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REVIEW

A BRIEF OVERVIEW OF SEVERAL RECENT ADVANCEMENTS OF TARGETED-THERAPIES AND ANTIBODY-CONJUGATE DRUGS FOR ADVANCED TRIPLE-NEGATIVE BREAST CANCER

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ABSTRACT: Breast cancer (BC) is among the most prevalent and aggressive cancers affecting women. One of the main subtypes of BC, triple-negative breast cancer (TNBC), is considered the most aggressive and it is associated with high mortality, poor prognosis, and early and frequent recurrence, especially in premenopausal women. Unlike other subtypes, hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) positive, TNBC does not have specific cellular receptor markers, which would favor response targeted treatments. For this reason, the conventional standard-of-care (SOC) for early onset TNBC consists of neoadjuvant/adjuvant chemotherapy, alone or in combination with surgery and/or radiotherapy despite its toxic and off-target side effects. In recent years considerable efforts have been made to identify specific predictive biomarkers for TNBC to open a window for more targeted and precise therapy to improve overall survival and quality of life. Along with immunotherapy immune checkpoint inhibitors, targeted-therapies with poly (ADP-ribose) polymerase (PARP) inhibitors and mammalian target of rapamycin (mTOR) inhibitors have emerged and show promising results. One of the most recent targeted therapies approved by the FDA and EMA is an antibody-conjugate drug (ACD or ADC) called sacituzumab govitecan (SG) (Trodelvy). The results of clinical trials point to Trodelvy as a potential novel targeted therapy for TNBC.

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Impact statement: Recent advancements in drug development have led to an expanded list of FDA and EMA approved drugs against triple-negative breast cancer.

Key words: *antibody-drug conjugate (ADC); breast cancer; triple-negative breast cancer (TNBC); sacituzumab govitecan (SG), targeted-therapy.*

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INTRODUCTION

Breast cancer (BC) is a genetically and clinically heterogeneous disease with different biological, clinical, and molecular characteristics (1). Molecular classifications divide breast cancer into six sub-groups: luminal A, luminal B, HER-2, basal, normal breast like and claudin-low (2). According to immunohistochemistry (IHC) or a combination of IHC and microarray expression methods (gene signatures), there are three main subtypes of BC: Hormone receptor positive – estrogen receptor (ER+) or progesterone receptor (PR+), human epidermal growth factor receptor 2 (HER2) positive, and triple-negative (low or absence of ER, PR, and HER2 amplification) (3).

More recent data on molecular classification of BC indicate prognostic associations which include intrinsic subtypes, integrative cluster subtypes, triple-negative sub-classification and mutation-based profiling (4). Triple-negative breast cancer (TNBC) accounts for 15-20% of all invasive breast cancers (5). Among the subtypes, TNBC is associated with high mortality, early and frequent recurrence and poor treatment response. Unfortunately, TNBC cases in premenopausal women and in women of African descent are more frequent compared to other subtypes (6). Additionally, there is a significant overlap of the *BRCA* (BReast CAncer) gene,

BRCA-associated TNBC phenotypes which may further contribute to a poor prognosis (7). However, it is important to mention that not all patients with TNBC harbor *BRCA* mutations.

Lehmann *et al*. (8) genetically profiled 587 TNBC patient tumor samples identifying different groups: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM) and luminal androgen receptor (LAR) (8). Their study determined the expression of cell-cycle regulating and specific DNA repair-related genes, abnormal activation of signaling pathways involved in cell migration, extracellular matrix-receptor interactions, and differentiation in order to subdivide the samples into various subtypes (8). Through the genomic classification of TNBC, there may be gradual advancements to more precise treatments and therapeutic targeting based on the specific subclassifications.

The latest clinical trials are mainly focusing on testing the efficacy of antibody-drug conjugates (ADCs). ADCs are biopharmaceutical drugs composed of highly selective monoclonal antibodies (mAb), a cytotoxic drug, and a chemical linker (see **Figure 1**). The mAbs are designed for tumor-associated antigens expressed at lower levels in normal (healthy) cells (9, 10). The cytotoxic drug will induce targeted cell death whereas the chemical linker is processed with the release of the cytotoxic agent in target cells. The first successful ADC administered ina clinical trials was used in patients with advanced metastatic carcinoma, colorectal and ovarian cancers in 1983 (11). Almost four decades later, after numerous clinical trials, ADCs are emerging as a promising targeted therapy for cancer (9).

