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REVIEW

Progress in systemic therapy for triple-negative breast cancer

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Abstract **Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer with a heterogeneous genetic profile. Chemotherapy exhibits substantial activity in a small subset of these patients. Drug resistance is inevitable. Major progress has been made in the genetic analysis of TNBC to identify novel targets and increase the precision of therapeutic intervention. Such progress has translated into major advances in treatment strategies, including modified chemotherapy approaches, immune checkpoint inhibitors, and targeted therapeutic drugs. All of these strategies have been evaluated in clinical trials. Nevertheless, patient selection remains a considerable challenge in clinical practice.**

Keywords triple-negative breast cancer; immunotherapy; targeted therapy

Introduction

Breast cancer is the most commonly diagnosed malignant tumor and is the leading cause of cancer deaths among women worldwide [1]. Triple-negative breast cancer (TNBC), which is conventionally defined by the absence of estrogen, progesterone, and human epidermal growth factor 2 (HER2) receptors, accounts for approximately 12% to 17% of all breast cancers [2]. Patients with TNBC have a relatively aggressive clinical course, with an earlier age of onset, more visceral metastases, and faster distant recurrence compared with patients with other breast cancer subtypes [3,4]. Treatments for TNBC have lagged behind those for other subtypes because they have been largely limited to chemotherapy, providing poor prognosis with a median survival of only 13 months [4–6]. Therefore, developing optimal therapeutic strategies for patients is crucial for alleviating the disease burden due to TNBC.

TNBC encompasses heterogeneous molecular profiles [2,7,8]. Various potentially druggable targets have been identified recently, ultimately heralding a new therapeutic horizon for TNBC beyond conventional chemotherapy [4,7]. Here, we summarize upcoming systemic treatment options for TNBC, including chemotherapy, immunotherapy, and targeted therapy (Fig. 1).

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Chemotherapeutic drugs

Despite being associated with low response rates and short response duration, chemotherapy remains the essential systemic treatment for TNBC. Given that deficient DNA damage repair represents a genetic feature in some patients, the evaluation of DNA-cross-linking platinum has been of interest in TNBC [9]. Two phase III randomized trials compared platinum with taxane as combined chemotherapies for metastatic TNBC. The first-line cisplatin plus gemcitabine regimen resulted in a median progression-free survival (PFS) of 7.73 months; such performance was significantly superior to that of paclitaxel plus gemcitabine in the control group (6.47 months, hazard ratio = 0.692) [10]. The Triple Negative Breast Cancer Trial (TNT) (NCT00532727) directly compared carboplatin with docetaxel as single agent chemotherapy in patients with metastatic TNBC, and a similar objective response rate (ORR; 31.4% versus 34.0%, $P = 0.66$) was observed [11]. The marginal benefits provided by these treatments warrant good alternatives in patients with metastatic TNBC.

In the setting of neoadjuvant treatment, chemotherapies are the only approved modality in most countries. In the GeparSixto trial, patients with TNBC exhibited significantly increased rates of pathological complete response (pCR) and improved disease-free survival (DFS) with the addition of carboplatin compared with the liposomal anthracycline and taxane control group [12,13]. In the

