Review Article

Narrative review of current status and recommendations in treatment for advanced triple-negative breast cancer

Yan Zhou, Jin Yang^

Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

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Correspondence to: Prof. Jin Yang. Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, 277W Yanta Road, Xi'an 710061, China. Email: yangjin@xjtu.edu.cn.

Background and Objective: The encouraging results of clinical trials for triple-negative breast cancer (TNBC) patients in recent years have gradually formed a system for the therapeutic regimen. As immunotherapy and precision therapy based on biomarkers have brought a new era to TNBC, it has become more crucial for clinicians to update the recommended treatment regimens for advanced TNBC patients.

Methods: We searched literatures related to the treatment for advanced TNBC from 2014 to 2022 on PubMed and sorted out them. In addition, the 2021–2022 guidelines in the part of treatment for advanced TNBC were downloaded on the official website of the guidelines referred to, which were summarized meanwhile.

Key Content and Findings: We summarized the current status of treatment for advanced TNBC from four aspects: immunotherapy, targeted therapy, antibody-drug conjugates (ADC) drug therapy and chemotherapy. The recommended therapeutic principles for the aspect of advanced TNBC in 2022 Chinese Society of Clinical Oncology (CSCO) guidelines were proposed in combination with international guidelines and conference recommendations.

Conclusions: It was emphasized that the detection and evaluation of biomarkers or targeting molecules should be the basis for choosing therapeutic regimens in this review and clinicians are supposed to accurately screen the population to achieve better treatment outcomes and prognosis for patients with advanced TNBC.

Keywords: Advanced triple-negative breast cancer (advanced TNBC); immunotherapy; targeted therapy; antibody-drug conjugates (ADC) drug therapy; biomarkers

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Introduction

Triple-negative breast cancer (TNBC) has been considered with the poor prognosis among breast cancers due to its strong aggressiveness, heterogeneity and lack of therapeutic targets (1). The encouraging results of clinical trials for TNBC patients in recent years have gradually formed a system for the therapeutic regimen. In this review, we will summarize the current status of treatment for advanced TNBC from four aspects: immunotherapy, targeted therapy, antibody-drug conjugates (ADC) drug therapy and chemotherapy. The subtype classification of TNBC has always been a hot issue due to its heterogeneity and the

^ ORCID: 0000-0002-2538-5176.

Table 1 The search strategy summary

Items	Specification
Date of search	2022/02/01–2022/02/23
Databases and other sources searched	https://pubmed.ncbi.nlm.nih.gov/
Search terms used	"Advanced triple-negative breast cancer" and "therapy" or "metastatic triple-negative breast cancer" and "therapy", detailed in Table S1
Timeframe	2014/01/01–2022/02/23
Inclusion and exclusion criteria	None
Selection process	The included literature was selected by author YZ and reviewed by author JY

corresponding therapeutic regimen varies according to the subtypes, including Lehmann typing (2), Fudan University Shanghai Cancer Center (FUSCC) typing (3), and recent typing based on $CD8^+$ tumor-infiltrating lymphocytes (TILs) spatial distribution (4). This suggests that the detection and evaluation of biomarkers in the TNBC patients for treatment selection of population is fundamental and crucial. Among the drugs recommended by various international guidelines and conferences, the detection of molecular biomarkers and evidence-based medical option have become the supporting basis for the treatment of advanced TNBC. In addition to summarizing important clinical trials and guideline recommendations, we will also highlight pharmaceutical and clinical research from China to provide more reference for international clinical physicians in this review. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-22-12/rc).

Methods

We searched literatures related to the treatment for advanced TNBC from 2014 to 2022 on PubMed and sorted out them, detailed in *Table 1* and Table S1. In addition, the 2021–2022 guidelines in the part of treatment for advanced TNBC were downloaded on the official website of the guidelines referred to, which were summarized meanwhile.