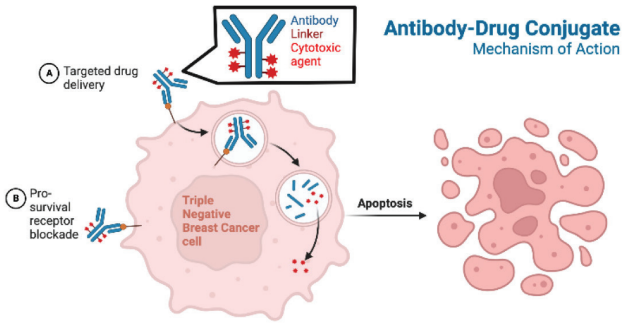

Figure 1. *Graphic represantiation of an antibody-drug conjugate (ADC) mechanism of action an antibody-drug conjugate (ADC) is composed of three components: monoclonal antibody (mAb), cytotoxic agent/drug, and a linker. The antibody will recognize a specific antigen target primarily expressed on the surface of the cancerous cells at higher levels compared to normal (healthy) cells. In this way, delivery is efficient and precise, reducing toxity to normal cells. An example of and ADC used in clinical trials in TNBC is Sacituzumab govitacan (Trodelvy). The antibody is designer to revognize the surface expression of Trop-2 and is connected to chemotherapeutic SN-38. Adapted from "Antibody-Drug Conjugate Mechanism of Action," by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates.*

STANDARD-OF-CARE FOR EARLY ONSET TRIPLE-NEGATIVE BREAST CANCER

Due to the molecular signatures of TNBC, patients do not benefit from therapies designed to target hormone receptors or HER2 (7). The conventional standard-of-care (SOC) for early onset TNBC, as is the case with other malignancies, consists of neoadjuvant/adjuvant chemotherapy, alone or in combination with surgery and/or radiotherapy (12). Neoadjuvant therapy has proven advantageous for early-stage TNBC based on the results of various trials including KEYNOTE-172 Phase 1b (NCT02622074), I-SPY2 Phase II (NCT01042379), KEYNOTE-522 Phase III (NCT03036488), and NeoTRIPaPDL1 Phase III (NCT02620280) which explored the effects of neoadjuvant chemotherapy with or without pembrolizumab or atezolizumab, immune checkpoint inhibitors that bind to protein PD-1 or PD-L1, respectively (52, 53, 57, 40).

In addition to the cytotoxic chemotherapy agents, platinum agents, which interfere with DNA repair mechanisms, and the use of antimetabolite adjuvant capecitabine, which inhibits DNA and RNA synthesis, have proven to be advantageous for the treatment of TNBC (15, 16). The role of the antimetabolite oral prodrug, capecitabine, has been tested in the adjuvant setting for early and metastatic BC (62). Several randomized controlled trials (RCTs), such as the FinXX trial, investigated the role of capecitabine standard adjuvant or neoadjuvant therapies in combination with docetaxel, epirubicin and cyclophosphamide and these trials demonstrated no clinical benefits (63). The CREATE-X trial evaluated adjuvant capecitabine in patients with HER2-negative BC who had not achieved a pathological complete response (pCR) after standard neoadjuvant chemotherapy (64). Both disease-free survival and overall survival were significantly improved in the capecitabine group, and the effect was more prominent in the subgroup of patients with TNBC (62, 64).

A downside to these agents are the off-target effects resulting in toxicity and severe side effects lowering quality of life for the individual patient (17). A way to manage the off-target effects is through surgical excision, a method to locally control the tumor; however, not all patients can

be candidates for surgical removal. Furthermore, surgery does not eliminate the possibility of future local or regional recurrence for TNBC (13).