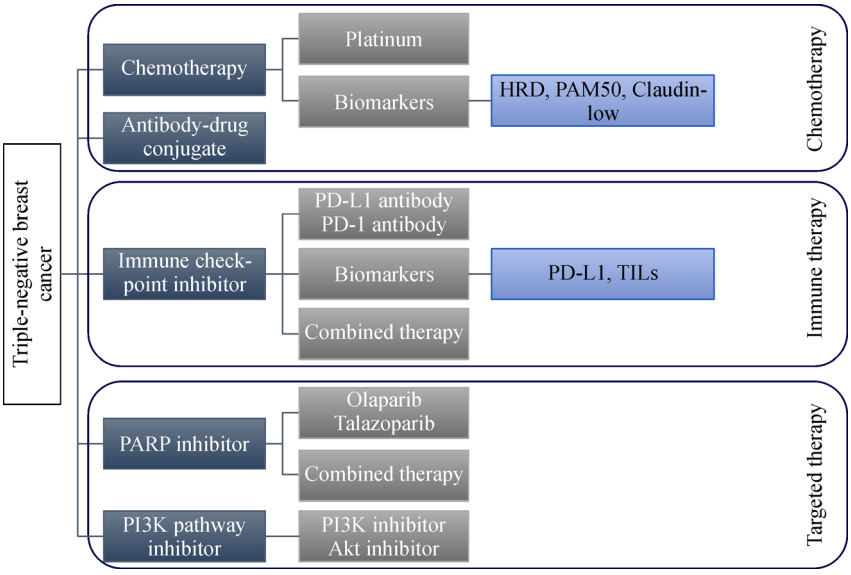

Fig. 1 Overview of recent improvements in systemic treatment for patients with metastatic TNBC. PARP, poly ADP (adenosine diphosphate)-ribose polymerase; HRD, homologous recombination deficiency; TILs, tumor-infiltrating lymphocytes.

Cancer and Leukemia Group B 40603 trial, the pCR rate was improved with the addition of neoadjuvant carboplatin. Although the study was unable to test for statistical significance, patients who achieved pCR presented better event-free survival (EFS) and overall survival (OS) than patients who did not [14,15]. Meanwhile, several randomized trials evaluated platinum plus taxane as neoadjuvant chemotherapy for TNBC, and encouraging efficacy was demonstrated [16]. The pCR rates were 38%–55%, with 3-year recurrence-free survival (RFS) of 79%–81% [17–19]. On the basis of these results, platinum-based chemotherapy can be considered an option for neoadjuvant treatment in patients with TNBC.

Alterations in a homologous recombination system are typical in some TNBCs, rendering cancers vulnerable to and indicative of DNA-damaging agents, such as platinum [20]. Cancers with homologous recombination deficiency (HRD) are usually associated with large regions of heterozygosity loss, telomeric allelic imbalance, and large-scale transition [20–22]. In neoadjuvant settings, increased pCR due to platinum treatment is observed in patients with HRD [23,24]. However, the predictive value of HRD status is less consistent in patients with metastatic TNBC. The results of the TNT trial suggested that a high HRD score does not predict increased benefit from carboplatin in the general population with metastatic TNBC [11]. In the Translational Breast Cancer Research Consortium 009 trial, HRD status was associated with responses to platinum [25]. The variation in genomic metrics used in each assay to calculate HRD scores may explain these differences.

Furthermore, several prognostic signatures that utilize specific panels of gene expression data, including the PAM50 and claudin-low signatures, have been evaluated in patients with TNBC who have received chemotherapy. The PAM50-based signature is a 50-gene subtype predictor developed using transcriptomic data, with significant prognostic and predictive information across all subtypes [26]. Gene expression analysis shows that 50% to 75% of TNBCs have a basal-like phenotype, and all the other intrinsic subtypes are present [27,28]. However, when focusing on triple-negative tumors, PAM50-defined subtypes fail to predict the benefit to individual chemotherapeutic agents. Significant associations between PAM50 signatures and pCR and DFS from chemotherapy were only identified within basal-like tumors but not within TNBC as a whole [29].

Claudin-low tumors, defined as the low gene expression of the tight junction proteins claudin and E-cadherin, have been characterized by the low to absent expression of luminal differentiation markers, and high enrichment for immune response genes and cancer stem cell-like features [30,31]. Compared with the basal-like subtypes, claudin-low tumors have similarly low luminal and HER2 gene expression, without highly expressing proliferation genes. The claudin-low subtype is present in 7% to 14% of all breast cancers and in 25% to 39% of TNBCs [30]. Using the MD Anderson Cancer Center breast cancer patient data set, researchers have observed several responses in claudin-low tumors after anthracycline/taxane-based chemotherapy despite an overall poor prognosis [30]. Compared with other breast cancer subtypes, claudin-low breast cancer cells are more likely to respond to anti-transforming growth factor (TGF)-β treatment by

increasing the number of tumor-initiating cells [32]. Furthermore, chemotherapy-resistant TNBCs exhibit increased markers of TGF-β signaling and cancer stem-like cells *in vivo* [33]. These findings support that the TGF-β inhibitor may represent a potential therapeutic strategy for overcoming chemotherapy resistance in TNBC, particularly in the claudin-low subtype.

Antibody–drug conjugates (ADCs)

ADCs offer a novel therapeutic approach for several solid tumors, including TNBC. Three ADCs, namely, Sacituzumab govitecan (IMMU-132), Glembatumumab vedotin (CDX-011), and Ladiratuzumab vedotin (SGN-LIV1A), exhibit promising antitumor activities in metastatic TNBC.

