



New Drugs

Breaking barriers in triple negative breast cancer (TNBC) – Unleashing the power of antibody-drug conjugates (ADCs)



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ABSTRACT

Antibody-drug conjugates (ADCs) represent a novel class of molecules composed of a recombinant monoclonal antibody targeted to a specific cell surface antigen, conjugated to a cytotoxic agent through a cleavable or non-cleavable synthetic linker. The rationale behind the development of ADCs is to overcome the limitations of conventional chemotherapy, such as the narrow therapeutic window and the emergence of resistance mechanisms. ADCs had already revolutionized the treatment algorithm of HER2-positive breast cancer. Currently, emergent non-HER2 targeted ADCs are gaining momentum, with special focus on triple-negative disease therapeutic landscape. Sacituzumab govitecan (SG) is an ADC consisting of a humanized monoclonal antibody hRS7 targeting *trophoblast cell surface antigen 2* (Trop2), linked to the topoisomerase I inhibitor SN-38 by a hydrolysable linker. It currently stands as the only non-HER2 targeted ADC that already received approval for the treatment of unresectable locally advanced or metastatic triple negative breast cancer (TNBC) in patients who had received two or more prior systemic therapies, with at least one for advanced disease. The purpose of these review is to analyze the available evidence regarding ADCs in TNBC, alongside with providing an overview on the ongoing and future research horizons in this field.

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Introduction

Triple-negative breast cancer (TNBC) is defined by the lack of expression of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) on tumor cells. It accounts for 15–20 % of newly diagnosed breast cancer (BC) cases and is distinguished by the least favorable prognosis among BC subtypes, along with a long-standing paucity of effective therapeutic options.[1,2] In the past few years, research breakthroughs have brought to light the significance of the TNBC microenvironment heterogeneity, revealing a dynamic relationship with cancer cell features and emphasizing the need for a more comprehensive view of TNBC as an ecosystem. This newfound understanding of TNBC's biology, coupled with the development of novel drugs beyond traditional chemotherapy (CT) - including poly-ADP ribose polymerase inhibitors (PARPis), antibody-drug conjugates (ADCs) and immune-checkpoint inhibitors (ICIs) - is revolutionizing the therapeutic landscape and offering new opportunities for both early-stage and advanced TNBC patients.[3] The aim of this review is to provide a comprehensive overview of the current evidence concerning ADCs in TNBC, exploring their potential as promising therapeutic agents in the management of this challenging BC subtype.

Antibody-drug conjugates

ADCs represent a novel class of molecules composed of a recombinant monoclonal antibody (MoAb) targeted to a specific cell surface antigen (sAg), conjugated to a cytotoxic agent (payload) through a cleavable or non-cleavable synthetic linker, with a defined drug-antibody-ratio (DAR). The rationale behind the development of ADCs is to overcome the limitations of conventional CT, such as the narrow therapeutic window and the emergence of resistance mechanisms. The primary mechanism of action of ADCs is known as the 'trojan horse' strategy, where the MoAb selectively delivers the cytotoxic agent to cells expressing the sAg, thereby reducing the risk of off-target systemic toxicities. Additionally, some ADCs exhibit a "by-stander effect", where the released payload can traverse back through the permeable membrane and act on surrounding tumor cells that lack the sAg. This feature enables the retention of activity even in tumors with heterogeneous target sAg expression. Moreover, the MoAb itself contributes to the antibody-dependent cellular cytotoxicity (ADCC). The pharmacokinetics and pharmacodynamics properties of ADCs depend on the characteristics of each component. The ideal ADC should consist of a MoAb with high binding affinity for the sAg and minimal immunogenicity. The linker should remain stable in the bloodstream and be easily cleavable inside the cells, as the free form of the payload is highly toxic. The sAg should be selected based on homogeneous expression among tumor cells and minimal representation in healthy tissues. The continuous pursuit of increasingly efficient ADCs remains an ongoing challenge in the field of oncology.[4,5] The potential of these innovative molecules to improve therapeutic outcomes while mitigating adverse effects has ignited substantial interest in their development and clinical application.

Antibody-drug conjugates in breast cancer

Currently, three ADCs are available for the treatment of BC. Trastuzumab emtansine (T-DM1) is an ADC composed of the anti-HER2 MoAb trastuzumab linked to the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor, with a DAR of 3.5.[4,6] T-DM1 is indicated for patients with advanced HER2-positive (HER2 +) BC and as post-neoadjuvant treatment for HER2 + early-stage BC with residual disease after neoadjuvant therapy based on trastuzumab and taxanes.[6–8].