Along with surgery and chemotherapy, radiation therapy is considered a SOC for early onset TNBC. However, similar to the former, the latter presents the drawback of off-target effects. To avoid major side effects and irritation to normal tissues, radiation doses are carefully determined by the radiotherapist or radiation oncologist (18). Radiation administered on the chest wall, nodal and non-nodal irradiation after mastectomy or breast-conserving surgery (BCS) in TNBC benefits patients and improve survival (19). On the other hand, partial-breast radiation therapy for TNBC is not beneficial (20). Furthermore, a study conducted by Wang *et al*. (2019) investigated the benefits of BCS in combination with adjuvant radiation therapy and concluded that for early staged TNBC patients there was a better prognosis with BCS and radiation rather than mastectomy alone (51). There is currently no SOC chemotherapy regimen for patients with relapsed/refractory TNBC (40). Patients with advanced TNBC are treated with anti-metabolites capecitabine and gemcitabine, non-taxane microtubule inhibitor eribulin, and DNA cross-linker platinums (40). These available treatments for advanced TNBC are not SOC and research is being conducted to develop new treatment options for patients, especially if surgery is not an option (40).

THE NEED FOR TARGETED THERAPIES FOR EARLY AND ADVANCED TNBC

In contrast to hormone receptor (ER/PR)-positive and HER2-positive breast cancers, TNBC does not respond to hormonal or anti-HER2 monoclonal antibody trastuzumab-based targeted therapies (21). For this reason, there is great effort aiming at developing targeted therapies specific for TNBC. In response to this unmet clinical need, the U.S. Food and Drug Administration (FDA), after numerous clinical trials, has approved several targeted therapies. Nonetheless, there is still an urgent demand to develop and test additional targeted therapies. Such targeted therapeutic drugs based on the specific TNBC subtype include PARP inhibitors, genotoxic agents for the BL1 subtype, mTOR inhibitors and growth factor inhibitors (lapatinib, gefitinib, and cetuximab) for the BL2 and M subtypes, phosphoinositide-3 kinase (PI3K) inhibitors, Src antagonists or antiangiogenic drugs for the MSL subtype, immune checkpoint inhibitors for the IM subtype, or anti-androgen receptor (AR) therapy for the LAR subtype (23). Continued research is being conducted to better characterize the molecular signature of TNBC and identify novel targeted therapies based on gene expression profiles.

TARGETED THERAPIES AND IMMUNOTHERAPIES

PARP inhibitors, mTOR inhibitors, immune checkpoint inhibitors

Through sophisticated analytical technologies in recent years researchers have acquired insight into different possible molecular biomarkers and targets for TNBC treatment and therapies. The targeted therapies that have emerged in recent years are promising. Despite significant efforts to find novel molecular biomarkers, only a few potentials have been identified such as noncoding RNAs (ncRNA), microRNAs (miRNA) and long noncoding RNAs (lncRNAs) (24). There is a relevant lack of predictive biomarkers. However, *BRCA1* and *BRCA2* mutations have been beneficial markers for targeted therapy. These genes encode for proteins involved in regulating cell growth and division, aiding in suppressing tumor growth through homologous recombination (HR) repair pathway. Approximately 10-30% of TNBC patients have a *BRCA* germline (*BRCA*g) mutation (25). BRCA1 and BRCA2-deficient tumors exhibit impaired homologous recombination repair (HRR) and synthetic lethality with PARP inhibitors (26).

PARP1 is a chromatin-associated enzyme involved in cell proliferation, DNA repair, maintenance of genome stability and pro-inflammatory signals while PARP2 regulates DNA damage response (28). Thus, PARP inhibitors target underlying defects in DNA repair causing a block in cancer cell division (29). The limitation of this therapy is that PARP inhibitors are often associated with resistance developed by tumor cells (30). Additionally, PARP inhibitors can only be used in specific patient subsets defined by their DNA repair biomarker signatures (28).

Numerous studies have been conducted utilizing PARP inhibitors on TNBC with *BRCA* mutations, and the results indicate promising response and outcome for patients (27). In 2018, the FDA approved olaparib and talazoparib to treat advanced-stage HER2-negative BC in patients with *BRCA1* or *BRCA2* mutation (*BRCA*g mutation) (40). The results from OlympiAD Phase III (NCT02000622) and EMBRACA

Phase III (NCT01945775) lead to the approval of olaparib and talazoparib, respectively (54-56). These PARP inhibitors are effective and improve patient survival compared to other physician choice standard chemotherapeutic agents, such as capecitabine, vinorelbine, eribulin, or gemcitabine (40).

