Review Article

The pathological and clinical landscape of refractory metastatic triple negative breast cancer: a narrative review

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Background and Objective: Triple negative breast cancer (TNBC) refers to a special subtype of breast cancer that is negative for the estrogen receptor, the progesterone receptors, and human epidermal growth factor receptor 2. As a group of diseases, it has strong heterogeneity. Refractory metastatic triple negative breast cancer (mTNBC) has even greater heterogeneity, more susceptibility to drug resistance, and faster progression, which makes it more difficult to treat effectively and significantly reduces a patient's overall survival. Therefore, in order to overcome this difficulty in clinical practice, we need to deeply understand the special subgroup by analyzing definition and prognostic factors of refractory mTNBC and describing the therapeutic status and future treatment directions.

Methods: Recent domestic and foreign guidelines, as well as clinical studies related to refractory mTNBC on PubMed and the China National Knowledge Infrastructure (CNKI) databases were retrospectively analyzed. The six keywords we selected were used for literature search. Two authors performed database searches independently, and disagreements over the results were mediated by a third reviewer.

Key Content and Findings: According to the guidelines, refractory mTNBC has not been clearly defined. Related studies indicated that tumor heterogeneity may be one of the main mechanisms of early relapse or drug resistance in refractory mTNBC. The clinical treatment options for refractory mTNBC are very limited. Although chemotherapy is the standard treatment, it is limited by poor efficacy and intolerance in the clinical stage. Therefore, in recent years, many studies have explored novel treatment options. Both immunotherapy and poly(ADP-ribose) polymerase (PARP) inhibitors have been selected as first-line treatment in clinical studies, but gained limited benefits. Indeed, clinical studies have shown good efficacy with novel ADCs, which may be promising in the clinical treatment of refractory mTNBC.

Conclusions: Currently, improving the survival time and quality of life of refractory mTNBC are major challenges for clinicians. Novel therapies including immunosuppressive agents, PARP inhibitors, and ADCs rather than chemotherapy alone have achieved good results in the exploration of first-line treatment for refractory TNBC patients, but this warrants further research and investigation.

Keywords: Refractory metastatic triple negative breast cancer; prognostic factors; chemotherapy; immunotherapy; antibody-drug conjugate (ADC)

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Introduction

Triple-negative breast cancer (TNBC) refers to a subgroup of breast cancer (BC) defined by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER-2), accounting for 15–20% of all BC subtypes (1). According to the latest epidemiological data from GLOBOCAN in 2020, the number of new BC cases in China reached 416,000, accounting for 18.4% of the global BC cases. For the first time BC surpassed lung cancer as the most common cancer (2), with a huge patient population. TNBC is highly aggressive, and about 46% of TNBC patients will develop distant metastasis (3). Due to the lack of definite and effective therapeutic targets, TNBC progresses rapidly and can easily become drug resistant. Relapsed and metastatic TNBC (mTNBC) has a poor prognosis, with a 5-year survival rate of less than 15% (4) and a median overall survival (OS) of only 9–17 months (5). The goals of treatment for patients with mTNBC are to prolong survival, relieve symptoms, and improve the quality of life. However, the rapid development of drug resistance and poor patient tolerance to existing regimens remain major challenges in the clinical settings.

To date, there is no standard definition for refractory mTNBC, and identifying the risk population, prognostic factors, and optimal therapeutic options will be valuable to the management of these patients. While clinical studies have examined mTNBC patients, there are still gaps between the study cohorts and real-world patients in clinical practice. Most studies have enrolled patients who received one line of therapy (usually first-line treatment), and few studies have explored the treatment strategies for refractory mTNBC (6-8). Therefore, the results of these clinical research might not accurately reflect nor address the real-world problems. Since refractory mTNBC patients do not meet the inclusion criteria in most clinical trials, only patients with TNBC that is responsive to chemotherapy have been enrolled, making it difficult for patients with refractory TNBC to obtain effective treatments. Therefore, a deeper understanding of refractory mTNBC will inherently facilitate the exploration of effective therapies. Herein, we explored the definition and prognostic factors of refractory mTNBC and analyzed the current status of mTNBC treatment, so as to provide a reference for the clinical selection of treatment strategies for patients with mTNBC. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3434/rc).