Trastuzumab deruxtecan (T-DXd) represents a new generation ADC consisting of a humanized HER2-targeted MoAb and a topoisomerase I inhibitor conjugated by a tetrapeptidic cleavable linker, with a DAR of 8.[9] T-DXd is currently approved for advanced HER2 + BC after one or

more prior anti-HER2 regimens. It has shown promising results as a treatment for HER2-low BC after prior CT in the metastatic setting or beyond recurrence during or within 6 months (mo) of completing adjuvant CT, owing to its by-stander effect [9–11].

Sacituzumab govitecan (SG) is another ADC that has gained significant prominence in the therapeutic landscape of BC. Its composition and role will be discussed in detail in the following sections.

Focus on non-HER2 targeted antibody-drug conjugates: Sacituzumab govitecan

Biochemical structure

Trophoblast surface antigen 2 (Trop2), also known as tumor-associated calcium signal transducer 2 (TACSTD2), is a cell surface glycoprotein that acts as a transmembrane transducer of intracellular calcium signals. The primary structure of the Trop2 protein is a 36 kDa polypeptide consisting of 323 amino acids, a single transmembrane surface glycoprotein.[12] Trop2 is composed of hydrophobic precursor peptide (AA 1–26), extracellular domain (AA 27–274), transmembrane domain (AA 275–297) and cytoplasmic tail (AA 298–323). The N-terminus of the Trop2 protein is the extracellular domain (TROP2EC), which is linked to the intracellular short tail (TROP2IC) by a unidirectional transmembrane helix (TM), thereby being immobilized on the membrane.[13] This protein seems to be highly conserved in species. The cytoplasmic tail of this molecule contains a highly conserved phosphatidylinositol 4, 5-bisphosphate (PIP2) binding sequence, suggesting that PIP2 plays an important role in signal transduction of Trop2. In addition to the PIP2 binding motif, it also contains conserved tyrosine and serine phosphorylation sites. Mutation of the serine residue at position 303 abolished the ability of Trop2 to stimulate tumor growth. Phosphorylation of this residue is the responsibility of protein kinase C (PKC) [13].

Trop2 is differentially expressed in many cancers. It signals cells for self-renewal, proliferation, invasion, and survival. It has stem cell-like qualities. Trop2 is expressed in many normal tissues, though in contrast, it is overexpressed in many cancers where it acquires prognostic significance.[12,14,15] Several ligands have been proposed that interact with Trop2. Trop2 signals the cells via different pathways and it is transcriptionally regulated by a complex network of several transcription factors.[14] Trop2 increases the expression of the proliferation marker Ki-67 and causes calcium ion Ca^{2+} to be mobilized from internal stores.[14] Trop2 expression downregulates p27 (cyclin-dependent kinase inhibitor 1B), activates *mitogen-activated protein kinase* (MAPK) signaling, which increases levels of phosphorylated *extracellular signal-regulated kinase* (ERK) 1 and 2. MAPK signaling and cell cycle progression can be further stimulated by Ca^{2+} . Trop2 increases levels of cyclin D1 and cyclin E, which help mediate ERK1/2 cell cycle progression (an increased percentage of cells enter the S phase). ERK signaling leads to induction of the AP-1 transcription factor.[14] It is a central regulator of tumor-associated target genes during carcinogenesis. AP-1 causes angiogenesis via *vascular endothelial growth factor* (VEGF), cell proliferation via the cyclins and cyclin-dependent kinases (CDKs), apoptosis via *pro-apoptotic bcl-2* (B-cell lymphoma 2) or Fas ligand (FasL), and causes cell invasion and metastasis via matrix metalloproteinases (MMPs).[14] SG is an ADC consisting of a humanized monoclonal antibody hRS7 targeting Trop2, linked to the topoisomerase I inhibitor SN-38 by a hydrolysable linker.

Pharmacokinetics and pharmacodynamics

After intravenous administration, SG cleared at a faster rate than the hRS7-unconjugated IgG, which was expected based on in vitro data demonstrating that the conjugate releases 50 % of its SN-38 payload every day. The clearance rate for SG was slightly faster than that measured by total SN-38, which likely reflects the methodological inefficiency for detecting SG when the substitution level becomes

markedly decreased (eg, ≤ 2) [16].