Immunotherapy

In recent years, the immunological characteristics of tumor microenvironment (TME) in breast cancer have been increasingly emphasized, especially in TNBC. There are differences in characteristics of TME between the primary and metastatic sites of early and advanced breast cancer. For instance, immunogenic components that can represent antigen processing related characteristics changed, such as decreased major histocompatibility complex (MHC) class I expression (5), as well as the decrease of immunomodulatory related genes and TILs of anti-tumor immunological activity in the metastatic sites (6). The changes of these immune-related characteristics in the occurrence and development of TNBC suggest that the application of immunotherapy in each stage of TNBC should tend to be more detailed, precise and individualized under the therapeutic principle. The results of the IMpassion130 study (7) bring the treatment of advanced TNBC into a new era with immune-checkpoint inhibitors (ICIs). In this section, we will detail significant guidelines for advanced TNBC immunotherapy based on the classification of monotherapy and combination therapy.

ICIs monotherapy

After preliminary confirmation of the efficacy of pembrolizumab monotherapy in the treatment for advanced TNBC in KEYNOTE-012 (8), the results of anti-programmed death (PD)-1/PD-L1 antibodies monotherapy in KEYNOTE-086 (9), TONIC (10) and KEYNOTE-119 (11) have been reported successively, as shown in *Table 2*. In KEYNOTE -119, combined positive score (CPS) representing the expression status of PD-L1, is a significant factor stratification for the benefit of objective response rate (ORR), overall survival (OS) and progression-free survival (PFS). Besides, the subgroup of tumor mutational burden (TMB) was also found to be related to OS. In KEYNOTE-158 (17), solid tumor patients with microsatellite instability-high (MSI-H) were also found to benefit from pembrolizumab monotherapy, suggesting the significance of using biomarkers to identify populations who

Table 2 Summarization about the clinical trials of immunotherapy in advanced triple-negative breast cancer