IMMU-132 comprises an active metabolite of irinotecan, SN-38, and a humanized anti Trop-2 monoclonal antibody, i.e., hRS7 IgG1κ [34]. Trop-2 is a transmembrane calcium signal transducer overexpressed in more than 85% of TNBCs [34,35]. SN-38 is coupled with anti-Trop-2 antibody through a cleavable CL2A linker, enabling its release to tumors intracellularly and in the tumor microenvironment [36]. IMMU-132 was evaluated in a phase II trial as a third-line or later line of therapy for patients with metastatic TNBC [35]. In 108 patients with heavily pretreated metastatic TNBC, IMMU-132 achieved an ORR of 34.3%, with a median duration of response of 9.1 months. Median PFS and OS were 5.5 and 13.0 months, respectively. Most common grade 3 or 4 adverse events were anemia and neutropenia. This drug is currently being investigated in a randomized phase III trial (NCT02574455) to compare with physician's choice of single-agent chemotherapy in patients with metastatic TNBC that has progressed after at least two regimens.

CDX-011 is an ADC in which monomethyl auristatin E (MMAE), a potent microtubule inhibitor, is coupled to a monoclonal antibody against gpNMB, a type I transmembrane protein that mediates cell adhesion, growth, and differentiation [37]. A phase II trial investigated the antitumor activity of CDX-011 via gpNMB expression in 124 patients with refractory advanced breast cancer, and preliminary evidence of activity was observed in patients with resistant metastatic TNBC [38]. In the unplanned subgroup analysis, ORR was 18% for patients with TNBC and 40% in gpNMB-overexpressing TNBC. However, in the randomized phase II METRIC study that compared CDX-011 with capecitabine in preselected patients with metastatic gpNMB-overexpressing TNBC, CDX-011 failed to demonstrate improvement in either PFS, ORR, or OS, leading to the discontinuation of the development of this ADC [39]. SGN-LIV1A is another ADC that conjugates MMAE with antibody targeting LIV-1, a transmembrane protein and downstream target of STAT3. In an ongoing phase I study, SGN-LIV1A monotherapy was generally well tolerated and associated with durable objective responses in 51 patients with heavily pretreated metastatic TNBC. ORR was 32%, with a clinical benefit rate of 36% [40]. Direct comparison between SGN-LIV1A and standard chemotherapy approach is warranted in future studies to confirm its efficacy.

Immune checkpoint inhibitors

Promising indication on the use of immune checkpoint inhibitors in TNBC has emerged over the last year, with the IMpassion130 study showing the most notable evidence (Table 1). In this trial, the combination of the anti-programmed death-ligand 1 (PD-L1) antibody, atezolizumab, with nab-paclitaxel as first-line treatment for patients with metastatic or locally advanced TNBC led to significantly longer PFS compared with the placebo plus nab-paclitaxel group (hazard ratio = 0.80, 95% confidence interval (CI) 0.69–0.92) [41]. Furthermore, a substantial OS benefit (25.0 versus 15.5 months) was demonstrated in the PD-L1-positive subgroup [41]. Another PD-L1 antibody, avelumab, only resulted in an ORR of 5.2% as monotherapy for metastatic TNBC [42]. With regard to PD-1 antibody, the phase II KEYNOTE-086 study demonstrated the strong antitumor activity of pembrolizumab monotherapy in patients with previously treated metastatic TNBC, achieving an ORR of 5.3%; furthermore, 62.5% of the respondents had a response duration of more than 12 months [43]. However, the phase III KEYNOTE-119 study, which compared pembrolizumab monotherapy with single-agent chemotherapy for the second- or third-line treatment of patients with metastatic TNBC, did not meet its primary endpoint in OS [44].

These results prompt the question of whether immune checkpoint inhibitors, particularly PD-1/PD-L1 antibodies, will truly transform the treatment paradigm in metastatic TNBC [50]. Although the preceding data are encouraging, several questions have arisen, including the most reliable biomarkers for predicting the efficacy of PD-1/PD-L1 inhibitors and which agent is the ideal partner for combined therapy.

