22]. These findings were confirmed by Shah et al., who reported that on exome sequencing of 102 primary TNBCs, *TP53* mutation

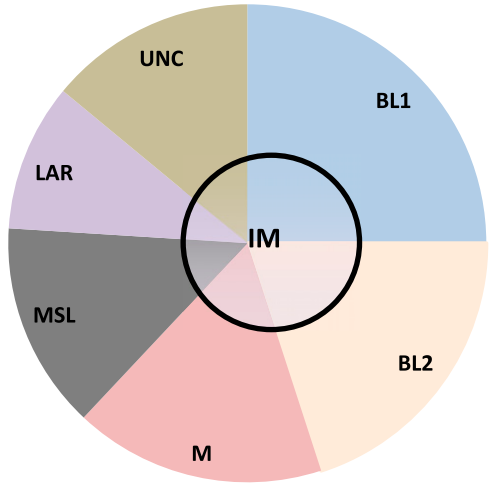

Figure 1. Proposed molecular subtypes of TNBC.

Abbreviations: BL1, basal-like 1; BL2, basal-like 2; IM, immunomodulatory (is likely distributed within all TNBC subtypes); LAR, luminal androgen receptor/luminal-like; M, mesenchymal; MSL, mesenchymal-stem cell-like; TNBC, triple-negative breast cancer; UNC, unknown classification.

was the most frequent clonal event (53.8%), followed by *PIK3CA* mutations (10.7%) [16]. To date, there are no available effective agents to target *TP53* mutations, although efforts to develop such agents are ongoing [23]. Absence of high-frequency, targetable oncogenic drivers in TNBC has hindered the development of successful therapeutic strategies [16, 24]. The frequency and coexistence of various genomic alterations in TNBC also evolve under the pressure of systemic chemotherapy. For example, profiling of residual TNBC tumor tissue after neoadjuvant chemotherapy revealed higher frequency of several potentially targetable alterations compared with basal-like primary breast cancers in TCGA. These included alteration in the phosphatase and tensin homolog (PTEN)/phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway (noted in 40% of samples); amplifications of *JAK2*; and *CDK6, CCND1, CCND2,* and *CCND3* amplification. Therefore, there are promising opportunities for studying targeted therapy in appropriately selected patients with residual disease after neoadjuvant chemotherapy. Several ongoing phase I/II studies are investigating phosphatidylinositol-3-kinase (PI3K) inhibitors in advanced TNBC, and early-phase studies are also assessing Janus kinase 2 and cyclin-dependent kinase inhibitors in hormone-negative breast cancer.

Molecular Similarities Between Basal-Like Breast Cancers and Serous Ovarian Cancer

Interestingly, TCGA analysis noted striking contrast between the basal-like breast cancers and luminal/human epidermal growth receptor 2 (HER2) breast cancer subtypes. However, comparison of basal-like breast cancers with high-grade serous ovarian cancers demonstrated prominent molecular similarities (*BRCA1* inactivation, *RB1* loss, high expression of *AKT1*, high frequency of *TP53* mutation, and *MYC* amplification) [22]. This is an important observation and suggests that common therapeutic strategies should be explored for serous ovarian cancer and TNBC (e.g., platinum agents, poly[ADP-ribose] polymerase [PARP] inhibitors [PARPi]).

Diagnosis and Clinical Behavior

Diagnosis of TNBC requires ER, PgR, and HER2 status testing. Testing and the cutoffs for ER, PR, and HER2 status were developed to determine the likelihood of response to endocrine and HER2-directed therapy, respectively, and not to specifically identify the "triple-negative" phenotype. Thus, during the past decade ER, PR, and HER2 cutoffs used to describe TNBC have varied. Most contemporary studies are now using the current American Society of Clinical Oncology–College of American Pathologists guidelines for determining ER/PgR and HER2 negativity (ER and PgR nuclear staining of less than 1% by immunohistochemistry [IHC] and HER2 IHC staining of 0 to 1+ or fluorescent in situ hybridization <2.0 if IHC 2+ or IHC not performed [2, 3].

TNBC is associated with not only higher but also an earlier risk for relapse. Hazard rates for distant recurrence are highest for TNBC in the first 2 years after diagnosis, and relapses after 5 years are uncommon [6, 25]. Compared with hormone-positive breast cancer, TNBC is characterized by a higher proportion of visceral relapse and short survival after development of metastatic disease [7, 26]. Median survival of patients with metastatic TNBC is only 12–18 months, compared with 5 years among patients with metastatic HER2-positive breast cancer, highlighting the pressing need for identification of more effective systemic therapies for this subgroup [27].

TNBC and Germline *BRCA* Mutation

Compared with other subtypes of breast cancers, women with TNBC have a higher prevalence of germline *BRCA* mutations [11, 12, 24, 28]. Various studies have demonstrated that 15%–20% of women with TNBC carry germline *BRCA1/2* mutations. Most genetic testing guidelines include TNBC subtype as an independent criterion for hereditary breast and/or ovarian cancer syndrome (HBOC) counseling and testing recommendation. The National Comprehensive Cancer Network guidelines recommend genetic risk assessment of all TNBC patients and HBOC testing for all TNBC patients aged $\leq$60 years regardless of family history (http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf). Despite these recommendations, financial constraints, insurance coverage, and access to genetic counseling/testing continue to be important challenges for optimal use of HBOC testing in the clinical setting [11].

Current State of Management of Early-Stage Disease

Systemic Chemotherapy

Because of the lack of molecular targets, chemotherapy is the only available systemic treatment for TNBC, and therefore adjuvant chemotherapy is recommended for TNBC patients with stage I (tumor size $>$0.5 cm)–III disease [4, 29–31]. Currently, the chemotherapy recommendations for early-stage TNBC are not unique to this subtype but are identical to the recommendations for other breast cancer subtypes. Most guidelines recommend anthracycline-taxane-based chemotherapy for stage I–III TNBC.