Methods

Published literature was searched using the PubMed and the China National Knowledge Infrastructure (CNKI) databases using the following keywords: “metastatic”, “refractory”, “triple-negative breast cancer”, “prognostic factors”, “treatment”, and “antibody-drug conjugates (ADCs)”. Database searches were performed independently by two reviewers, and disagreements were resolved by discussion and consultation with a third reviewer. All papers published in English from 2007 to February 2022 (mainly those published in the past 5 years) were searched, including original articles, reviews, and treatment guidelines. Articles that satisfied the inclusion criteria were manually searched and included in the reference list of our current analysis. Studies that were not related to breast cancer or focusing on early-stage TNBC were excluded. *Table 1* summarizes the retrieval and selection process for this analysis.

Discussion

Definition of refractory mTNBC

According to the United States Food and Drug Administration (FDA) (9), disease-free interval (DFI) is defined as the interval from the completion of surgery or adjuvant chemotherapy to the diagnosis of recurrence. For patients receiving neoadjuvant therapy, DFI is calculated from the end of surgery. Refractory mTNBC may be clinically manifested as early recurrence (usually reaching the peak of local or distant recurrence/metastasis about 1 year after surgery/adjuvant therapy, i.e. DFI ≤12 months) (10) and high level of drug resistance; with change of therapy occurring at least once during the treatment, along with disease progression (11). Some clinical trials briefly described refractory mTNBC when selecting the research subjects or enrollment criteria. Kim *et al.* (5), in a retrospective analysis of the real-world data of TNBC patients (n=451), defined refractory mTNBC as TNBC with local or distant recurrence/metastasis within one year after adjuvant therapy. The refractory mTNBC cohort was composed of patients with disease that recurred after surgery and adjuvant therapy (n=207, 45.9%; DFI ≤12 months) and patients in whom the disease progressed to stage IV during neoadjuvant chemotherapy (NAC) (n=44, 9.6%). After first-line palliative chemotherapy, the overall survival (OS) (14.3 months *vs.* 24.8 months) and progression-free survival (PFS) significantly differed between the refractory mTNBC group (55.7%, DFI ≤12 months) and the non-refractory

Table 1 A summary of the literature search strategy

Items	Specification
Date of search	February 1, 2022 to February 7, 2022
Databases and other sources searched	PubMed and China National Knowledge Infrastructure (CNKI)
Search terms used	"metastasis", "refractory", "triple-negative breast cancer", "prognostic factor", "treatment", "antibody-drug conjugate"
Timeframe	1991–2022
Inclusion and exclusion criteria	Inclusion criteria: 1. Prognostic factors and treatment of metastatic triple-negative breast cancer 2. Published literature, including studies, review papers, treatment guidelines Exclusion criteria: 1. Literature not related to breast cancer 2. Studies related to early triple-negative breast cancer
Selection process	Two authors searched the database independently. A third reviewer mediated any disagreements between the two researchers

mTNBC group (29%, DFI >12 months) (both P<0.001). Wang *et al.* (12) conducted a retrospective study and found that patients with very-early-relapsed TNBC (average DFI: 11 months) had higher tumor mutational burden (TMB) and more gene mutations (137 *vs.* 54) compared to non-recurrence TNBC patients, indicating that early-relapsed refractory mTNBC has higher intratumor heterogeneity, which is associated with higher probability of drug resistance, faster cancer progression, and poorer prognosis. Many clinical studies have shown that chemotherapy, targeted therapy, and immunotherapy had no survival benefit in patients with a DFI of less than 12 months (13-15).

Another clinical manifestation of refractory mTNBC is the high incidence of treatment-related adverse reactions or drug discontinuation in patients who could not tolerate first-line treatment regimens. Anthracyclines and taxanes remain the commonly used first-line chemotherapy drugs for advanced TNBC. They are highly toxic and may not be tolerated by some patients, which seriously affects the therapeutic response. The tnAcity study (16) showed that grade 3 or higher adverse events (AEs) occurred in 77–84% of mTNBC patients receiving the first-line combination chemotherapies, and up to 23–45% of the patients discontinued the drug due to AEs. As a result, patients with advanced disease could not benefit from first-line drugs. Notably, about 20% of TNBC patients are 65 years or over. Due to the high incidence of comorbidities, the use of multiple drugs, and the pre-existing physical weakness or dysfunction, these patients are not suitable for chemotherapy. The proportion of elderly TNBC patients receiving chemotherapy is dramatically lower than that in younger patients (53.2% *vs.* 91.1%) (17).