Several other signaling pathways have been analyzed and tested for TNBC treatment. The PI3K/protein kinase B (AKT) signaling pathway, which is involved in angiogenesis, tumor proliferation and inhibition of apoptosis, is an important target for BC treatments. Due to the potential of the PI3K/AKT pathway to cause resistance to immunotherapy and chemotherapy, various inhibitors targeting the pathway components have been evaluated in multiple clinical trials (40). For patients with advanced TNBC, various PI3K/AKT inhibitors have been studied in combination with other therapies such as paclitaxel and immunotherapies. The EPIK-B3 Phase III trial (NCT04251533) plans to assess the effect of alpelisib, an oral PI3K inhibitor, with nab-paclitaxel (40). In LOTUS Phase II trial, ipatasertib, a pan-AKT inhibitor, was assessed with first-line paclitaxel and improved Progression Free Survival (PFS) in locally advanced or metastatic TNBC (60). The IPATunity130 Phase III trial (NCT03337724) is assessing the efficacy of ipatasertib + paclitaxel for phosphatase and tensin homolog (PTEN)/PI3K/AKT-altered advanced TNBC or HR+, HER2-negative breast cancers, to corroborate the results from the LOTUS trial (61). When investigating the possible role of the PI3K pathway and the mTOR pathway for TNBC treatment, it remains unclear if the inhibition of these pathways has a significant effect on tumor growth and for this reason must be further investigated (31). In recent years, a combination of the mTOR inhibitor, Everolimus, with tyrosine kinase inhibitors (TKIs) has been effective for treatment of TNBC carrying activating mutations of the PI3K (32). Additional clinically investigated drugs include stimulator of interferon genes (STING) agonists involved in activation of the transmembrane protein, STING, utilized in the innate immune response, immune checkpoint inhibitor, Maternal Embryonic Leucine Zipper Kinase (MELK) inhibitors, which inhibit the mitotically regulated kinase MELK overexpressed in TNBC, and many other agents based on the genetic profile of the individual TNBC patient (33, 34). A characteristic of TNBC that may prove beneficial for treatment is the fact that TNBC cells are more immunogenic compared to the other BC subtypes (35). Since TNBC cells may exhibit high levels of programmed cell death-ligand 1 (PD-L1), a regulatory molecule expressed in T cells with immunoregulatory function, immunotherapies have been developed, such as atezolizumab and pembrolizumab, anti-PD-L1 antibodies (36-38). Based on the IMpassion130 trial (NCT02425891), the immunochemotherapy approach of utilizing atezolizumab in combination with nanoparticle albumin-bound (nab)-paclitaxel has become SOC for patients with PD-L1^{+}, unresectable, locally advanced, or metastatic TNBC (40). These immune checkpoint inhibitors (ICIs) are quite promising novel therapies specifically for TNBC leading to durable tumor remission and prolonged anti-tumor immunity (39). Despite the development of novel agents for specific subtypes of TNBC, only a fraction of patients responds to immune checkpoint or PARP inhibitors and often develop resistance and relapse (40). For this reason, clinical studies have been conducted and are underway to further assess the synergy and crosstalk that exists between PARP inhibition and the PD-L1/PD-1 immune checkpoints (58). Such clinical trials include MEDIOLA Phase I/II trial (NCT02734004) in which the combination of olaparib and durvalumab, an immunotherapeutic that binds to PD-L1, is studied in patients with *BRCA*g mutation metastatic BC (59) as well as the DORA Phase II trial (NCT03167619) evaluating olaparib with or without durvalumab in patients with advanced TNBC (40).

Due to the limited range of scope of current immunotherapy targeted treatments, further investigation is needed in the networks of DNA damage response (DDR), cell surface or intracellular receptors, cell surface markers, and signaling pathways for selective drug delivery and ADCs. This need is widely recognized and has contributed to the development and ultimate approval of therapeutic drugs for TNBC. However, the list of approved FDA drugs for treating TNBC is limited in number (**Table 1**).