Despite receiving standard anthracycline-taxane-based chemotherapy, a substantial proportion (30%–40%) of patients with early-stage TNBC develop metastatic disease and die of the cancer [32–34]. Even with overall poor outcomes, it is evident

that a subset of TNBC patients respond well to standard-of-care chemotherapy combinations and that patients who achieve pathological complete response (pCR) after neoadjuvant chemotherapy have excellent long-term survival. However, despite achieving higher rates of pCR with conventional chemotherapy, TNBC phenotype is associated with higher relapse rates than hormone receptor-positive and HER2-positive breast cancers, a phenomenon known as the triple-negative paradox [5–7, 35]. This paradox is primarily driven by very high relapse rates in the subgroup of TNBC patients with residual disease after neoadjuvant chemotherapy. Therefore, there is a need to develop predictive markers to identify TNBC patients who are likely to have excellent outcomes with standard chemotherapy so that research efforts can be focused on patients who are most likely to recur after standard neoadjuvant therapy.

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Local Therapy: Surgery and Radiation

Several large retrospective analyses from individual clinical trials have demonstrated that tumor infiltrating lymphocytes (TILs) are prognostic in early-stage TNBC [36–39]. Presence and increasing percentage of TILs are associated with better response to anthracycline-based neoadjuvant chemotherapy and improved long-term survival in TNBC patients treated with adjuvant anthracycline chemotherapy. However, it is not yet clear whether the prognostic effect of TILs reflects underlying favorable tumor biology or whether TILs can in fact predict improved response to certain chemotherapy drugs. TILs are not yet part of routine clinical pathology reports, although efforts to standardize pathological evaluation and reporting of TILs are ongoing [40]. Prospectively integrating TILs into neoadjuvant trials for TNBC may help to better stratify patients and identify good-prognosis subgroups that may not need therapy intensification. Future research efforts will also assess the clinical utility of TILs in the setting of immune checkpoint inhibitors (programmed death 1 [PD-1] and programmed death ligand 1 [PD-L1] blockade). In the past decade, several retrospective transcriptional gene expression profiling investigations have sought to identify multigene signatures that can predict response to chemotherapy with anthracycline or taxane or both in TNBC [41–43]. One such signature is being prospectively evaluated in the setting of a neoadjuvant study (https://clinicaltrials.gov/ct2/show/NCT02276443). Currently, we do not have any clinically available biomarkers to identify TNBC patients who are likely to have excellent response and outcome with standard anthracycline/taxane neoadjuvant therapy, although efforts to identify such markers are aggressively being pursued.

Local Therapy: Surgery and Radiation

The principles for local therapy (surgery and radiation) for breast cancer are applied in a similar fashion for all breast cancer subtypes, and there are no TNBC-specific recommendations for local management. During the past decade, mastectomy rates in women with breast cancer have been rising in the U.S., and this trend has been noted with TNBC as well. Some of the recent studies suggest that more than 50% of women with operable TNBC are choosing to undergo mastectomy [44, 45]. High prevalence of germline mutations, family history of breast cancer, and availability of acceptable reconstruction options are all factors that likely contribute to the high mastectomy rates, especially in younger women with TNBC.

Role of Novel Chemotherapy and Biologics in Early-Stage Disease

Attempts to improve upon the fourth-generation adjuvant anthracycline/taxane chemotherapy regimens in TNBC have thus far been unsuccessful. Studies have demonstrated that addition of a fourth chemotherapy drug (gemcitabine) to an anthracycline/cyclophosphamide/taxane backbone or substitution of paclitaxel for novel chemotherapy (ixabepilone) does not improve outcomes in early-stage TNBC [46–48]. Angiogenesis is considered to be an important target for cancer therapy. Of agents in this class, bevacizumab has been the most widely studied in breast cancer.

In 2008, the U.S. Food and Drug Administration (FDA) approved bevacizumab (Avastin, a vascular endothelial growth factor inhibitor; Genentech, South San Francisco, CA, https://www.gene.com) in combination with paclitaxel as a first-line treatment for metastatic HER2-negative breast cancer based on the progression-free survival improvement noted with addition of bevacizumab to weekly paclitaxel in the Eastern Cooperative Oncology Group 2100 trial [49]. However, subsequent trials assessing addition of bevacizumab to first-line chemotherapy (AVADO and RIBBON-1 trials) failed to show a significant benefit in overall survival despite small improvements in progression-free survival [50, 51]. A meta-analysis of phase III trials with bevacizumab as first-line treatment for metastatic breast cancer demonstrated improved progression-free survival; however, no significant improvement in overall survival was observed, and addition of bevacizumab was associated with a significant increase in grade 3–4 toxicities [52]. On the basis of these data, the FDA revoked the metastatic breast cancer approval of bevacizumab in 2011. Subgroup analysis of some trials that added bevacizumab or sorafenib (an oral multikinase inhibitor, with antiproliferative and antiangiogenic activity) to chemotherapy showed a hint of greater benefit in TNBC patients [53, 54]. Unfortunately, randomized studies of adjuvant bevacizumab have failed to demonstrate improvement in overall survival in patients with TNBC [55, 56]. It is possible that a subgroup of TNBC may benefit from antiangiogenesis therapy, but lack of markers to predict benefit from such an approach and modest toxicity associated with antiangiogenesis agents have limited further development of this class of agents for TNBC.