Most Chinese and foreign guidelines have not clearly defined refractory mTNBC, and only a few studies or reviews have briefly described refractory mTNBC (5,11,18,19). In addition, most clinical trials excluded patients with refractory mTNBC, leading to lower concerns about these patients, for whom timely identification of the disease in its early stage and precise treatments are particularly important. Therefore, more accurate definition of refractory mTNBC should be developed.

Pathogenic mechanisms and disease characteristics of refractory mTNBC

TNBC is actually a group of highly heterogeneous diseases (including multiple subtypes), and different subtypes of tumor cells activate different signaling pathways and have different responses to treatment. A possible mechanism for early relapse (DFI ≤12 months) or drug resistance in refractory mTNBC is tumor heterogeneity (20). It is generally believed that tumor heterogeneity originates from tumor stem cells. Breast cancer stem cells can self-renew and differentiate, possess a strong ability to regenerate tumors, and are easily resistant to chemotherapy in the early stage of treatment, leading to early tumor recurrence

and metastasis (21). Genetic instability is another cause of tumor heterogeneity. Compared with hormone receptor-positive and HER2-positive breast cancers, TNBC has a high degree of chromosomal instability (22), which can increase the adaptability of TNBC tumor cells and make them rapidly acquire resistance to chemotherapy (23).

Tumor heterogeneity can be divided into inter- and intra-tumor heterogeneity. Inter-tumor heterogeneity is characterized by the different subtypes and disease characteristics of the same type of tumor. For example, 60% of mTNBC patients are <60 years old and 70% of mTNBC patients also have visceral metastasis and multiple modes of metastasis and spread (6). The disease characteristics of mTNBC, including younger age and visceral metastasis, also indicate that refractory mTNBC is more aggressive and has a worse prognosis. Intratumoral heterogeneity is reflected in the presence of different tumor cell populations (with different molecular and phenotypic characteristics) within the same tumor specimen. This has been recognized as one of the main determinants of treatment resistance and treatment failure and the leading cause of low OS in patients with metastatic tumors (24).

The heterogeneity of TNBC has been identified in large-scale comprehensive genomic analyses. Specific gene changes in tumor cells can activate different pathways that lead to tumor heterogeneity, followed by tumor resistance to many traditional treatments. These pathways include the Notch signaling pathway, the WNT/β-catenin pathway, the Hedgehog pathway, and the phosphatidylinositol 3-hydroxy kinase (PI3K)/protein kinase B (PKB, also known as AKT)/mechanistic target of rapamycin (mTOR) pathway. This latter pathway is mainly activated by PIK3CA mutation or amplification, PTEN deletion, or AKT mutation (25). This pathway is one of the main mechanisms that induces TNBC treatment resistance and promote tumor cell proliferation and metastasis. The *PIK3CA* gene mutation can phosphorylate PI3K and activate the downstream effector molecule AKT. The activated AKT can inhibit glycogen synthase kinase-3 (GSK3) and Bad kinase or increase the transcriptional activity of nuclear factor-kappa B (NF-κB), thus promoting the proliferation and metastasis of tumor cells. It can also phosphorylate and activate the mTOR signaling pathway, affecting cell growth and the cell cycle. Thus, the pathway downstream of PI3K signaling is extremely complex, resulting in higher heterogeneity in refractory mTNBC. The PI3K family comprises multiple classes and isoforms. Although there is much research and development related to PI3K/AKT/mTOR pathway inhibitors, it remains unclear who will actually benefit from these drugs (25). Simply inhibiting a certain PI3K isoform may lead to drug resistance due to the presence of compensatory mechanisms in tumor cells. Balko *et al.* detected a relatively higher frequency of PTEN deletion or mutation in TNBC patients (26). *PTEN* is a tumor suppressor gene and plays a negative regulatory role in the PI3K/AKT signaling pathway. The deletion of PTEN can readily lead to excessive activation of AKT (13) and thus, promote tumor growth. In addition, research has shown that the expression of PI3K and AKT in drug-resistant breast cancer cells is higher than that in non-resistant cells (24). Therefore, the activation of the PI3K/AKT pathway is associated with drug resistance in refractory breast cancer.