In the IMpassion130 trial, PD-L1 positive was defined as the $> 1\%$ expression of PD-L1 on immune cells (ICs), which appears to select a subgroup of patients expected to achieve improved efficacy from PD-L1 antibody [41,51]. Patients with PD-L1 negative TNBC may not benefit from the combination of atezolizumab and nab-paclitaxel. VENTANA SP142 IHC assay was utilized to assess PD-L1 expression on tumor cells (TCs) and ICs in this IMpassion130 study. The positive rate of PD-L1 expression was 34% in ICs exclusively, 2% in TCs exclusively, and 7% in both types of cells [51]. Thus, the expression of PD-L1 on ICs via SP142 assay was selected as the criteria for interpreting patients with TNBC. However,

Table 1 Efficacy of immune checkpoint inhibitors in TNBC clinical trials

Drug	Patients	Intervention	Efficacy	Identifier
Pembrolizumab				
	27 Advanced PD-L1+ TNBC	Pembrolizumab 10 mg/kg Q2W	ORR, 18.5% mPFS, 1.9 months mOS, 11.2 months	NCT01848834 Ref [45]
	170 Advanced, pretreated TNBC, 61.8% PD-L1+	Pembrolizumab 200 mg Q3W	ORR, 5.3% mPFS, 2.0 months mOS, 9.0 months	NCT02447003 Ref [43]
	84 Advanced, untreated PD-L1+ TNBC	Pembrolizumab 200 mg Q3W	ORR, 21.4% mPFS, 2.1 months mOS, 18.0 months	NCT02447003 Ref [46]
	107 Advanced TNBC, ⩽2 prior lines of chemotherapy	Eribulin + pembrolizumab 200 mg Q3W	ORR, 25.6% mPFS, 4.1 months mOS, inestimable	NCT02513472 Ref [47]
Nivolumab				
	67 Advanced TNBC	Irradiation, CTX, cisplatin or doxorubicin, or no induction, followed by nivolumab 3 mg/kg Q2W	ORR, 20% (overall), 8% (irradiation), 8% (CTX), 23% (cisplatin), 35% (doxorubicin), 17% (no induction)	NCT02499367 Ref [48]
Atezolizumab				
	116 Advanced TNBC	Atezolizumab 15 or 20 mg/kg, or 1200 mg, Q3W	ORR, 10% mPFS, 1.4 months mOS, 8.9 months	NCT01375842 Ref [49]
	451 Advanced, untreated TNBC, 40.9% PD-L1+	Nab-paclitaxel ± atezolizumab 840 mg Q2W	ORR, 56.0% mPFS, 7.2 months mOS, 21.3 months	NCT02425891 Ref [41]
Avelumab				
	58 Advanced, pretreated TNBC	Avelumab 10 mg/kg Q2W	ORR, 5.2% mPFS, 5.9 months mOS, 9.2 months	NCT01772004 Ref [42]

ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; TNBC, triple-negative breast cancer; CTX, cyclophosphamide.

considerable gaps remain in our knowledge of this test, including heterogeneity in the technical aspect and the differential expression of PD-L1 on TCs and ICs. Various assays utilize diverse antibodies and target distinct cells to detect PD-L1 expression in different tumor types. The assessment of TCs' PD-L1 instead of ICs' using the PD-L1 IHC 22C3 pharmDx kit has also been approved as a predictive biomarker in several solid tumors, such as non-small-cell lung cancer [52]. The best method to assess PD-L1 expression in TNBC should be further harmonized.

Various potential biomarkers are currently being explored to predict the efficacy of immune checkpoint inhibitors. The preliminary results of the KEYNOTE-173 trial suggested that a high amount of tumor-infiltrating lymphocytes (TILs) before treatment is significantly associated with high pCR rates and ORR in primary TNBC treated with pembrolizumab combined neoadjuvant chemotherapy [53]. In the IMpassion130 study, $CD8^+$ TILs predicted the benefit of atezolizumab plus nab-paclitaxel in PFS and OS; by contrast, stroma TILs only predicted PFS improvement; furthermore, PD-L1 expression remains to be the most reliable biomarker for patient selection [51]. Moreover, multiple gene signatures, tumor mutation burden, and microsatellite instability are associated with clinical response after PD-1/PD-L1 antibody treatment in other solid tumors, such as melanomas and lung and colorectal carcinomas [54–56]. However, these biomarkers have not yet been tested in patients with metastatic TNBC, and their role in predicting response to PD-1/PD-L1 antibodies remains to be defined.