Role of Platinum Agents

Sporadic and germline cases of *BRCA* mutation-associated TNBC share several pathological and molecular similarities [32, 57, 58]. The phenotypic and molecular similarities between *BRCA1* mutation-associated and sporadic TNBC have led many to surmise that a significant proportion of *BRCA* wild-type TNBCs may involve *BRCA1* pathway dysfunction through alternative mechanisms. Thus, *BRCA1*-directed therapeutic approaches (such as platinum agents and PARPi are being explored for a general population of patients with TNBC. Platinum agents are

Table 2. Neoadjuvant clinical trials with platinum agents in triple-negative breast cancer

Study [Reference]	Design	Chemotherapy regimen	*N*	pCR[a] (%)	
				Control	Platinum
von Minckwitz et al., GeparSixto [71]	Randomized phase II	Paclitaxel 80 mg/m^2 + NPLD 20 mg/m^2 weekly + Bev 15 mg/kg every 3 wk ± carboplatin AUC; 1.5–2 times weekly × 18 wk	315	42.7	53.2
Sikov et al., Alliance 40603 [70]	Randomized phase II (2 × 2 factorial design)	Weekly paclitaxel 80 mg/m^2 × 12 ± carboplatin AUC 6; every 3 wk × 4→AC every 2 wk × 4 ± Bev 10 mg/kg every 2 wk × 9	433	41	54
Alba et al., GEICAM/2006-03 [130]	Randomized phase II	EC × 4 cycles → docetaxel 75 mg/m^2 ± carboplatin AUC 6; every 3 wk × 4 cycles	94	30	30
Tamura et al., NCC-Japan [72]	Randomized phase II	Weekly paclitaxel 80 mg/m^2 × 12 ± carboplatin AUC 5; every 3 wk × 4→CEF every 3 wk × 4	75	26	62
Rugo et al., ISPY-2 [131]	Randomized phase II	Weekly paclitaxel 80 mg/m^2 × 12 ± carboplatin AUC 6 every 3 wk × 4 and veliparib 50 mg b.i.d. p.o.→AC; every 2 wk × 4 cycles	71	26 (est.)	52 (est.)
Gluz et al., German Women's Health Care Study Group [73]	Randomized phase II	Weekly nab-paclitaxel 125 mg/m^2 + carboplatin AUC 2 or gemcitabine 1,000 mg/m^2 on day 1, 8 every 3 wk × 4 cycles	336	28	45
Wang et al., Chinese Academy of Med Sciences [75]	Randomized phase II	Carboplatin AUC 5 + paclitaxel 175 mg/m^2 every 3 wk × 4–6 vs. epirubicin 75 mg/m^2 + paclitaxel 175 mg/m^2; 3 wk × 4–6 cycles	92	16	39
Sharma et al., PROGECT [76]	Observational	Carboplatin AUC 6 + docetaxel 75 mg/m^2 every 3 wk × 4–6 cycles vs. AC × 4 cycles→taxane × 4 cycles	92	42	65
Kern et al. [74]	Retrospective	Carboplatin AUC 6 + docetaxel 75 mg/m^2 every 3 wk × 6 cycles	30	—	50
Telli et al., PrECOG 0105 [68]	Single arm	Carboplatin AUC 2 + gemcitabine 1,000 mg/m^2 days 1 and 8 + iniparib 5.6 mg/kg on days 1, 4, 8, 11 every 3 wk × 4–6 cycles	80	—	36
Silver et al. [61]	Single arm	Cisplatin 75 mg/m^2 every 3 wk × 4 cycles	28	—	22

[a]pCR defined as ypT0/isN0.

Abbreviations: AC, Adriamycin (doxorubicin) and cyclophosphamide; AUC, area under the curve; Bev, bevacizumab; CEF, cyclophosphamide, epirubicin, and 5-flourouracil; EC, epirubicin and cyclophosphamide; est., estimated; NPLD, nonpegylated liposomal doxorubicin; pCR, pathological complete response.

not new to the treatment of breast cancer. In the 1980s, cisplatin was evaluated in advanced breast cancer in two phase II studies and demonstrated significant single-agent frontline activity, with response rates in the range of 50%–54% [59, 60]. Because of its toxicity, cisplatin was subsequently abandoned and replaced by other active agents with more favorable toxicity profiles (taxanes, fluoropyridines). However, more recently there has been renewed interest in exploring platinum agents in TNBC and *BRCA* mutation-associated breast cancers.

Repair of platinum-induced interstrand crosslinks invokes *BRCA1*-mediated homologous recombination (HR), and there is abundant clinical and in vitro evidence that *BRCA1*-deficient cells are hypersensitive to platinum agents [61–63]. Observational, small neoadjuvant, and metastatic studies have demonstrated that *BRCA* mutation-associated breast cancers are sensitive to platinum agents [61, 63–67]. In a phase II study, single-agent cisplatin yielded an impressive 80% response rate in *BRCA1* mutation-associated metastatic breast cancer [63]. A recent randomized phase III trial demonstrated that in unselected metastatic TNBC, carboplatin and docetaxel were equal in efficacy as first-line treatment [65]. However, in *BRCA* mutation-associated TNBC, carboplatin yielded a superior response rate and progression-free survival compared with docetaxel.

Growing evidence suggests that platinum compounds may be active in a significantly larger number of TNBC patients beyond germline *BRCA* mutation carriers [68, 69]. Recent studies have focused on the role of platinum agents when used as a component of neoadjuvant therapy (Table 2). Three randomized studies have demonstrated that the addition of neoadjuvant carboplatin to anthracycline/taxane-based chemotherapy improves pCR in patients with stage I–III TNBC (pCR improved from 41% to 54% with addition of carboplatin) [70–72]. Other investigators studying anthracycline-free platinum regimens have reported encouraging pCR rates ranging from 36% to 65% [68, 73–76].

The improvement in pCR attained with the addition of carboplatin to anthracycline/taxane chemotherapy comes at the cost of increase in toxicity. In both Cancer and Leukemia Group B (CALGB) 40603 and GeparSixto, dose reductions or omissions were needed in 40%–50% of patients. Furthermore, the long-term

outcomes from the addition of platinum in the neoadjuvant setting are not yet clear. Event-free survival (EFS) and overall survival (OS) data from CALGB 40603 and GeparSixto clinical trials were recently presented [77, 78]. In GeparSixto, 3-year EFS improved 44% with the addition of concurrent carboplatin to an anthracycline + taxane + bevacizumab chemotherapy backbone. On the other hand, in CALGB 40603 the addition of sequential carboplatin did improve pCR rate, but 3-year EFS or OS did not significantly improve. In both trials, the positive effect of pCR on long-term outcomes (EFS and OS) was confirmed and the hazard ratios for 3-year EFS favored carboplatin. However, neither of these two trials was powered sufficiently for EFS and OS endpoints and thus cannot be considered definitive studies to answer the question of clinical utility of platinum agents for early-stage TNBC.