In the FUTURE study (18), the most frequently mutated genes in chemotherapy-resistant refractory mTNBC identified by gene sequencing included *TP53* (72%), *PIK3CA* (18%), *PTEN* (10%), *KMT2D* (9%), and *TSC2* (9%). Considering the heterogeneity of refractory mTNBC, the investigators grouped the subjects with refractory mTNBC according to TNBC subtype and genomic characteristics and administered different targeted therapies, including CDK4/6 inhibitors, programmed cell death protein 1 (PD-1) inhibitors, poly(ADP-ribose) polymerase (PARP) inhibitors, and vascular endothelial growth factor receptor (VEGFR) targeted drugs. The results showed that the median treatment time of the intention-to-treat (ITT) population was improved compared with front-line treatment (3.5 *vs.* 2.4 months, P=0.02), and the objective response rate (ORR) was 29.0% [95% confidence interval (CI): 18.7–41.2%]. Although the differences were statistically significant, the benefits of existing targeted therapy and the benefit populations remain unclear, and targeted drugs that can overcome tumor heterogeneity and exert curative effects are urgently needed.

Advances or evolution in clinical treatment decisions for refractory mTNBC

Influencing factors and treatment options for early relapsed refractory mTNBC

Although many clinical studies have explored the treatment options and potential predictors of recurrence in breast cancer patients, few reports have focused on the prognostic factors related to survival after recurrence. Multivariate analysis showed that DFI ≤12 months, previous history of chemotherapy, age <50 years, visceral metastasis, and alkaline phosphatase (ALP) >120 U/L were all independently

associated with poor prognosis (27). At the 2021 San Antonio Breast Cancer Symposium® (SABCS®) meeting, Rugo proposed the concept of stratified treatment for TNBC with a DFI of ≤12 months. As an independent prognostic factor, DFI ≤12 months has increasingly been investigated, and it was found in up to 20–45.9% of TNBC patients (5,6,13,28). Although DFI ≤12 months is an independent factor for poor prognosis in mTNBC patients, only one clinical study on TNBC patients with DFI ≤12 months is currently underway (Impassion132, NCT03371017) (29). In other studies, refractory TNBC in the exclusion criteria or included as a simple subgroup analysis (13,14,16). Overall, it was found that TNBC patients with DFI ≤12 months after neoadjuvant/adjuvant therapy derived limited benefit from first-line treatments regardless of the treatment regimen.

TNBC is chemotherapy-sensitive, and therefore chemotherapy remains the mainstay of standard treatment for mTNBC. However, most mTNBC results from distant recurrence of the initially local invasive breast cancer (stage I–III), and only 14% of patients are newly diagnosed at stage IV. mTNBC is usually resistant to previous drugs such as taxanes and anthracyclines (30). Therefore, Chinese guidelines (31,32) recommend that treatments for TNBC patients who have failed taxane (or anthracycline) therapy (that is, patients with DFI ≤12 months or disease progression during salvage therapy, for at least two completed cycles) should be switched to other chemotherapy single-agent or combination regimens in the advanced stage. However, when the single-agent or dual-agent first-line chemotherapy was administered to mTNBC patients, the PFS (3.5–4.77 *vs.* 5.4–9.1 months) and OS (11.3–19.5 *vs.* 18.07–25.8 months) were poorer in patients with DFI ≤12 months compared to patients with DFI >12 months (13,15,28). The LOTUS study (13) compared the effect of the PI3K/AKT inhibitor ipatasertib plus paclitaxel versus paclitaxel monotherapy in mTNBC patients with DFI ≤12 months. While the PFS and OS were improved in the combination therapy group compared to the monotherapy group (4.4 *vs.* 3.5 months and 14.3 *vs.* 11.3 months, respectively), it was not satisfactory, and this may be explained by the high heterogeneity of mTNBC itself, but may also be related with the complex downstream signaling pathway of PI3K/AKT. The results of the KEYNOTE-355 study (14) on immunotherapy showed that pembrolizumab combined with chemotherapy as the first-line treatment of mTNBC achieved significant benefits in PD-L1-positive patients with a combined positive score (CPS) ≥10 (OS: 23.0 *vs.* 16.1 months; HR =0.73; 95% CI: 0.55–0.95). Unfortunately, in this latter study, patients with DFI 6–12 months showed no PFS nor OS benefit after first-line chemotherapy combined with pembrolizumab. The US FDA has approved the PARP inhibitors olaparib and talazoparib for the treatment of germline BRCA-mutated mTNBC. The EMBRACA study (15) compared the value of tarazoparib alone versus chemotherapy and found that first-line treatment conferred PFS benefit (5.7 *vs.* 3.5 months; HR =0.56) but no OS benefit in patients with DFI <12 months. It is therefore obvious that mTNBC patients with DFI ≤12 months have poor prognosis. There are few first-line treatment options, and therapies that are currently available appear to have limited value.