SG is internalized in tumor cells and here the linker undergoes hydrolysis at lysosomal acid pH, thus allowing to release SN-38 intracellularly [17,18]. However, the internalization of SG may not be very efficient. In early efforts to establish Trop2 targeting, tumor uptake of the carrier mAb 131I-RS7 was $\sim 7\%$ to 16% of the initial dose/gm in a Trop2 TNBC xenograft - ~ 2 -fold higher than a control 131I-mAb [18]. The spontaneous linker hydrolysis in SG releases a significant amount of the SN-38 cargo, more than with other ADCs - which are generally designed to avert spontaneous drug release. Thus, the antitumor effects of SG are due to a conventional ADC mechanism, a by-stander effect, systemically released SN-38, or a combination thereof [18]. Of note, the exposure, or AUC, of the SN-38 released from SG over a three-week cycle is over 15-fold higher than that from irinotecan at their maximally tolerated doses [18].

SN-38 is mainly metabolized by the liver via the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), a member of a family of enzymes having a role in the detoxification of various endogenous and exogenous substances. UGT1A1 converts SN-38 to the inactive SN-38 glucuronide (SN-38G) form, similarly to irinotecan. With SG, large concentrations of SN-38 are not eliminated rapidly in the intestines but, rather, are excreted more slowly over 3 days. It has been reported that SN-38G levels were more predictive of diarrhea in patients who received irinotecan instead of SN-38, with an AUC for SN-38G of $4.416 \pm 3.816 \mu\text{g/mL/hour}$ and an SN-38G/SN-38 AUC ratio of nearly 10:1 [19]. Most SN-38 in serum is bound to IgG, with median total SN-38 levels in the 10 mg/kg group of 4234 and 1334 ng/mL at 30 min and day 1, respectively, whereas free SN-38 levels were just 95.3 ng/mL (2.3 %) and 56.9 ng/mL (4.5 %) at these same times, respectively [16].

Patients with the UGT1A1 *28/*28 haplotype were somewhat more likely to experience grade (G) ≥ 3 neutropenia than those with the *1/*1 or *1/*28 haplotypes; however, because approximately 40 % of these patients did not experience G ≥ 3 neutropenia, and with approximately 40 % of those with the other haplotypes experiencing G ≥ 3 neutropenia, it is a matter of debate if the management of a neutropenic event is more appropriate than screening for patients who have UGT1A1 mutant types and dose adaptation on the basis of UGT1A1 genotype [16].

Step-by-step approval process

The phase I/II basket trial IMMU-132-01 was the first to evaluate the single-agent activity, safety and tolerability of SG in heavily pretreated patients with advanced cancer of different histologies, including breast, urothelial, lung cancer and others, who had exhausted standard therapeutic options. The dose-escalation phase evaluated SG at the schedules of 18 mg/kg, 12 mg/kg, 10 mg/kg, and 8 mg/kg in 21-day treatment cycles, revealing a reassuring pharmacological profile at doses of 8 and 10 mg/kg. The cohort expansion phase focused on the 10 mg/kg schedule since it demonstrated a doubled overall response rate (ORR) of 22 % compared to 10 % with 8 mg/kg [16,20]. Within the trial, a population of 108 metastatic TNBC patients was included, with a median of 3 prior lines of therapy (ranging from 2 to 10). SG exhibited an ORR of 33.3 %, a clinical benefit rate (CBR) of 45.4 %, a median progression free survival (PFS) of 5.5 months, and a median overall survival (OS) of 13.0 months [20]. Based on these results, in April 2020, the Food and Drug Administration (FDA) granted SG accelerated approval for patients with metastatic TNBC who had previously received at least two lines of treatment in the advanced setting. In the subsequent randomized confirmatory phase III ASCENT trial, SG was compared to therapy of physician choice (TPC), which encompassed eribulin, vinorelbine, capecitabine, or gemcitabine. The trial included patients who had received at least 2 prior lines of treatment and those who progressed within 12 months after the end of (neo)adjuvant therapy. Among the patients, 100 % had previously received taxanes, 82 % had received anthracyclines, 66 % carboplatin, 27 % immune check point inhibitors (ICIs), and 7 % PARPis. The primary endpoint was PFS in patients