We need adequately powered studies to determine the long-term benefits of platinum agents in early-stage TNBC. The optimal dose, sequence, and chemotherapy backbone for efficacious incorporation of platinum into treatment of early-stage TNBC are also not yet known. Several ongoing randomized phase III trials are evaluating various schedules and combinations of platinum in early-stage TNBC. NRG-BR003 (NCT02488967), Chinese TPPC (NCT02455141), and the Korean PEARLY (NCT02441933) studies are all evaluating efficacy of sequential adjuvant platinum (platinum vs. placebo) when added to Adriamycin (doxorubicin) and cyclophosphamide (AC)/epirubicin and cyclophosphamide followed by taxane chemotherapy backbone. Eastern Cooperative Oncology Group–American College of Radiology Imaging Network 1131 (NCT02445391) will study adjuvant platinum in TNBC patients who have basal-like residual disease after neoadjuvant anthracycline/taxane chemotherapy. Neoadjuvant Brightness (NCT02032277) is assessing addition of carboplatin or carboplatin + PARPi (veliparib) to AC, followed by paclitaxel in TNBC patients stratified by germline *BRCA* status. GeparOcto (NCT02125344) will evaluate addition of weekly carboplatin, bevacizumab, or both to neoadjuvant anthracycline/taxane backbone. Another phase II neoadjuvant study is comparing AC followed by paclitaxel plus carboplatin to anthracycline-free docetaxel plus carboplatin regimen (NCT02413320).

While we await the completion and outcomes from these randomized studies, oncologists are still faced with decisions about the utility of platinum agents for TNBC in day-to-day practice. The ideal approach for patients and physicians is to seek participation in one of the many ongoing platinum trials. If a suitable trial is not available, the decision for incorporation of platinum into neoadjuvant treatment of a patient with TNBC should be individualized. Although long-term outcome data are not clear, the individual patient benefit from attainment of pCR may still justify use of neoadjuvant platinum in select patients. Most important, given the molecular heterogeneity of TNBC, it is very likely that platinum agents will benefit only a subgroup of patients with TNBC. Ongoing and future translational studies (described in the following section) are focusing on identifying TNBC patients most likely to benefit from platinum therapy.

Homologous Recombination Defects and DNA-Damaging Therapy

HR is a DNA repair mechanism responsible for repair of double-strand DNA breaks. *BRCA1/2* and other Fanconi anemia pathway genes (*RAD51D, NBN, ATM*) are key components of the HR-mediated DNA repair. Germline *BRCA1/2* mutations are the prototype molecular alterations that confer homologous recombination deficiency and sensitivity to DNA damaging therapy.

Inherited and acquired defects in homologous recombination, a phenotype called, as mentioned earlier, "BRCAness," may lead to therapeutic exploitation in breast cancer. To this end, development and clinical evaluation of platforms to identify markers of BRCAness have been a subject of intense investigation, especially in TNBC, a subtype thought to be enriched for BRCAness [58, 79–83]. Approximately 10%–20% of TNBCs harbor detectable germline *BRCA1/2* mutations [12, 22, 24, 61, 84]. However, DNA repair may be altered through other mechanisms, such as somatic or germline mutation in other genes, DNA methylation, or attenuated mRNA expression. It is estimated that if these factors beyond germline *BRCA* mutations are comprehensively evaluated, 50%–60% of TNBC will demonstrate HR deficiency or BRCAness, making it an attractive selection and response biomarker for DNA-damaging therapy, such as platinum compounds and PARPi (Fig. 2) [58, 68, 80, 81, 85]. It is speculated that DNA-damaging therapy may be most active in tumors with germline *BRCA* mutations and in *BRCA* wild-type tumors that harbor the BRCAness phenotype.

Germline *BRCA* mutation status is beginning to emerge as an important predictive marker of response to platinum agents in TNBC. The randomized TNT study demonstrated that in the metastatic setting, patients with germline *BRCA1* or *BRCA2* mutation experienced significantly greater response and progression-free survival with carboplatin compared with docetaxel [65]. A smaller nonrandomized study also demonstrated that rate of response to platinum (first-/second-line treatment) in metastatic TNBC was significantly higher in germline *BRCA1/2* carriers than in noncarriers [69]. In the GeparSixto neoadjuvant study, TNBC patients with germline *BRCA1/2* or *Rad 50/51c* (another gene involved in DNA repair) mutations had higher overall pCR rates and larger increments in the pCR rate with the addition of carboplatin [86]. The significance of germline *BRCA* mutation status to predict selective response to platinum agents is being prospectively evaluated in an ongoing randomized neoadjuvant trial (INFORM) that is comparing four cycles of cisplatin with four cycles of doxorubicin/cyclophosphamide in patients with germline *BRCA* mutations (NCT01670500).

> Interestingly, in the GeparSixto study, a strongly positive family history of breast and/or ovarian cancer, even in the absence of an identifiable mutation, was also associated with a higher incremental increase in pCR rate with the addition of carboplatin.

Interestingly, in the GeparSixto study, a strongly positive family history of breast and/or ovarian cancer, even in the absence of an identifiable mutation, was also associated with a higher incremental increase in pCR rate with the addition of carboplatin. This latter group accounted for 30% of patients enrolled in the trial. This observation supports the notion that other multigenic alterations (beyond germline *BRCA* mutations) affecting HR-DNA repair pathway are present in a substantial proportion of TNBC patients.