CLINICAL TRIALS FOR EMERGING TARGETED THERAPY

In recent years, several clinical trials have been conducted to study the effects of numerous ADC as potential BC targeted therapies. The results of ADC clinical trials have been presented at major oncology conferences, such as ESMO and ASCO. Although most ADC clinical trials have focused on the subtype HER2-positive breast cancer, there is growing interest in investigating the potential efficacy of ADCs for treating TNBC.

Table 1. *Table of Therapeutic Drugs for Triple-Negative Breast Cancer (TNBC) as of September 2021. Drugs that have been approved by the FDA for patients with TNBC include Paclitaxel, Doxorubicin, Ixabepilone, Pembrolizumab, Atezolizumab, and Trodelvy.*

DRUG NAME	TARGET	DRUG TYPE	DOSAGE FORM	FDA APPROVAL DATE
Liposomal Doxorubicin (Doxil)	Anthracycline – Top2, Topoisomerase II DNA intercalation	Chemical	IV infusion	February 1999
Paclitaxel protein-bound particles for injectable suspension (Abraxane)	Taxane – microtubule target	Chemical	IV infusion	January 2005
Ixabepilone (Ixempra)	Taxane – microtubule target	Chemical	IV infusion	October 2007
Atezolizumab (Tecentriq) in combination with nab-paclitaxel (Abraxane)	PD-L1	Monoclonal antibody	IV infusion	March 2019
Pembrolizumab (Keytruda) in combination with chemotherapy	PD-1	Monoclonal antibody	IV infusion	November 2020
Sacituzumab govitecan-hziy (Trodelvy)	Trop2, Topoisomerase I	ADC	IV infusion	April 2020

ADC: antibody-drug conjugate; PARP: poly (ADP-ribose) polymerase; PD-1: programmed cell death protein 1; Trop2: trophoblast cell surface antigen 2; PD-L1: programmed cell death ligand 1.
Source: Mandapati 2022 "Triple negative breast cancer: approved treatment options and their mechanisms of action" and FDA.gov drugsatfda. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approved-drugs-breast-cancer.

Antibody-drug conjugate: trastuzumab deruxetcan

Another subclassification of BC is HER2-low BC. HER2-low advanced BC is characterized by low levels of HER2 receptor protein and may include both hormone receptor-positive and hormone receptor-negative breast cancers (15). Promising results have emerged from the clinical trial DESTINY-Breast04 (NCT03734029) testing the ADC, trastuzumab deruxetcan, and its effects on HER2-low advanced BC (15). Patients with HER2-low metastatic BC who were treated with trastuzumab deruxetcan resulted in longer progression-free and overall survival compared to the physician's choice of chemotherapy (15). Of the 557 patients, 63 (11.3%) were hormone receptor-negative, a small proportion of patients. The median progression-free survival for the hormone receptor-negative cohort was 8.5 months (95% CI, 4.3 to 11.7) in the trastuzumab deruxetcan group and 2.9 months (95% CI, 1.4 to 5.1) in the physician's choice group while the median overall survival was 18.2 months (95% CI, 13.6 to not evaluable) in the trastuzumab deruxetcan group and 8.3 months (95% CI 5.6 to 20.6) in the physician's choice group (15). These results not only point to a possible targeted therapy for HER2-low advanced BC but may provide further evidence for a tailored treatment for TNBC.

Antibody-drug conjugate: sacituzumab govitecan

A handful of ADC has been approved by the European Medicine Agency (EMA) and the FDA. The ADC called Sacituzumab govitecan (SG) (Trodelvy) was approved by the FDA in April 2021 and by EMA in November 2021 (41, 42). SG consists of a monoclonal antibody designed against human trophoblast cell-surface antigen 2 (TROP-2) linked to a cytotoxic drug called SN-38. TROP-2 is a protein expressed on the surface of TNBC cells as well as other epithelial and metastatic breast cancers. SN-38, an active metabolite of irinotecan, is a topoisomerase inhibitor, which blocks the enzyme topoisomerase I, involved in copying DNA of the cell (42). The mechanism of this ADC action is initially mediated by anti-TROP-2 monoclonal antibody binding to the TROP-2 protein on the breast cancer cell surface. Then, the cytotoxic agent, SN-38, is delivered into the cancerous cells where it becomes active and inhibits cancer cells proliferation (43). Thus, SG is considered a promising new targeted therapy for locally advanced or metastatic TNBC (mTNBC) (41). Several clinical trials have been conducted since the development of ADC, SG (**Table 2**). A phase I/II single group study was done to evaluate the activity of SG in a cohort of 108 TNBC patients who had undergone two prior treatment methods (NCT01631552). The