without brain metastases (mts), while secondary endpoints included PFS in the intention-to-treat (ITT) population, OS in both populations, ORR, duration of response (DoR), quality of life (QoL), and safety. SG provided a PFS advantage compared to TPC (5.6 vs 1.7 mo, HR: 0.41), and the median OS was prolonged by 5.4 months (12.1 vs 6.7 mo, HR 0.48) in the population without brain mts. The ORR was 35 % with SG and 5 % with TPC [21]. The ASCENT trial was stopped early due to compelling evidence of efficacy, leading to SG's full FDA approval in April 2021 for patients with unresectable locally advanced or metastatic TNBC who had received two or more prior systemic therapies, with at least one for advanced disease. European Medicines Agency (EMA) granted approval in November 2021 with the same indications. Agenzia Italiana del Farmaco (AIFA) approval was obtained in August 2022; it should be noted that patients who received a single line of therapy in the advanced setting must have progressed within 12 months after the end of (neo) adjuvant therapy.

Triple negative breast cancer updated therapeutic algorithm

Until a few years ago, single-agent CT was the standard of care for TNBC, as no identifiable molecular targets were known. However, recent research efforts have focused on achieving a more precise genomic and molecular characterization of TNBC, leading to the identification of novel biomarkers and personalized therapeutic algorithms. First-line systemic treatment is tailored based on the predictive value of tumor Programmed Death-Ligand 1 (PD-L1) expression and germline *Breast Cancer gene (BRCA)* 1 and 2 mutational status.

For PD-L1 positive (PD-L1 +) TNBC, the combination of ICIs with CT represented a paradigm shift [22–24]. Studies such as IMpassion130 demonstrated that the combination of atezolizumab with nab-paclitaxel resulted in a PFS and OS advantage in PD-L1 + population (Ventana SP142 PD-L1 assay). Similarly, pembrolizumab combined with CT showed a survival advantage in tumors with PD-L1 Combined Positive Score (CPS) > 10 (IHC 22C3 pharmDx assay) [25,26]. For patients with germline *BRCA* mutations (gBRCAm), recommended first line treatment options include platinum-based (cisplatin or carboplatin) CT or PARPis if accessible [27,28].

In PD-L1 negative (PD-L1-) and *BRCA* wild type (BRCAwt) TNBC, CT remains the only available option. The choice of the CT regimen depends on factors such as previous neo/adjuvant treatment and relative DFI, patient conditions, comorbidities, and safety profile. Typically, single-agent CT is preferred over combination therapy, as the latter often provides only modest clinical benefit without a survival advantage and increases the risk of toxicities. After progression on first-line therapy and upon exhaustion of the targeted options, the treatment algorithm in later lines relies on sequential single-agent CT, which may offer limited PFS advantage. In this context, SG has already been incorporated into major Oncology Guidelines as a more beneficial treatment option with a favorable safety and tolerability profile [22,23].

Clinical practice insights

Prescribing information

SG is administered at a dose of 10 mg/kg via intravenous infusion once weekly on days 1 and 8 of 21-day schedule, until disease progression or unacceptable toxicity. Determination of Trop2 expression and UGT1A1 mutational status is not required before initiating treatment. An upfront SG dose reduction is not needed if a UGT1A1*28 allele variant is known, but a closer patient monitoring is recommended for both heterozygous and homozygous form. The first infusion requires three hours, while the subsequent infusions could be administered in one or two hours. A post-infusion observation period of at least 30 min is recommended. In the event of an infusion-related reaction, SG administration should be interrupted or slowed down. Permanent discontinuation is necessary if a life-threatening infusion-related reaction occurs.

An antiemetic prophylaxis regimen consisting of two or three drugs (dexamethasone with either a 5-HT3 serotonin receptor antagonist or a neurokinin-1 receptor antagonist) is recommended. Premedication with antipyretics, H1 and H2 histamine receptor blockers, and corticosteroids may be used for patients who have experienced prior infusion reactions [29] [Fig. 1].