Study	Sample size	Regimen	Results	Reference
ICIs monotherapy				
KEYNOTE-012	32	Pembrolizumab	ORR: 18.5%; mPFS: 1.9 months; mOS: 11.2 months	(8)
KEYNOTE-086	193	Pembrolizumab	Higher TILs levels were associated with significantly improved ORR (OR =1.26, P=0.01) and DCR (OR =1.22, P=0.01); ORR in ITT: 5.3% (ORR in patients with PD-L1+ *vs.* PD-L1−: 5.7% *vs.* 4.7%); mPFS: 2.0 months; mOS: 9.0 months; PD-L1 expression significantly correlated with TILs levels (ρ=0.4962, P<0.001)	(9)
KEYNOTE-119	622	Pembrolizumab or capecitabine/ eribulin/ gemcitabine/ vinorelbine	The higher PD-L1 CPS, the more obvious ORR, PFS and OS benefit were observed. ORR in ITT: 9.6% *vs.* 10.6%; ORR in patients with CPS ≥1: 12.3% *vs.* 9.4%; ORR in patients with CPS ≥10: 17.7% *vs.* 9.2%; ORR in patients with CPS ≥20: 26.3% *vs.* 11.5%; mPFS in ITT: 2.1 *vs.* 3.3 months; mPFS in patients with CPS ≥10: 2.1 *vs.* 3.4 months; mOS in ITT: 9.9 *vs.* 10.8 months; mOS in patients with CPS ≥10: 12.7 *vs.* 11.6 months	(11)
TONIC	67	Nivolumab	ORR: 20.0%; mPFS: 1.9 months	(10)
ICIs combination therapy				
IMpassion 130	902	Atezolizumab or placebo plus nab-paclitaxel	$CD8^+$ TILs and PD-L1 were both related to PFS and OS benefits. ORR in ITT: 56.0% *vs.* 45.9%; ORR in patients with PD-L1+: 58.9% *vs.* 42.6%; mPFS in ITT: 7.2 *vs.* 5.5 months; mPFS in patients with PD-L1+: 7.5 *vs.* 5.3 months; mOS in ITT: 21.0 *vs.* 18.7 months; mOS in patients with PD-L1+: 25.4 *vs.* 17.9 months; PFS in patients with PD-L1+: HR =0.62, 95% CI: 0.49–0.78; OS in patients with PD-L1+: HR =0.67, 95% CI: 0.53–0.86	(7,12)
KEYNOTE-355	847	Pembrolizumab or placebo plus nab-paclitaxel/ carboplatin/ gemcitabine	The higher PD-L1 CPS, the more obvious PFS and OS benefit were observed. ORR in ITT: 41.0% *vs.* 35.9%; ORR in patients with CPS >1: 45.2% *vs.* 37.9%; ORR in patients with CPS >10: 53.2% *vs.* 39.8%; mPFS in ITT: 7.5 *vs.* 5.6 months; mPFS in patients with CPS >1: 7.6 *vs.* 5.6 months; mPFS in patients with CPS >10: 9.7 *vs.* 5.6 months; PFS in patients with CPS >10: HR =0.65, 95% CI: 0.49–0.86	(13)
IMpassion 131	651	Atezolizumab or placebo plus paclitaxel	ORR in ITT: 53.6 *vs.* 47.5; ORR in patients with PD-L1+: 63.4% *vs.* 55.4%; mPFS in ITT: 5.7 *vs.* 5.6 months; mPFS in patients with PD-L1+: 6.0 *vs.* 5.7 months; mOS in ITT: 19.2 *vs.* 22.8 months; mOS in patients with PD-L1+: 22.1 *vs.* 28.3 months; PFS in patients with PD-L1+: HR =0.82, 95% CI: 0.60–1.12; OS in patients with PD-L1+: HR =1.11, 95% CI: 0.76–1.64	(14)
FUTURE	69	Camrelizumab plus nab-paclitaxel or other arms	Arm C (immunotherapy) achieved the highest ORR (52.6%, 95% CI: 28.9–75.6%) in the ITT population	(15)
SWOG S1609	17	Ipilimumab plus nivolumab	ORR: 18.0%; mPFS: 2.0 months; mOS: 12.0 months	(16)
FUTURE-C-PLUS	46	Camrelizumab, nab-paclitaxel plus famitinib	ORR: 81%; 12 months-OS: 84.2% (95% CI: 73.4–95.0); 18 months-OS: 73.6% (95% CI: 52.0–95.2)	(15)

ICIs, immune checkpoint inhibitors; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; TIL, tumor-infiltrating lymphocyte; OS, overall survival; OR, odds ratio; DCR, disease control rate; ITT, intention-to-treat; CPS, combined positive score; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

will benefit from immunotherapy monotherapy. In addition, due to the imbalance between immunosuppression and immune-stimulation of TME during tumor development, some studies (18) have found that the lines of therapy affected therapeutic effect. Therefore, the choice of ICIs monotherapy for metastatic TNBC is not common in international guidelines, and should be considered carefully by clinicians taking into account the individuals and number of therapeutic lines.