Recent advances in antibody-drug conjugates (ADCs) have shed new light on the treatment of mTNBC that are highly heterogeneous or drug resistant. Sacituzumab govitecan (SG) is a novel antibody-drug-conjugate (ADC) that targets trophoblast cell surface antigen-2 (Trop-2). The expression of Trop-2 can be as high as 88% in mTNBC patients (33). SG, with its bystander effect of a new-generation of ADCs, may have a good therapeutic effect on mTNBC showing strong heterogeneity. The ASCENT study (19) for the first time, explored and demonstrated the efficacy and safety of SG monotherapy in treating relapsed and refractory mTNBC. The inclusion criteria in this latter study were as follows: mTNBC patients who received ≥1 line of therapy (and DFI <12 months); mTNBC patients who received ≥2 lines of therapy; and mTNBC patients with brain metastases. The authors showed that SG could significantly prolong PFS and OS in patients with relapsed or refractory mTNBC, demonstrating the survival benefits of SG in this patient population. SG monotherapy for relapsed and refractory mTNBC significantly improved PFS (5.7 *vs.* 1.5 months; HR =0.41; P<0.001) and OS (10.9 *vs.* 4.9 months; HR =0.51; P<0.001) in the second-line treatment subgroup with DFI ≤12 months. Subgroup analysis further showed that SG appeared to be more beneficial than earlier-line therapy (HR =0.39 for patients who had received 2–3 treatments and HR =0.48 for patients who had received >3 lines of treatment). It is speculated that first-line SG treatment in refractory mTNBC patients with DFI ≤12 months may provide breakthrough benefits, and further clinical explorations are warranted.

Treatment options for refractory mTNBC patients who are intolerant to first-line therapy

According to European Society for Medical Oncology (ESMO) Clinical Practice Guideline for the diagnosis, staging, and treatment of patients with metastatic breast

cancer (MBC) (34), mTNBC patients with a stage IV disease as the first diagnosis and DFI >12 months should primarily undergo biomarker testing and then be provided with the optimal first-line treatment protocol (immunotherapy combined with chemotherapy, PARP inhibitors, or chemotherapy alone or in combination) according to the expression status of the biomarkers. However, unlike patients with early-stage breast cancer, most MBC patients must receive lifelong treatments, which are inevitably associated with a large number of treatment-related toxicities. A survey in patients with advanced breast cancer found that patients diagnosed with MBC had lower levels of overall quality of life (QoL) and increased information needs (e.g., whether the tumor has metastasized, how to manage side effects, and whether there are ways to prevent treatment-related side effects) (35) Therefore, drug tolerance and QoL are particularly important in these patients. For patients with refractory mTNBC, the diagnosis and treatment decision-making process must consider drug tolerance, so as to improve the QoL.

Whether first-line immunotherapy for mTNBC can remarkably prolongs survival remains controversial. Research on atezolizumab for the first time confirmed that first-line immunosuppressive agents can achieve survival benefits in PD-L1-positive TNBC patients. However, the results of two phase III studies [IMpassion130 (36) and IMpassion131 (37)] differed significantly. Roche made the voluntary decision to withdraw the indication for the use of first-line atezolizumab for PD-L1-positive mTNBC, casting a shadow over the treatment of TNBC with PD-L1-targeted immune checkpoint inhibitors (ICIs). Based on the KEYNOTE-355 study, the 2022 v1 NCCN breast cancer guidelines recommend PD-L1-positive (CPS ≥10) mTNBC patients receive first-line treatment with pembrolizumab combined with chemotherapy (38), which has not yet been approved in China (39). Immunotherapy needs to be combined with chemotherapy, and the poor safety and tolerance of such combinations are remain a clinical concern (40). Research on atezoliz and pembrolizumab has demonstrated that the incidence of grade 3 or above adverse events reached 50–78%, the drug withdrawal rate was 16–18%, and the dose reduction rate was as high as 40%. In addition to safety, there are also limitations in patients who can benefit from immunotherapy. The previous study has shown that only 40% of TNBC patients expressed PD-L1 (33), and less than 20% of patients obtained benefits from immunotherapy, suggesting that not all TNBC patients are responsive to immunotherapy (41). Both the OlympiAD study (on olaparib) (42) and the phase III EMBRACA study (on tarazoparib) (15) showed that these two PARP inhibitors, when used in first-line settings, could confer PFS benefits to *BRCA*-mutated mTNBC patients. However, the OS benefit was not significant in neither the ITT population nor the TNBC subgroups. There were also issues with intolerance, with 55–78% of patients experiencing serious AEs, resulting in 4.9–6.2% of patients discontinuing the treatment and 25.4–66% of patients requiring dose adjustments (42-44). There are still large differences in the specific details of BRCA gene testing recommendations in domestic and foreign guidelines. Testing for *BRCA* gene mutation is not popular among Chinese populations (45). The currently recommended next-generation sequencing (NGS) still has technical problems (32). In addition, only about 11% of TNBC patients carry *BRCA* mutations (46), and thus only a small proportion of mTNBC patients can use PARP inhibitors. Therefore, there are still some limitations in the use of PARP inhibitors as first-line therapy for mTNBC patients with DFI >12 months.