Currently, a standard platform for detecting HR deficiency or BRCAness beyond germline *BRCA* mutations has not reached routine clinical application. However, several promising assays are emerging and have been retrospectively evaluated. The homologous recombination deficiency (HRD) assay developed by Myriad Genetics Inc. (Salt Lake City, UT, https://www.myriad.com) evaluates tumor genome loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions, which are all indirect measures of tumor genomic instability. High HRD scores are highly correlated with defects in *BRCA1/2* and are associated with sensitivity to neoadjuvant platinum-based chemotherapy in TNBC [68, 83]. An array comparative genomic hybridization (aCGH) signature resembling *BRCA1*- and *BRCA2*-mutant breast cancers has also been reported to predict response to high-dose platinum therapy in a retrospective study [87, 88]. In addition to genomic instability, tumors with BRCAness may also exhibit characteristic gene expression patterns. A 44-gene DNA-damage response deficiency signature, which was developed in cohorts enriched for germline *BRCA1/2* and Fanconi anemia mutations, predicted favorable response to chemotherapy with 5-flourouracil, epirubicin, and cyclophosphamide in patients with triple-negative breast cancer [81]. All of the assays described here are compatible with formalin-fixed, paraffin-embedded tissues, making them suitable for evaluation in prospective studies. An ongoing neoadjuvant trial (TBCRC 030, NCT01982448) is randomly assigning patients to cisplatin or weekly paclitaxel to assess the ability of the HRD assay to predict pathological complete response with platinum versus taxane in TNBC patients without a *BRCA* mutation. Another ongoing study is using the aCGH *BRCA*-like assay to determine whether neoadjuvant intensified alkylating chemotherapy improves the response rates in tumors with HRD (NCT01057069). An upcoming randomized phase II trial (S1416) will use multiple BRCAness markers to predict benefit from addition of PARPi to platinum chemotherapy in metastatic TNBC.

Using functional measures of HR pathway deficiency, rather than relying on documented changes in specific genes, should identify more patients who might benefit from DNA-damaging therapies. If appropriately validated, HRD assays could have a tremendous effect on treatment of TNBC by identifying patients most likely to benefit from DNA-damaging agents, such as platinum salts and/or PARPi.

Identification and Development of Novel Targeted Agents: Promise on the Horizon

Immune Checkpoint Inhibitors

As our understanding of the relationship between breast cancer biology and immunity is expanding, it is allowing for new advances in immunotherapy for breast cancer patients. Cancers use multiple mechanisms to evade the immune response. PD-1 is an antigen expressed on activated T cells, pro-B cells, natural killer cells, dendritic cells, and monocytes. PD-1 and its ligands, PD-L1 and PD-L2, play a major role in maintenance of T-cell tolerance [89, 90]. PD-1 and PD-L1 are aberrantly expressed in basal-like breast cancer [91, 92]. Their expression parallels that of the TILs, suggesting negative feedback activation as part of the immune reaction. Preclinical data support the concept that blockade of immune checkpoints may be an effective treatment strategy for TNBC. Supporting these preclinical findings, there is now emerging evidence of the clinical efficacy of agents targeting PD-1/PD-L1 in TNBC.

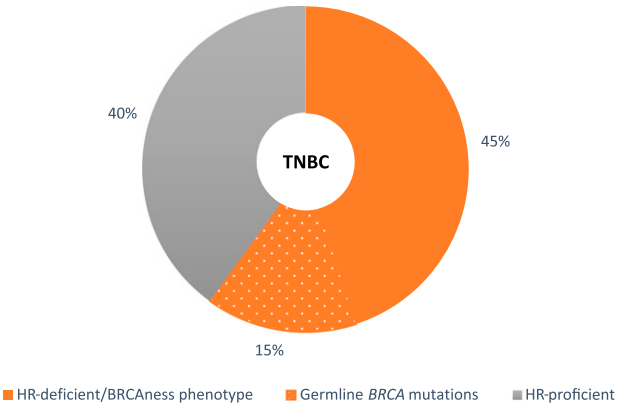

Figure 2. HR deficiency in triple-negative breast cancer.
Abbreviations: HR, homologous recombination; TNBC, triple-negative breast cancer.

Pembrolizumab (MK-3475), a monoclonal antibody specific for PD-1, was evaluated in a phase I study of 32 TNBC patients. In this heavily pretreated population, pembrolizumab led to an overall response rate of 18.5%, including one complete response and four partial responses. Another phase I clinical trial evaluated atezolizumab (MPDL3280A), an anti-PD-L1 monoclonal antibody, in nine metastatic TNBC patients and demonstrated a similar overall response rate of 33%, including one complete response and two partial responses [93, 94]. On the basis of these encouraging phase I data, both of these antibodies are now being evaluated in larger studies. A randomized phase III trial will assess nab-paclitaxel with or without atezolizumab (MPDL3280A) in patients with previously untreated metastatic TNBC (IMpassion130, NCT02425891). A phase III study will evaluate the addition of neoadjuvant atezolizumab (MPDL3280A) to carboplatin and nab-paclitaxel in patients with locally advanced TNBC (NCT02620280). An upcoming randomized phase III trial (Southwestern Oncology Group [SWOG] 1418) will assess efficacy of adjuvant pembrolizumab compared with placebo in TNBC patients who have residual disease after neoadjuvant chemotherapy. Another phase II study is assessing pembrolizumab plus doxorubicin in patients with metastatic TNBC (NCT02648477). Nivolumab (another PD-1 antibody) is being studied in combination with various chemotherapy drugs and radiation in advanced TNBC in the TONIC trial (NCT02499367). Studies with these promising immune checkpoint inhibitors are still at their beginning in TNBC, with many interesting clinical trials ongoing. Results of these ongoing trials will direct the future application of immune therapy in TNBC.