ICIs combined with chemotherapy

The immunomodulatory effect of chemotherapy on TME makes it one of the most suitable combined options for immunotherapy, and the positive results of IMpassion130 (7,12) and KEYNOTE-355 (13) employing atezolizumab and pembrolizumab in combination with chemotherapy in metastatic TNBC respectively proved it, among which KEYNOTE-355 led to Food and Drug Administration (FDA) approval of pembrolizumab in combination with chemotherapy. It is worth noting that the benefit of OS in KEYNOTE-355 is limited to patients with CPS ≥10, and patients with a short disease-free interval (DFI) may have limited survival benefit due to chemotherapy resistance, which lead the patients with DFI <12 months were recommended to receive combination with non-paclitaxel drugs. Besides, different subgroups of chemotherapeutics also had different clinical outcomes (the paclitaxel group and nab-paclitaxel group had longer PFS durations than other types of chemotherapy). In fact, paclitaxel may not be an effective immunomodulatory partner like nab-paclitaxel for reasons such as the repeated use of steroids in weekly paclitaxel therapy, as reflected in the negative results of IMpassion131 (14). In addition, in the Chinese clinical trial FUTURE (15), the ORR of intention-to-treat (ITT) patients reached 52.6% when camrelizumab combined with nab-paclitaxel was applied to immunomodulation-typing TNBC patients divided according to molecular detection results. The European Society for Medical Oncology (ESMO) 2021 expert board (19) recommended the regimens of atezolizumab combined with nab-paclitaxel or pembrolizumab combined with chemotherapy as the first-line therapy for metastatic TNBC patients with PD-L1 positive, while the National Comprehensive Cancer Network (NCCN) 2022 guidelines set CPS ≥10 as the standard cut-off value for pembrolizumab combined with chemotherapy (20). Therefore, patients who use anti-PD-1/PD-L1 antibodies should be evaluated by CPS and other immune-related biomarkers and select suitable chemotherapeutic partners. More biomarkers should also be explored and promoted in clinic to screen for patients who may benefit from immunotherapy in combination with chemotherapy.

Doublet ICIs combined therapy

Currently, the most commonly used ICIs are anti-PD-1/PD-L1 antibodies, however other immune checkpoints are also used for immunotherapy drugs, such as anti- cytotoxic T-lymphocyte-associated protein (CTLA)-4 antibody. The combination of the two ICIs targeting PD-1/PD-L1 and CTLA-4 respectively could enhance anti-tumor immune effect. In the SWOG S1609 study (16), the combination of ipilimumab and nivolumab in 17 advanced metaplastic breast cancer patients who recurred after chemotherapy showed no new safety signals and ORR reached 18%. The ORR of 33 advanced solid tumors patients from ETCTN-9844 trial (21) who received nivolumab combined with ipilimumab reached 16%, including a complete response in TNBC and a statistically significant increase in CD8/FoxP3 ratio. Recently, another study (22) showed that KN046 (recombinant humanized PD-L1/CTLA-4 bispecific antibody) could be enriched targeted to TME with high expression of PD-L1 and exhaust regulatory T cells (T_{reg}) that suppresses tumor immunity, which suggests that bispecific immune checkpoint antibody may be the trend of immunotherapy in the future.

Other potential for combined immunotherapy regimens

The selection of other therapies except chemotherapy combined with immunotherapy should be based on the regulating effect on tumor immune microenvironment and the mechanism of combating ICIs resistance, among which antiangiogenic drugs play an outstanding synergistic effect in the combined application of immunotherapy. As an example, a Chinese trial (23) showed that the ORR of advanced TNBC patients received camrelizumab combined with apatinib reached 47.4% in the later lines therapy group. In the FUTURE-C-PLUS trial (15), camrelizumab, nab-paclitaxel and famitinib triplet combination treated immunogenicity TNBC patients (CD8 positive) whose PFS reached 13.6 months. The combination of immunotherapy with antiangiogenic agents with or without chemotherapy showed us more possibilities of immunotherapy combined with other drugs, and suggested us exploring the combined

Table 3 Summarization about the clinical trials of targeted therapy in advanced triple-negative breast cancer