drug was administered intravenously with a concentration of 10 mg/kg on days 1 and 8 of a 21-day cycle. The Overall Response Rate (ORR) was 33% and the median duration of response (DOR) was 7.7 months. The median progression-free survival (PFS) was 5.5 months, and the median overall survival (OS) was 13 months. The confirmatory ASCENT Phase III study of a cohort of 529 patients evaluated SG compared to physician's choice of chemotherapy, *e.g.*, eribulin, gemcitabine, capecitabine or vinorelbine. The ASCENT Phase III study showed great promise and was granted accelerated approval by the FDA based on the results of the IMMU-132-01 Phase II clinical trial treatment of adult mTNBC. Thus, SG is the first ADC approved by the FDA specifically for relapsed or refractory mTNBC (40). However, this targeted therapy has some relevant side effects, including anemia, neutropenia, and gastroenteritis (44).

DISCUSSION

The five pillars of cancer treatment consist of surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. While great progress has been made in certain BC subtypes to have more than one option as standard-of-care (SOC) therapies, TNBC still remains treated with SOC consisting of neoadjuvant/adjuvant chemotherapy alone or in combination with surgery and/or radiation. Thus, there is urgent need to move beyond these treatments and uncover possible predictive biomarkers or immune checkpoint markers that could help in developing novel targeted therapies and immunotherapies for TNBC patients.

The technology and principle of ADC is very revolutionary since it links a monoclonal antibody to a cytotoxic agent, thereby allowing for precise targeted treatment against tumor cells. Emerging evidence shows that SG is one of the most effective ADCs for TNBC (43). Although SG has been approved by EMA and FDA for metastatic TNBC, further investigations must be conducted with the goal of comparing this ADC with multiple standard-of-care chemotherapies (43).

CONCLUSIONS AND FUTURE DIRECTION

In conclusion, studies of heterogeneity and subtypes of TNBC have opened the doors to many possible therapeutics that will one day overtake the SOC of neoadjuvant/adjuvant chemotherapy, alone or in combination with surgery and/or radiotherapy. Taxane- and anthracycline-based combination chemotherapy remains the standard-of-care for early-stage TNBC while advanced stage usually consists of chemotherapy, targeted therapy and immunotherapy (14). The treatment options available for patients are dictated by the stage of the tumor, local or metastasized (7). However, the estimated five-year TNBC survival rates greatly decrease depending on the status of metastasis. The five-year survival rate for a patient with localized TNBC is 91.3%. For patients with regional spread to lymph nodes, the five-year survival is 65.8% whereas for patients with distant metastasis to bones, liver, or lungs is 12.0%, as shown in **Table 3** (Surveillance, Epidemiology, and End Results (SEER) 2020 (46)). These estimates establish a baseline for the likelihood that a treatment will be successful. When comparing the five-year relative survival percentages in **Table 3**, it is evident that TNBC, labeled ('HR-/HER2-'), has the lowest survival percentage compared to all other subtypes. There are many factors contributing to this outcome including stage at diagnosis, environmental factors, age, race, standard-of-care, and availability of treatments. For this reason, the development of pharmaceutical drugs aimed at targeting TNBC is imperative.

With the recent EMA and FDA approval of SG, the potential future treatments for TNBC appear very promising. With the use of this ADC, there is limited off-target toxicity to normal cells since the monoclonal antibody is acting against an antigen or receptor expressed at low levels on the healthy cells, reducing therefore the level of toxicity usually associated with chemotherapy. Since the antibody portion of the ADC can be modified for specific cell surface antigens or receptors, this targeted therapy can be widely adapted (47). Thus, further investigation is needed to identify potential cell surface antigens and receptors specific to TNBC.