PARPi

PARP enzymes recognize DNA damage and facilitate DNA repair to maintain genomic stability. Preclinical studies demonstrate that PARP inhibition in the presence of *BRCA* deficiency leads to synthetic lethality. PARPi have shown preclinical and clinical activity in targeting tumors with pre-existing DNA repair defects, in particular *BRCA1*- and *BRCA2*-deficient advanced breast and ovarian tumors [95–102]. The FDA has recently approved

monotherapy with olaparib, a PARPi, as a first-in-class drug to treat germline *BRCA* mutation-associated advanced refractory ovarian cancers (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427554.htm). Several ongoing studies are assessing the activity of PARPi alone or in combination with chemotherapy for germline *BRCA*-associated metastatic and early-stage breast cancers. A randomized phase III (Olympia AD NCT02032823) study is evaluating adjuvant olaparib in patients with germline *BRCA*-associated TNBC or high-risk hormone-positive breast cancer. An ongoing phase II/III trial is comparing carboplatin and paclitaxel with or without ABT-888 (veliparib) in patients with *BRCA* mutation-associated advanced breast cancer (NCT01506609). Two phase III randomized trials (OlympiaAD and EMBRACA) and are comparing chemotherapy of physician's choice with the single-agent PARPi olaparib and talazoparib (BMN-673), respectively, in *BRCA* mutation-associated advanced breast cancer (NCT01945775, NCT02000622).

Because a substantial proportion of TNBCs are thought to harbor DNA repair defects, it might be possible to extend the observation of PARPi sensitivity of germline *BRCA*-associated tumors to *BRCA* wild-type TNBCs that harbor a BRCAness phenotype. Accordingly, PARPi are being explored in the general population of patients with TNBC. As monotherapy, PARPi have demonstrated limited activity in breast cancer not associated with *BRCA* mutation [101, 103]. The efficacy of PARPi in *BRCA* wild-type TNBC is likely to be observed only in tumors with a BRCAness phenotype and not in all *BRCA* wild-type TNBC. Furthermore, *BRCA* wild-type TNBC with a BRCAness phenotype may harbor only partial homologous recombination defects, and PARPi monotherapy may lead to "synthetic sickness" rather than synthetic lethality, necessitating the presence of robust DNA-damaging chemotherapy with PARP inhibition to achieve cell death. Thus, several studies are also looking at combination of PARPi and platinum-based DNA-damaging chemotherapy in TNBC. The Brightness study (NCT02032277) will assess the activity of veliparib in combination with carboplatin in neoadjuvant setting in both *BRCA*-associated and wild-type TNBC. SWOG 1416 will use a combination of PARPi and cisplatin to test for PARPi activity in both *BRCA*-associated and BRCAness phenotype metastatic TNBC.

PI3K/AKT/mTOR Pathway Inhibitors

Inhibition of PI3K and the downstream components AKT and mTOR are recognized as promising targets for treatment of breast cancer. Activating mutations in *PIK3CA* are noted in 9% of primary basal-like breast cancers [22]. However, inferred PI3K pathway activation, through loss of PTEN and inositol polyphosphate 4-phosphatase type II (INPP4B), frequently occur in basal-like breast cancers [22, 104–106].

This high frequency (approximately 50%) of PI3K pathway alteration in TNBC makes this pathway a promising target for therapeutics, and inhibitors of PI3K, AKT, and/or mTOR are in clinical development. Two randomized phase II studies are evaluating AKT inhibitors (AZD5363, GDC-0068) in combination with paclitaxel as front-line treatment for metastatic triple-negative breast cancer (PAKT/NCT02423603, NCT02162719). Another randomized phase II study will assess the efficacy of preoperative GDC-0068 in combination with paclitaxel in stage I–III TNBC (NCT02301988).

A phase II, single-arm study of BYL719 (a selective PI3K α inhibitor) monotherapy in the second-line setting for advanced metastatic breast cancer (NCT02506556) is under way. Another ongoing phase I/II study is evaluating combination of BYL719 with nab-paclitaxel in HER2-negative metastatic breast cancer (NCT02379247).

PI3K blockade promotes HR deficiency by downregulating *BRCA1/2* and thus sensitizing *BRCA*-proficient tumors to PARP inhibition [107, 108]. To capitalize on these findings, a phase I study of the pan-PI3K inhibitor BKM120 in combination with the PARPi olaparib in patients with metastatic TNBC is ongoing (NCT01623349).

Heat Shock Protein 90 and Histone Deacetylase Inhibitors

Histone deacetylase (HDAC) modulates the transcription rate and the protein levels of several components of the DNA-damage response cascade [109–114]. Heat-shock protein 90 (HSP90) chaperones "client" proteins into their native conformations, regulating multiple aspects of protein function. Multiple components of the HR and nonhomologous end joining DNA repair machinery (e.g., *CHK1*, *BRCA1*, *BRCA2*, *RAD51*, *FANCA*) are clients of HSP90 [115–117]. HDAC inhibitors induce hyperacetylation of HSP90 and dissociate client proteins, such as BRCA1, from the chaperone. In vitro studies have also demonstrated that HDAC inhibitor vorinostat and HSP90 inhibitor AUY922 were ranked near the top for inducing the HRD-like gene expression profiles in TNBC cell lines [118]. Thus, treatment with HDAC inhibitors can increase the therapeutic efficacy of DNA-damaging agents, such as platinum compounds in TNBC. Indeed, in vitro studies show that cotreatment with a pan-HDAC inhibitor and cisplatin synergistically induced apoptosis of both *BRCA1*-mutant and *BRCA1*-proficient cell lines and HDAC inhibitor treatment induces synergistic lethality with PARPi and cisplatin in triple-negative breast cancer cell lines [119–121].