Study	Sample size	Regimen	Results	Reference
PARP inhibitors				
OlympiAD	150	Olaparib or capecitabine/eribulin/vinorelbine/gemcitabine	ORR: 54.7% *vs.* 21.2%; mOS: 17.4 *vs.* 14.9 months; PFS: HR =0.43, 95% CI: 0.29–0.63; OS: HR =0.93, 95% CI: 0.62–1.43	(24)
EMBRACA	190	Talazoparib or capecitabine/eribulin/vinorelbine/gemcitabine	ORR: 61.8% *vs.* 12.5%; PFS: HR =0.60, 95% CI: 0.41–0.87; OS: HR =0.90, 95% CI: 0.63–1.28	(25)
BROCADE3	243	Veliparib or placebo plus carboplatin and paclitaxel	ORR: 77.6% *vs.* 77.6%; mOS: 35.0 *vs.* 30.0 months; mPFS: 16.6 *vs.* 14.1 months; PFS: HR =0.72, 95% CI: 0.52–1.01	(26)
PI3K-AKT pathway inhibitors				
LOTUS	166	Ipatasertib or placebo plus paclitaxel	mPFS in ITT: 6.2 *vs.* 4.9 months; mPFS in patients with low PTEN expression: 6.2 *vs.* 3.7 months; PFS in ITT: HR =0.60, 95% CI: 0.37–0.98; PFS in patients with low PTEN expression: HR =0.59, 95% CI: 0.26–1.32	(27)
PAKT	140	Capivasertib or placebo plus paclitaxel	PFS was correlated with the subgrouping of PIK3CA/AKT1/PTEN alterations. mPFS in ITT: 5.9 *vs.* 4.2 months; mPFS in patients with PIK3CA/AKT1/PTEN alterations: 9.2 *vs.* 3.7 months; PFS in ITT: HR =0.74, 95% CI: 0.50–1.08; PFS in patients with PIK3CA/AKT1/PTEN alterations: HR =0.30, 95% CI: 0.11–0.79	(28)

PARP, poly (ADP-ribose) polymerase; ORR, objective response rate; mOS, median overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; mPFS, median progression-free survival; PI3K, phosphatidylinositol 3 kinase; AKT, serine/threonine kinase; PTEN, phosphatase tensin homologue deleted on chromosome 10; ITT, intention-to-treat.

drugs that can synergistically modulate anti-tumor immune effect with ICIs in more directions.

Targeted therapy

The immune characteristics of the TME in TNBC patients are the foundation of immunotherapy, while the characteristics of molecular genetics provide the basis for targeted therapy.

Poly (ADP-ribose) polymerase (PARP) inhibitors

The homologous recombination deficiency (HRD) including tumorigenic germline mutations of BRCA1/2 based on PARP-mediated DNA repair constituted the basis of targeted treatment for TNBC. In TNBC patients with human epidermal growth factor receptor 2 (HER2) negative and breast cancer susceptibility gene 1/2 (gBRCA 1/2) mutation, the benefit of PFS was demonstrated in the treatment of olaparib groups and talazoparib groups from the OlympiAD trial (24) and EMBRACA trial (25) respectively. In the BROCADE3 study (26), median PFS of patients who received veliparib combined with platinum chemotherapy reached 14.5 months, which showed the synergistic effect of platinum and PARP inhibitors. It is valuable to note that veliparib treatment was continued in patients with no disease progression at the time of chemotherapy ended, so whether the benefit of PFS came from combination chemotherapy or maintenance of veliparib needs further to be observed and explored. The above studies are detailed in *Table 3*. The ESMO 2021 expert committee recommended PARP inhibitors as the first-line treatment regimen superior to chemotherapy in metastatic TNBC patients with gBRCA1/2 mutation (19), while there are similar recommendations in the 2022 NCCN (20) and 2021 AGO (29) guidelines. On the premise that there is no approval of indication for PARP inhibitors in China, based on the enrolled population of platinum-sensitive characteristics in above trials, we will

recommend PARP inhibitors or platinum drugs as the first-line treatment regimen.