The future aims for breast cancer research and pharmaceutical drug development, specifically with regards to TNBC, should be centered on the understanding of the molecular complexity of the disease, improving the efficacy of current treatments, discovering reliable predictive biomarkers, determining mechanisms and pathways to overcome resistance to treatments and continuing to develop and test novel targeted treatments to improve survival rate and quality of life for patients.

Table 2. *Partial list of Clinical Trials for Sacituzumab Govitecan (SG) in Triple Negative Breast Cancer taken from clinicaltrials.gov as of September 2022.*

STATUS	STUDY TITLE	CONDITIONS	INTERVENTIONS
Recruiting	Trilaciclib in patients receiving Sacituzumab Govitecan-hziy for Triple Negative Breast Cancer	Triple negative breast cancer	Drug: Trilaciclib Drug: Sacituzumab Govitecan-hziy
Recruiting	Study of Sacituzumab Govitecan-hziy (SG) in Japanese Participants with advanced solid tumors or Triple-negative Breast Cancer	Advanced Solid tumors or Triple-negative Breast Cancer	Drug: Sacituzumab Govitecan-hziy
Recruiting	Study of Sacituzumab Govitecan-hziy versus treatment of Physician's choice in patients with previously untreated metastatic Triple-Negative Breast Cancer	Triple Negative Breast Cancer PD-L1 Negative	Drug: Sacituzumab Govitecan-hziy Drug: Paclitaxel Drug: nab-Paclitaxel Drug: Gemcitabine Drug: Carboplatin
Active, not recruiting	Sacituzumab Govitecan in Chinese Patients with mTNBC of at least 2 prior treatments	Metastatic Triple-negative Breast Cancer	Biological: Sacituzumab Govitecan
Recruiting	Study of Sacituzumab Govitecan-hziy and Pembrolizumab versus treatment of Physician's Choice and Pembrolizumab in Patients with Previously untreated, locally advanced inoperable or metastatic Triple-Negative Breast Cancer	Triple Negative Breast Cancer PD-L1 positive	Drug: Sacituzumab Govitecan-hziy Drug: Pembrolizumab Drug: Paclitaxel Drug: nab-Paclitaxel Drug: Gemcitabine Drug: Carboplatin
Not recruiting	Preventive stRategy for IMMU132-relatED AEs in TNBC	Triple Negative Breast Cancer Breast Cancer	Drug: Sacituzumab Govitecan Drug: Loperamide Drug: Granulocyte Colony-Stimulating Factor
Recruiting	Sacituzumab Govitecan +/- Pembrolizumab in metastatic TNBC	Breast Cancer Triple Negative Breast Cancer PD-L1 Negative	Drug: Sacituzumab Govitecan Drug: Pembrolizumab
Active, not recruiting	A study of Sacituzumab with chemoimmunotherapy to treat advanced Triple-Negative Breast Cancer after prior therapies	Advanced Triple Negative Breast Cancer	Biological: N-803 Biological: PD-L1 t-haNK Drug: Sacituzumab Govitecan-hizy Drug: Cyclophosphamide
Not yet recruiting	Safety and efficacy analysis of an antibody associated with a chemotherapy for Patients with a Triple Negative Metastatic Breast Cancer	Triple Negative Breast Cancer Metastatic Breast Cancer	Drug: Sacituzumab Govitecan
Recruiting	Sacituzumab Govitecan in Primary HER2-negative Breast Cancer	HER2-negative Breast Cancer Triple Negative Breast Cancer	Drug: Capecitabine Drug: Carboplatin Drug: Cisplatin Drug: Sacituzumab Govitecan
Completed Has results	Trial of Sacituzumab Govitecan inn Participants with refractory/relapsed metastatic triple-negative breast cancer (TNBC)	Breast Cancer	Drug: Sacituzumab Govitecan Drug: Eribulin Drug: Capecitabine Drug: Gemcitabine Drug: Vinorelbine