Clinical studies of HSP90 and HDAC inhibitors are in early stages right now. An ongoing phase I study is assessing safety and dosing of an HSP90 inhibitor (AT13387) and paclitaxel combination in advanced TNBC (NCT02474173). An upcoming preoperative trial is studying combination of ganetespib (HSP90 inhibitor) with paclitaxel (NCT02637375). On the basis of preclinical synergy of HSP90 and PARPi, an upcoming phase I study will assess combination of PARPi (BMN 673) and HSP90 inhibitor (AT13387) in advanced solid tumors, including TNBC (NCT 02627430). A phase II trial investigating combination treatment of entinostat (HDAC inhibitor) and the DNA methyltransferase inhibitor azacitidine in patients with chemotherapy-resistant advanced TNBC is also under way (NCT01349959). An ongoing phase I/II study is evaluating combination of cisplatin with romidepsin (class I HDAC inhibitor) in metastatic TNCB or *BRCA* mutation-associated HER2-negative metastatic breast cancer (NCT02393794).

Androgen-Targeted Therapy

On immunohistochemistry, approximately 10%–15% of TNBCs express AR [122–124]. On gene expression analysis, 12% of TNBCs (LAR or highly enriched for AR and classified as the LAR

Table 3. Selected active clinical trials of novel agents in treatment of triple negative breast cancer.

Class/trial details	Phase	NCTN number
Immune checkpoint inhibitors		
Nab-paclitaxel ± atezolizumab (MPDL3280A) in previously untreated TNBC (IMpassion130)	III	NCT02425891
Neoadjuvant carboplatin and nab-paclitaxel ± atezolizumab (MPDL3280A) in locally advanced TNBC	III	NCT02620280
Study of single-agent pembrolizumab vs. single-agent chemotherapy for metastatic TNBC (MK-3475-119/KEYNOTE-119)	III	NCT02555657
Adjuvant pembrolizumab in TNBC patients with residual disease after neoadjuvant chemotherapy.	III	—
Pembrolizumab + doxorubicin in metastatic TNBC	II	NCT02648477
Nivolumab in combination with various chemotherapy drugs in advanced TNBC (TONIC trial)	II	NCT02499367
PARPi		
Adjuvant olaparib in patients with germline *BRCA*-associated TNBC or high-risk hormone-positive breast cancer (Olympia AD)	III	NCT02032823
Carboplatin and paclitaxel with or without veliparib (ABT-888) in patients with *BRCA* mutation-associated advanced breast cancer	II	NCT01506609
Talazoparib (BMN 673) monotherapy vs. physicians' choice chemotherapy in metastatic breast cancer patients with germline *BRCA1*/2 mutations (EMBRACA study)	III	NCT01945775
Olaparib monotherapy vs. physicians' choice chemotherapy in metastatic breast cancer patients with germline *BRCA1/2* mutations. (OlympiAD)	III	NCT02000622
Addition of ABT-888 + carboplatin vs. addition of carboplatin to standard neoadjuvant chemotherapy vs. standard neoadjuvant chemotherapy in both *BRCA*-associated and wild-type TNBC (Brightness study)	III	NCT02032277
Cisplatin ± ABT-888 in in both *BRCA*-associated and wild-type metastatic TNBC (SWOG 1416).	II	–
Talazoparib (BMN 673) monotherapy in *BRCA1/2* wild-type advanced TNBC with homologous recombination deficiency as assessed by the HRD assay or germline/somatic mutation in HR pathway genes	II	NCT02401347
HSP90 and HDAC inhibitors		
AT13387 (HSP90 inhibitor) + paclitaxel in advanced TNBC	I	NCT02474173
Ganetespib (HSP90 inhibitor) + paclitaxel in advanced TNBC	I	NCT02637375
AT13387 (HSP90 inhibitor) + BMN 673 (PARP inhibitor) in advanced solid tumors, including TNBC	I	NCT 02627430
Entinostat (HDAC inhibitor) + azacitidine in advanced breast cancer	II	NCT01349959
Romidepsin (HDAC inhibitor) + cisplatin in metastatic TNBC or *BRCA* mutation-associated HER2-negative MBC	I/II	NCT02393794
PI3K/AKT/mTOR pathway inhibitors		
Paclitaxel ± ipatasertib (GDC-0068) in first-line metastatic TNBC	II	NCT02162719
Paclitaxel ± AZD5363 in first-line metastatic TNBC (PAKT)	II	NCT02423603
Preoperative GDC-0068 in combination with paclitaxel in women with stage I–III TNBC	II	NCT02301988
BYL719 monotherapy, in advanced metastatic breast cancer (second-line setting)	II	NCT02506556
BYL719 with nab-paclitaxel in HER2-negative metastatic breast cancer	I/II	NCT02379247
BKM120 in combination with the PARPi olaparib in metastatic TNBC	I	NCT01623349
Androgen targeted therapy		
Taselisib (GDC-0032) and enzalutamide in patients with AR-positive (≥10%) metastatic TNBC	I/II	NCT02457910
Platinum agents		
Adjuvant AC followed by paclitaxel ± carboplatin in triple-negative breast cancer (NRG-BR003)	III	NCT02488967
Adjuvant treatment of EC followed by weekly paclitaxel or weekly paclitaxel plus carboplatin (TPPC)	III	NCT02455141
Anthracyclines followed by taxane to anthracyclines followed by taxane + carboplatin as (neo) adjuvant therapy (PEARLY)	III	NCT02441933
ECOG-ACRIN 1131 adjuvant platinum vs. placebo in TNBC patients who have basal-like residual disease after neoadjuvant anthracycline/taxane chemotherapy	III	NCT02445391
Addition of neoadjuvant carboplatin or carboplatin + PARPi (veliparib) to paclitaxel followed by AC in TNBC patients stratified by germline *BRCA* status (Brightness study)	III	NCT02032277
Addition of weekly carboplatin, bevacizumab, or both to neoadjuvant anthracycline/taxane backbone	III	NCT02125344
Comparison of neoadjuvant paclitaxel + carboplatin followed by AC and docetaxel + carboplatin	II	NCT02413320
4 cycles of neoadjuvant cisplatin vs. 4 cycles of AC in patients with germline *BRCA* mutations (INFORM)	II	NCT01670500