Phosphatidylinositol 3 kinase (PI3K)-serine/threonine kinase (AKT) pathway inhibitors

AKT is a downstream targeted molecule of PI3K, therefore AKT inhibitors ipatasertib and capivasertib were used to treat metastatic TNBC patients with low phosphatase tensin homologue deleted on chromosome 10 (PTEN) expression and PIK3CA/AKT1/PTEN alterations in LOTUS trial (27) and PAKT trial (28) respectively (see details in *Table 3*). In addition, a phase I study (30) used a triplet combination of ipatasertib, atezolizumab and paclitaxel to obtain 73% ORR in patients with advanced TNBC, which suggests that PTEN deficiency may be the mechanism of ICIs resistance, and therefore PI3K-AKT pathway inhibitors may also be selected as combinations with immunotherapy in TNBC.

ADC drug therapy

ADC drugs could precisely produce cytotoxic effects on tumor cells expressing the antigen through recombinant monoclonal antibodies, while minimize cytotoxicity to normal tissue. Sacituzumab govitecan (SG) was approved by FDA and recommended by the 2022 NCCN Guidelines (20) for the later line treatment of patients with metastatic TNBC, which targets on the trophoblast cell surface antigen 2 (TROP2). ASCENT study (31) showed that regardless of TROP2 expression levels, patients received SG acquired PFS and OS benefits compared to patients received chemotherapy, among which the group with low TROP2 expression had the least benefit.

In addition, the proportion of patients in TNBC with low HER2 expression is about 38.3%, in which the clinical efficacy of new ADC drugs with bystander effect, has emerged. A study (32) showed the role of trastuzumab deruxtecan (T-DXd, DS8201) in patients with low HER2 expression was as well as in luminal breast cancer. Besides, some studies (33) showed that the ORR of breast cancer patients with low HER2 expression received disitamab vedotin (RC-48) treatment could reach 39.6%. For the aspect of combination with ADC drugs, in the arm VI of BEGONIA study (33), it was observed that DS8201 combined with durvalumab in the treatment of breast cancer patients with low HER2 expression could achieve lasting remittance regardless of the expression of PD-L1. It suggests the potential of ADC drugs in combination with ICIs and the evaluation of biomarkers including HER2, TROP2, and PD-L1 should be carefully considered. In general, ADC drugs will be more widely used in advanced breast cancer with low HER2 expression in the future.

Chemotherapy

The drugs of chemotherapy including anthracyclines, taxanes, anti-metabolites (capecitabine and gemcitabine) and microtubule inhibitors (vinorelbine and eribulin) were recommended by 2022 NCCN guidelines (20) for the treatment of advanced TNBC. While platinum drugs are still the indispensable choice of chemotherapy in China, many studies including CBCSG006 and GAP trial (34,35) demonstrated the combination of cis-platinum with gemcitabine or nab-paclitaxel could be the rescue chemotherapy in advanced TNBC, in which the biomarkers such as gBRCA1/2 mutation could be correlated with therapeutic effect (36). Eribulin, capecitabine and vinorelbine were recommended by ESMO 2021 expert committee for the later lines and subsequent rescue chemotherapy of metastatic TNBC (19). Eribulin has been the emerging chemotherapy drug in recent years, of which 301 study (37) showed that the OS of patients with metastatic TNBC in eribulin treatment group was significantly prolonged by 5 months compared with capecitabine treatment group. Besides, the advanced breast cancer patients who have previously been treated with anthracyclines and taxanes benefited from utidelone plus capecitabine in UTD1 trial (38). Therefore, the choice of chemotherapy agents, whether for monotherapy or combination therapy, is crucial as a significant component of advanced TNBC treatment.

Conclusions

In this review, feasible options for therapying advanced TNBC were summarized, and recommended therapeutic principle for the aspect of advanced TNBC in 2022 Chinese Society of Clinical Oncology (CSCO) guidelines were proposed in combination with international guidelines and conference recommendations, as shown in *Figure 1*. Among them, it is emphasized that the detection and evaluation of biomarkers or targeting molecules should be the basis for choosing therapeutic regimens, which was not highlighted in the 2021 CSCO. In addition, the drugs including