Safety and adverse events management

The most common toxicities of any grade observed with SG include nausea, diarrhea, fatigue, neutropenia, and anemia. These AEs were recorded in both the IMMU-132-01 and ASCENT trials and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The most frequent grade 3 (G3) or higher AEs included neutropenia, febrile neutropenia, leukopenia, anemia, and diarrhea. Additionally, the trials reported that the majority of these AEs were manageable with supportive care. Unlike some other ADCs, SG did not show an increased risk of interstitial lung disease or cardiovascular toxicity. The rates of treatment discontinuation due to AEs were relatively low, with 3 % in IMMU-132-01 trial and 5 % in the ASCENT trial. Approximately 60 % of patients receiving SG experienced diarrhea, and 10 % of them experienced it as G3 toxicity [20,21]. In clinical trials, SG showed a lower incidence of diarrhea compared to irinotecan. As

anticipated, this difference could possibly be attributed to the slow elimination of large amounts of SN-38 over three days with SG, as opposed to the rapid excretion in the intestines seen for irinotecan [16]. Diarrhea can be classified into two types: early onset and delayed onset, each with a specific pathogenetic mechanism. Early-onset diarrhea is linked to the cholinergic effects caused by damage to the enteric nervous system. It is often characterized by concurrent symptoms such as abdominal pain, sweating, and salivation, thus referred to as the “cholinergic syndrome”. In these situations, atropine may be helpful, and its administration could be considered as prophylaxis before subsequent SG infusions. Delayed diarrhea is linked to gut mucositis and alterations in the microbiota. Symptomatic medications, primarily loperamide, along with appropriate dietary adjustments, form the basis of its treatment. In case of refractory diarrhea, alternative options include octreotide or tincture of opium. Neutropenic colitis is an exceedingly rare AE that necessitates antibiotic therapy [30,31].

SG-induced neutropenia can be managed through dose reduction, dose delay, or with the support of granulocyte-colony stimulating factor (G-CSF). Primary prophylaxis with G-CSF is not routinely recommended, but secondary prophylaxis for a G3 AE could be considered with a different approach based on the day of the cycle on which it occurs. Specifically, if neutropenia occurs on day 1 of the 21-day schedule, the introduction of daily G-CSF (filgrastim or biosimilar) for two or three