(continued)

Table 3. (continued)

Class/trial details	Phase	NCTN number
Comparison between cisplatin and weekly paclitaxel to assess the ability of the HRD assay to predict pathological complete response in TNBC patients without a *BRCA* mutation (TBCRC 030)	II	NCT01982448
Neoadjuvant intensified alkylating chemotherapy in tumors with homologous recombination deficiency as assessed by the aCGH *BRCA*-like assay	II/III	NCT01057069
CXCR1/2 (stem cell pathway)		
Double-blind study of paclitaxel in combination with reparixin or placebo for metastatic TNBC (FRIDA)	II	NCT02370238
Cyclin-dependent kinases		
Dinaciclib and epirubicin hydrochloride in treating patients with metastatic TNBC	I/II	NCT01624441
c-Met		
Study evaluating the safety and efficacy of onartuzumab (MetMAb) ± bevacizumab in combination with paclitaxel in patients with metastatic TNBC	II	NCT01186991
Aurora kinase inhibitor		
ENMD-2076 (aurora + angiogenic kinase inhibitor) in previously treated locally advanced/ metastatic TNBC	II	NCT01639248
Death receptors		
Nab-paclitaxel ± tigatuzumab in metastatic TNBC	II	NCT01307891
CSF1 inhibitor		
PLX 3397 and eribulin in patients with metastatic breast cancer with phase II limited to TNBC	Ib/II	NCT01596751
Antibody-drug conjugate		
Study of glembatumumab vedotin (CDX-011) in patients with metastatic, *gpNMB*-overexpressing TNBC (METRIC)	II	NCT01997333

Abbreviations: AC, Adriamycin (doxorubicin) and cyclophosphamide; AR, androgen receptor; CSF-1, colony stimulating factor 1; ECOG-ACRIN, Eastern Cooperative Oncology Group–American College of Radiology Imaging Network; HDAC, histone deacetylase; HER2, human epidermal growth receptor 2; HRD, homologous recombination deficiency; HSP90, heat shock protein 90; mTOR: mammalian target of rapamycin; NCTN, National Clinical Trials Network; PARPi, poly(ADP-ribose) polymerase inhibitors; PIK, phosphatidylinositol-3-kinase; SWOG, Southwestern Oncology Group; TNBC, triple-negative breast cancer.

subtype) [14]. AR IHC is often used as a surrogate for the LAR subtype. Compared with other TNBC subtypes, the AR+ subtype appears to be relatively chemoresistant but displays better long-term prognosis. Primary tumor AR analysis has demonstrated that AR+ TNBC patients exhibit lower pCR rates with anthracycline/taxane chemotherapy, however, and have better disease-free survival and overall survival compared with AR− TNBC patients [125]. Similarly, a retrospective neoadjuvant analysis also demonstrated that the LAR molecular subtype is associated with lower pCR rates compared with other TNBC subtypes [126]. Preclinical data demonstrates that pharmacological inhibition of AR by bicalutamide greatly decreased cell viability and tumor growth [14, 16]. The TBCRC001 phase II proof-of-concept trial of bicalutamide (oral AR inhibitor) in 26 patients with metastatic AR+ (IHC ≥ 10%) TNBC demonstrated a clinical benefit rate of 19% at 24 weeks [127]. A recent study reported encouraging activity of a next-generation, novel androgen-targeted drug, enzalutamide, in AR+ TNBC. This trial enrolled 118 women with AR+ TNBC. More than 50% of the patients received enzalutamide as a first- or second-line therapy for their metastatic disease. Of the 75 patients who could be evaluated for response, the response rate and clinical benefit rate were 8% and 35%, respectively [128]. In addition to AR IHC, this trial also reported on the positive association of molecular assays (PREDICT AR) for identification of TNBC patients most likely to benefit from this approach [129]. Together, these emerging data provide a strong rationale for prospectively identifying AR+ TNBC patients and aligning these patients to clinical trials of androgen-targeted therapies.

In addition to AR dependency, LAR TNBC cell lines commonly harbor activating mutation in the kinase domain of PIK3CA and display sensitivity to PIK3CA inhibitors [14]. Thus, the antiandrogen and PI3K inhibitor combination is also being explored in a phase I/II study of taselisib (GDC-0032) and enzalutamide in patients with AR+ (≥10%) metastatic TNBC (NCT02457910)

Other Agents

In addition to the agents described here, other targeted agents are also under development in TNBC (Table 3). Reparixin (inhibitor of interleukin-8 activation of CXCR1/CXCR2 chemokine receptors) is being tested in combination with paclitaxel in a randomized phase II study. Antibody drug conjugate CDX-011 (glembatumumab vedotin) is being compared with capecitabine in a randomized phase II study in patients with glycoprotein NMB-overexpressing, metastatic TNBC (the METRIC study). Several other agents are also being investigated in early-phase studies (Table 3).

Conclusion

TNBC is a small but heterogeneous subtype of breast cancer. Because of the lack of approved targeted therapy, chemotherapy remains the mainstay of treatment for early and advanced disease. Modern technology platforms have contributed immensely to our current understanding of the molecular diversity of this subtype. These molecular advances have enabled us

to start ascertaining promising therapeutic targets in TNBC. Numerous experimental approaches are under way, and several encouraging drug classes, such as immune checkpoint inhibitors, PARPi, platinum agents, and PI3K inhibitors, are being investigated in clinical trials. Current research efforts are focused on optimizing the traditional drugs by applying them to patients and tumors that will benefit the most, and by studying newer drugs in biologically selected patient subgroups. New-generation TNBC trials are beginning to embed the concept of heterogeneity, and investigations in smaller molecularly identified subgroups of TNBC are emerging. TNBC is a complex disease, and it is likely that several different targeted approaches will be needed to make meaningful strides in improving the outcomes.

Disclosures

Priyanka Sharma: Novartis, Celgene (RF).

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