ADCs are a class of drugs that link biologically active cytotoxic drugs to monoclonal antibodies (mAbs) through chemical bonds. These are then transported to target cells to exert therapeutic effects. They have the high toxicity of chemotherapy drugs and the high specificity of targeted therapy. SG is the first novel ADC targeting Trop-2. The phase III ASCENT study confirmed that SG was superior compared to chemotherapy in the second- or higher-line treatment of refractory mTNBC as it significantly prolonged PFS (5.6 *vs.* 1.7 months; HR =0.41; 95% CI: 0.32–0.52; P<0.001) and OS (12.1 *vs.* 6.7 months; HR =0.48; 95% CI: 0.38–0.59; P<0.001). In addition SG was found to have a better safety profile compared to chemotherapy. The most common AEs of grade 3 or higher were neutropenia (33% *vs.* 51%), leukopenia (5% *vs.* 10%), diarrhea (1% *vs.* <10%), anemia (5% *vs.* 8%), and febrile neutropenia (2% *vs.* 6%). The drug discontinuation rate (4.7% *vs.* 5.4%) and dose reduction rate were also lower in the SG group compared to the chemotherapy group (19). SG was well tolerated, and it significantly improved the patient's health-related quality of life (HRQoL). AEs did not negatively affect the patient's overall quality of life nor function (47). Compared with the safety of the current standard therapy (PARPi/immunotherapy/chemotherapy) for mTNBC, SG had the lowest drug discontinuation rate and dose adjustment rate(14,16,19,42,44). In the subgroup analysis, SG also achieved PFS (7.1 *vs.* 2.4 months; HR =0.22; 95%

CI: 0.12–0.40) and OS (15.3 *vs.* 8.2 months; HR =0.37; 95% CI: 0.22–0.64) benefits in elderly patients aged ≥65 years. Thus, SG may become the preferred first-line regimen for treatment-intolerant mTNBC patients or elderly patients (≥65 years old).

Further investigations on the role of ADC in treating refractory mTNBC

Currently, the clinical treatment options for refractory mTNBC are very limited. PARP inhibitors and immunosuppressants still have many limitations due to the low expression rates and associated technical problems. Although chemotherapy remains the standard treatment in most mTNBC patients, drug resistance leads to low response rates, and high toxicities lead to poor patient tolerance. Thus, new therapeutic drugs are urgently needed.