STATUS	STUDY TITLE	CONDITIONS	INTERVENTIONS
Active, not recruiting	Sacituzumab Govitecan in TNBC	Invasive Breast Cancer Triple Negative Breast Cancer ER-negative Breast Cancer PR-negative breast cancer HER2-negative breast cancer	Drug: Sacituzumab Govitecan Drug: Pembrolizumab
Recruiting	Atezolizumab + Sacituzumab Govitecan to prevent recurrence in TNBC (ASPRIA)	Breast Cancer Triple Negative Breast Cancer Residual Cancer Circulating Tumor DNA	Drug: Atezolizumab Drug: Sacituzumab Govitecan
Recruiting	Study to Evaluate the Safety and Efficacy of Magrolimab Combination Therapy in Adults with unresectable, locally advanced or metastatic triple-negative breast cancer	Triple-Negative Breast Cancer	Biological: Magrolimab Drug: Nab-paclitaxel Drug: Paclitaxel Drug: Sacituzumab Govitecan
Recruiting	Avelumab with Binimetinib, Sacituzumab Govitecan, or Liposomal Doxorubicin in treating patients with Stage IV or unresectable, recurrent triple negative breast cancer	Stage III Breast Cancer Stage IIIA Breast Cancer Stage IIIB Breast Cancer Stage IIIC Breast Cancer Stage IV Breast Cancer Invasive Breast Carcinoma Recurrent Breast Carcinoma Triple-Negative Breast Carcinoma Unresectable Breast Carcinoma	Biological: Anti-OX40 Antibody PF- 04518600 Drug: Avelumab Drug: Binimetinib Biological: Utomilumab Drug: Liposomal Doxorubicin Drug: Sacituzumab Govitecan
Recruiting	A study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations in patients with metastatic or inoperable locally advanced triple-negative breast cancer	Triple Negative Breast Cancer	Drug: Capecitabine Drug: Atezolizumab Drug: Ipatasertib Drug: SGN-LIV1A Drug: Bevacizumab Drug: Chemotherapy (Gemcitabine + Carboplatin or Eribulin) Drug: Selicrelumab Drug: Tocilizumab Drug: Nab-Paclitaxel Drug: Sacituzumab Govitecan
Completed Has results	Study of Sacituzumab Govitecan-hziy (IMMU132) in adults with epithelial cancer	Gastric Adenocarcinoma Small Cell Lung Cancer Carcinoma Breast Stage IV Triple Negative Breast Cancer	Drug: Sacituzumab Govitecan-hziy (SG)

Based on the various filters applied (Female, not yet recruiting, recruiting, enrolled by invitation, completed, clinical trial), there are seventeen clinical trials worldwide which seek or have sought to better understand the function and mechanism of the antibody-drug conjugate (ADC), Sacituzumab govitecan (SG) either in combination with other drugs or alone. There have been two completed clinical trials for SG. These results do not include Scopus.gov clinical trial results, thus eliminating grant clinical trials. Source: clinicaltrials.gov.

Table 3. *5-year relative survival percent, female breast subtypes by SEER.*

SUBTYPE	LOCALIZED	REGIONAL	DISTANT
HR+/HER2-	100.0%	90.1%	31.9%
HR-/HER2-	91.3%	65.8%	12.0%
HR+/HER2+	98.8%	89.3%	46.0%
HR-/HER2+	97.3%	82.8%	38.8%
Unknown	96.1%	76.4%	15.6%
Total	99.1%	86.1%	30.0%

The 5-year survival rate presents the percentage of survival of patients after five years. In this table, TNBC is identified as subtype 'HR-/HER2'. Data was collected over the span of 6 years in women of all ages, races living in the 22 registered areas of the United States (see list below). Table taken from National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER) Program, 2020. Data source: SEER 22 areas (San Francisco, Connecticut, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, Georgia excluding ATL/RG, Idaho, New York, Massachusetts, Illinois, and Texas).

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Conflict of interests

The authors have declared no conflict of interests.

Authors' contributions

SB and AM worked on the conception of the work. SB worked on drafting and revising it critically for important intellectual content. AM provided approval for publication of content. SB and AM agree to be accountable for all aspects of the work.

Availability of data and materials

The data underlying this article are available in the public domain, using various datasets primarily from ClinicalTrials.gov, PubMed, GCO, SEER, U.S. FDA, EMA *etc*.

Ethical approval

N/A.

Publication ethics

Plagiarism

This is a review article and all original studies are cited as appropriate.

Data falsification and fabrication

The contents of the article are original and any overlaps with other articles are by the Authors themselves and appropriately cited.

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