Similarly, selecting the ideal chemotherapeutic partner for PD-1/PD-L1 antibodies is essential. Apart from the nab-paclitaxel used in the IMpassion130 study, various chemotherapeutic agents have been assessed as immune induction treatments ahead of PD-1 antibodies in patients with TNBC. In the phase II TONIC trial, patients with metastatic TNBC received a 2-week induction of single-agent chemotherapy, including cyclophosphamide, cisplatin, or doxorubicin, followed by continuous treatment of a PD-1 antibody, i.e., nivolumab [48]. Compared with an ORR of 17% without induction, the ORR was 35% in the doxorubicin cohort, 23% in the cisplatin cohort, and 8% in

the cyclophosphamide cohort [48]. Doxorubicin may modulate the tumor microenvironment by increasing T cell infiltration and T-cell receptor diversity, accordingly increasing the efficacy of PD-1/PD-L1 antibody in patients with TNBC [48]. Eribulin, a novel microtubule inhibitor, was also evaluated in combination with pembrolizumab in patients with metastatic TNBC. The ORR of eribulin plus pembrolizumab was 29.2% as first-line therapy for patients with metastatic TNBC. Meanwhile, pembrolizumab monotherapy achieved an ORR of 23% in a previous study [47]. Given that most of these data were generated in studies with limited sample size, further study on a large scale is warranted in patients with TNBC.

Poly adenosine diphosphate ribose polymerase (PARP) inhibitors

Data from The Cancer Genome Atlas identified BRCA1/2 mutations in nearly 20% of patients with TNBC [57]. These tumor-suppressor genes encode proteins involved in the repair of double-strand breaks in DNA; meanwhile, enzymes from the PARP family are central to the repair of single-strand breaks in DNA [20]. Thus, PARP inhibitors are believed to provide clinically meaningful benefit to patients with BRCA1/2 mutated TNBC. The randomized phase III OlympiAD trial enrolled patients with a germline BRCA mutation and HER2-negative metastatic breast cancer to receive olaparib, an oral PARP inhibitor, or treatment of the physician's choice. In the TNBC subgroup, median PFS was significantly longer in the olaparib group than in the standard therapy group (hazard ratio = 0.43, 95% CI 0.29–0.63); by contrast, no statistically significant improvement was shown in OS (hazard ratio = 0.93, 95% CI 0.62–1.43) [58,59]. Another PARP inhibitor, talazoparib, was also evaluated in a phase III randomized trial. In this study, patients with germline BRCA1/2 mutated advanced breast cancer were assigned to talazoparib or single-agent chemotherapy. Similarly, median PFS was improved in the talazoparib group (hazard ratio = 0.60, 95% CI 0.41–0.87) [60].

Several clinical trials on PARP inhibitors are under way. The phase III PARTNER study (NCT03150576) is currently recruiting TNBC and/or germline BRCA mutated patients to evaluate the addition of olaparib to neoadjuvant platinum-based chemotherapy in the setting of neoadjuvant treatment. With regard to other drugs, veliparib and niraparib are PARP inhibitors with a definite effect on ovarian carcinoma [61,62]. The phase III clinical trials that would evaluate these drugs in HER2-negative metastatic BRCA-associated breast cancer just completed enrollment (NCT02163694, NCT01905592).

Recently, the safety and efficacy of PARP inhibitors combined with PD-1/PD-L1 inhibitors were evaluated in patients with TNBC, demonstrating promising and strong clinical benefits. The TOPACIO/KEYNOTE-162 study is a phase II trial of 55 patients with advanced TNBC receiving niraparib plus pembrolizumab, regardless of their BRCA or PD-L1 status [63]. The most common treatment-related adverse events with grade 3 or higher were anemia (18%), thrombocytopenia (15%), and fatigue (7%). ORR was 21% in the entire cohort and 47% in BRCA mutated patients, with the duration of response ranging from 4.6 months to 15.9 months. The MEDIOLA study assessed the efficacy and safety of olaparib plus durvalumab, a PD-L1 antibody, in patients with germline BRCA mutated HER2-negative metastatic breast cancer [64]. The preliminary results in 34 patients showed an ORR of 56% and a median duration of response of 9.2 months. Further investigation of PARP inhibitors in combination with PD-1/PD-L1 antibody is warranted in large-scale studies to confirm these findings

PI3K pathway inhibitors

In TNBC, most of the genetic aberrations occur within the PI3K-AKT-mTOR pathway [57]. The majority of mutations activate PI3K located in PIK3CA, being observed in approximately 9% of primary TNBCs and likely more in advanced TNBCs [65]. The most relevant nodes localized at downstream PI3K is AKT, and the pathway is regulated by PTEN to a large extent. Aberrations in PIK3CA and PTEN, accounting for 40%–60% of TNBC, are mutually exclusive in most instances [4]. Several clinical trials have evaluated PI3K or AKT inhibitors in TNBC.