As a Trop-2-targeted ADC, SG was developed by coupling humanized IgG1 antibody targeting Trop-2 antigen to SN-38, the metabolically active product of the chemotherapeutic drug irinotecan, through a hydrolyzable CL2A linker (48). Trop-2 is a transmembrane glycoprotein and has a strong capability to mediate endocytosis (49). This unique endocytosis mechanism can effectively overcome problems associated with downstream signaling and expand the therapeutic window of drugs. Trop-2 is hardly expressed in normal tissues but has high/moderate expression in a variety of epithelial tumor cells. In TNBC, its expression can reach as high as 88% (33). Unlike the hypertoxic payloads used in other ADCs, the SN-38 used in SG is the active metabolite of the chemotherapeutic drug irinotecan and has an anti-tumor activity 100–1,000 times that of irinotecan (50). Meanwhile, as a topoisomerase I inhibitor, SN-38 can avoid the cross-resistance of previous treatments (51). The linker CL2A is cleavable through pH sensitivity. It can slowly release active drugs in tumor cells or in the tumor microenvironment and produce a bystander effect. Meanwhile, the free SN-38 is membrane permeable and can permeate the membrane again after endocytosis, thus killing adjacent cells through the bystander effect to further enhance the killing efficiency on tumor cells with low expression of Trop-2. SG enters the human body and binds to Trop2 on the surface of tumor cells before entering tumor cells through target-mediated endocytosis. The CL2A linker breaks under specific pH conditions, releasing SN-38 to kill tumor cells (51). The high drug-to-antibody ratio (7.6:1) of SG provides a high concentration of toxic small-molecule drugs (52). However, SN-38 exists in a non-glucuronidated active form with a closed lactone ring before it is released, maximizing the therapeutic effect while significantly reducing toxicity (53) and improving patient tolerance.

The phase III ASCENT study evaluated the efficacy of SG versus physician-selected chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with relapsed or refractory mTNBC. It showed that in the ITT population, SG significantly prolonged PFS (4.8 *vs.* 1.7 months; HR =0.43; 95% CI: 0.35–0.54) and OS (11.8 *vs.* 6.9 months; HR =0.51; 95% CI: 0.41–0.62). In addition, SG significantly improved ORR (35% *vs.* 5%) and prolonged the median duration of response (DoR) (6.3 *vs.* 3.6 months; HR =0.39; 95% CI: 0.14–1.07) regardless of Trop-2 expression status and BRCA mutations (19). Therefore, routine Trop-2 detection is not recommended in the NCCN guidelines (38). Due to its good efficacy, SG has been recommended as the preferred second-line treatment for advanced TNBC by the 2021 ESMO guidelines for metastatic breast cancer (34), the 2022 National Committee on Computer Network (NCCN) breast cancer guidelines (38), the American Society of Clinical Oncology (ASCO) guidelines on chemotherapy and targeted therapy for advanced HER2-negative breast cancer guidelines, and the 6th International Consensus Conference for ABC (ABC6) (54).

Notably, patients in the ASCENT study had received an average of 4 lines of treatment and patients with DFI <12 months were enrolled to receive SG after receiving 100% of systemic therapy for the advanced disease. It is expected that SG treatment may achieve better benefits in patients who have received standard second-line treatment and have a progression-free interval of <12 months.

Summary and prospects

TNBC is a unique subtype of breast cancer, and the currently available treatments do not meet the survival needs of patients. Refractory mTNBC is highly heterogeneous and can easily develop drug resistance. There is no effective treatment for patients with DFI ≤12 months and who show chemotherapy resistance. However, a growing number of studies are still devoted to exploring potentially effective treatment strategies for refractory mTNBC. Both immunotherapy and PARP inhibitors have been investigated in the first-line settings. For immunotherapy, however, results from relevant research were contradictory, biomarker testing is technically unsatisfactory, and the specific patients that may benefit from immunotherapy remain unclear. PARP inhibitors have brought certain PFS benefits but

failed to improve the OS. In addition, only a limited patient population may benefit from PARP inhibitors. Indeed, considerable number of patients cannot tolerate first-line immunotherapy combined with chemotherapy or PARP inhibitors, and the dose needs to be adjusted or reduced. Novel ADCs have shown impressive response rates and PFS benefits as monotherapy or combination therapy in treating mTNBC. SG has shown 6-month OS benefits in the second- and higher-line treatment of refractory mTNBC, with good safety profile. Thus, SG may become the first-line treatment of choice for mTNBC patients with DFI ≤12 months, those who are intolerant to first-line treatment, and/or patients over 65 years old. Besides, relevant literature have shown a certain relationship between the activation of PI3K/AKT pathway and drug resistance of refractory breast cancer. Surprisingly, PI3K inhibitors and AKT inhibitors are currently in phase II clinical trials, which are expected to identify specific beneficiaries in the future. Of note, there is a limitation that cannot be ignored. Although the clinical studies we discussed on refractory mTNBC were derived from multiple phase III clinical trials, this particular population was only a small subgroup, rather than the main subjects of clinical studies, and the analysis results were not convincing enough. Therefore, prospective and large-scale studies on first-line treatment with novel strategies are warranted to further determine the optimal treatment options for refractory mTNBC.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3434/coif). The authors have no 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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