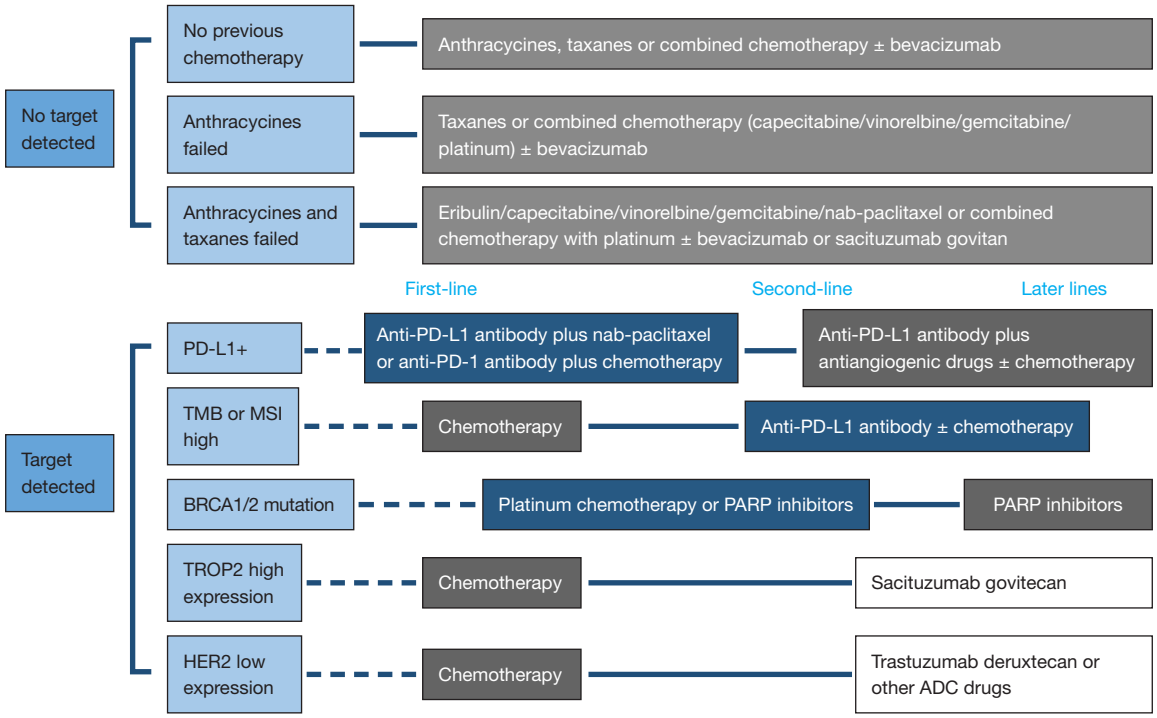

Figure 1 Recommended therapeutic regimens for advanced triple-negative breast cancer. PD-1/L1, programmed death-1/legend 1; TMB, tumor mutational burden; MSI, microsatellite instability; BRCA1/2, breast cancer susceptibility gene 1/2; TROP2, trophoblast cell surface antigen 2; HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; ADC, antibody-drug conjugates.

eribulin incorporated into China's health insurance system should be encouraged to use by Chinese clinicians so as to provide patients with more cost-effective and precise treatment. Meanwhile, the patients prepare to use the drugs that have not yet been approved in China, including ICIs such as pembrolizumab, need to be accurately screened for treatment based on biomarkers. In all, clinicians are supposed to carefully follow the guidelines, accurately screen the population and encourage patients to participate in clinical trials to achieve better treatment outcomes and prognosis for patients with advanced TNBC.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-22-12/rc).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-22-12/coif). Both authors report that they are supported by National Natural Science Foundation of China (No. 82002794). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 The detailed search terms

Search terms No.	Search contents
1	“advanced triple-negative breast cancer” and “therapy”
2	“metastatic triple-negative breast cancer” and “therapy”
3	“advanced TNBC” and “therapy”
4	“metastatic TNBC” and “therapy”

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