Buparlisib is an oral pan-PI3K inhibitor with encouraging antitumor activity in TNBC cell lines [66]. However, the BELL-4 study, a randomized placebo-controlled phase III clinical trial, failed to demonstrate the benefit of adding buparlisib to paclitaxel in advanced HER2-negative breast cancer [67]. In the TNBC cohort, patients who received buparlisib exhibited worse prognosis than those in the placebo group, with a median PFS of 5.5 months versus 9.3 months (hazard ratio = 1.86, 95% CI 0.91–3.79). Even in a subgroup of 125 patients with PIK3CA activation or loss of PTEN, patients with TNBC still did not benefit from the addition of buparlisib (hazard ratio = 1.17, 95% CI 0.63–2.17).

Two AKT inhibitors, namely, ipatasertib and capivasertib, have shown preliminary yet substantial efficacy in randomized, placebo-controlled phase II clinical trials. The LOTUS study randomized 124 patients with advanced TNBC to receive first-line paclitaxel with or without ipatasertib. The addition of ipatasertib to paclitaxel prolonged patients' PFS from 4.9 months to 6.2 months (hazard ratio = 0.60, 95% CI 0.37–0.98) [68]. In the settings of neoadjuvant treatment, however, the FAIRLANE study suggested that adding ipatasertib to paclitaxel during early TNBC did not significantly improve pCR rate

Table 2 Ongoing clinical trials of PI3K-AKT-mTOR pathway inhibitors in TNBC

Category	Intervention	Biomarker eligibility	Phase	Identifier
PI3Kα inhibitor	Alpelisib + enzalutamide	Androgen receptor and PTEN positive	I	NCT03207529
PI3Kβ inhibitor	AZD8186 + docetaxel	PTEN or PIK3CB mutated	I	NCT03218826
PI3Kγ inhibitor	IPI-549	Not required	I	NCT02637531
PI3K/mTOR inhibitor	PF-05212384 + docetaxel/cisplatin/ dacomitinib	Not required	I	NCT01920061
pan-Akt inhibitor	Ipatasertib + carboplatin ± paclitaxel	Not required	I	NCT03853707
pan-Akt inhibitor	Ipatasertib + paclitaxel /placebo	PIK3CA/AKT1/PTEN-altered	III	NCT03337724
Akt/ERK inhibitor	ONC201	Not required	II	NCT03733119

[69]. A phase III trial of first-line ipatasertib for patients with activated PI3K-pathway TNBC was launched (NCT03337724). Similar to ipatasertib, capivasertib plus paclitaxel improved median PFS from 4.2 months to 5.9 months compared with paclitaxel plus placebo (hazard ratio = 0.75, 95% CI 0.52–1.08) in the PAKT study [70]. Notably, no compelling difference in efficacy was observed among the PI3K/AKT/PTEN altered TNBC tumors in most of these studies, highlighting the importance of biomarker assessment to effectively inform the selection of these inhibitors. Ongoing trials assessing PI3K-AKT-mTOR pathway inhibitors are listed in Table 2.

Summary and perspective

Knowledge of TNBC treatment has promptly increased during the past few years. On the basis of a specific genetic profile, appropriate chemotherapy regimens can be selected for TNBC. The novel delivery of chemotherapeutic drugs, such as ADCs, may precisely attack tumor cells with improved efficacy. Immunotherapy, particularly PD-1/PD-L1 antibodies, appears to be a promising treatment approach for TNBC. Meanwhile, appropriate partners for combination therapy and predictive biomarkers remain largely unknown. Major advances have been made in the targeted therapy for TNBC, such as PARP and PI3K pathway inhibitors. New challenges should be addressed, for example, in identifying potential responders at baseline before treatment. Optimal molecular portraits should be offered to all patients with TNBC. Combined therapies and new drugs will be promising in TNBC as the understanding of resistance mechanism evolves.

Compliance with ethics guidelines

Hongnan Mo and Binghe Xu declare no conflict of interests. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000. Given that this study is a review article, obtaining informed consent was unnecessary.

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