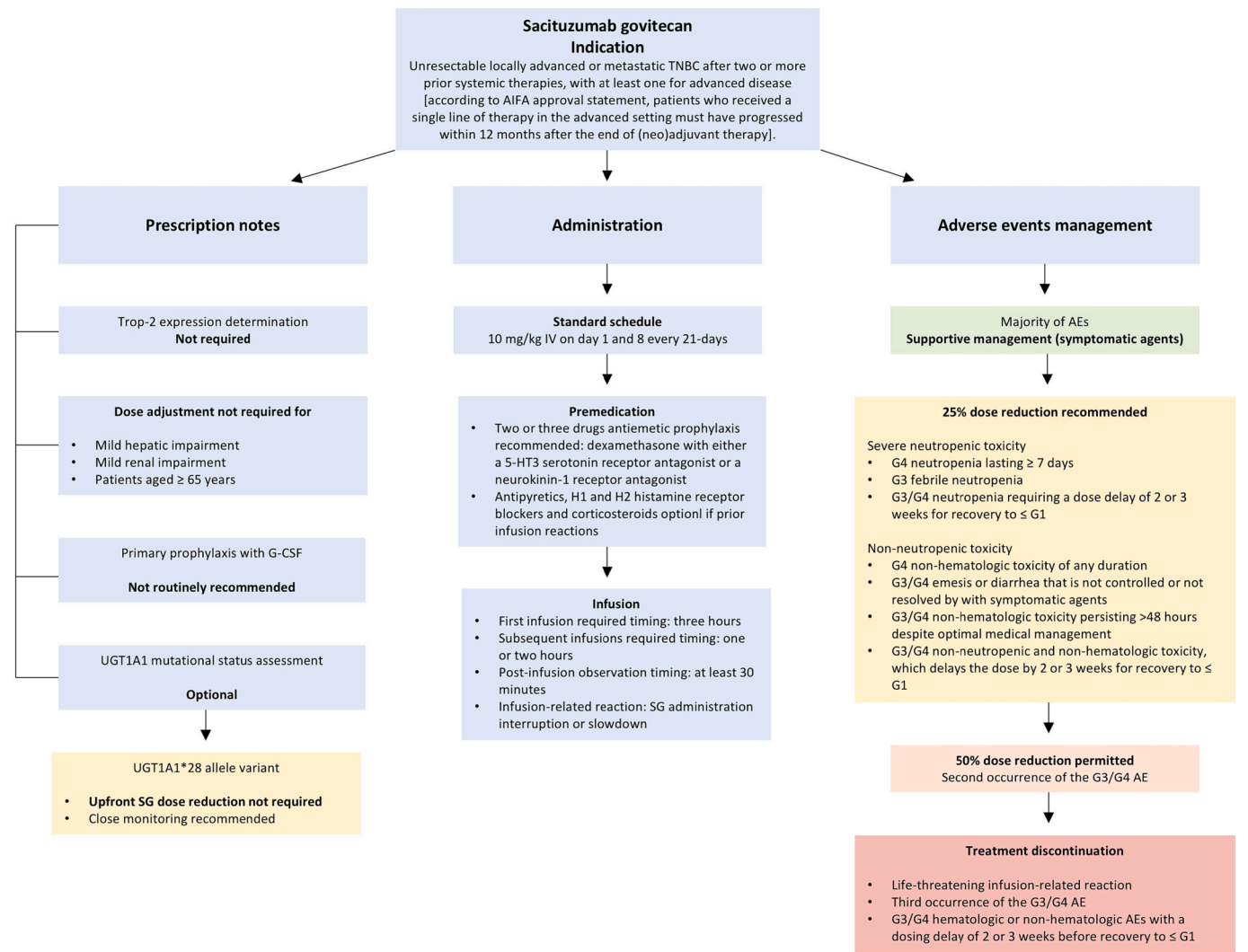


Fig. 1. Sacituzumab govitecan clinical practice notes: indications, prescribing information and adverse events management. AEs: adverse events; G1: grade 1; G3: grade 3; G4: grade 4; G-CSF: granulocyte colony stimulating factor; IV: intravenous; TNBC: triple negative breast cancer; UGT1A1: uridine diphosphate-glucuronosyl transferase 1A1.

consecutive administrations can be considered. On the other hand, if neutropenia occurs on day 8, long-acting pegylated G-CSF (pegfilgrastim or biosimilar) can be administered 24–48 h after the SG infusion [30,31]. In the ASCENT trial, G-CSF was used overall (as secondary prophylaxis or treatment) in 49 % of patients in the SG arm and in 23 % of patients in the TPC arm [21]. Febrile neutropenia should be managed as per clinical practice by excluding possible sources of infection and initiating appropriate antibiotic therapy if necessary. The ASCENT study included a retrospective analysis focusing on the UGT1A1 genotype. It was found that the homozygous *28/*28 variant was associated with an increased risk of $\geq$ G3 neutropenia, febrile neutropenia, diarrhea, and a higher proportion of treatment discontinuation due to AEs (*28/*28: 6 %; *1/*28: 1 %; *1/*1: 2 %) [24].

In the case of AEs $\geq$ grade 2 (G2), SG dose modifications are allowed. The rate of AEs-related dose reduction was similar in both treatment arms of the ASCENT trial, with 22 % in the SG arm and 26 % in the TPC arm [21].

A 25 % dose reduction is recommended for the first occurrence of severe neutropenic toxicity, which is defined as grade 4 (G4) neutropenia lasting $\geq$ 7 days, G3 febrile neutropenia or G3/G4 neutropenia requiring a dose delay of 2 or 3 weeks for recovery to $\leq$ G1. Similarly, a dose reduction is also indicated for non-neutropenic AE which are defined as G4 non-hematologic toxicity of any duration, G3/G4 emesis or diarrhea that is not controlled or not resolved by with symptomatic agents, G3/G4 non-hematologic toxicity persisting $>$ 48 h despite optimal medical management, or G3/G4 non-neutropenic and non-hematologic toxicity, which delays the dose by 2 or 3 weeks for recovery to $\leq$ G1. In case of a second occurrence of the above-mentioned AEs, a 50 % dose reduction is permitted. Treatment discontinuation is necessary upon the third occurrence of these AEs, or in the case of G3/G4 hematologic or non-hematologic AEs with a dosing delay of 2 or 3 weeks before recovery to $\leq$ G1. No dose adjustment is required for patients with mild hepatic impairment (bilirubin $\leq$ 1.5 times the upper limit of normal (ULN) and aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) $<$ 3 times ULN). The safety profile of SG has not been evaluated in case of moderate or severe hepatic impairment (serum bilirubin $>$ 1.5 times ULN, or AST and ALT $>$ 3 times ULN without liver metastases, or liver metastases and AST and ALT $>$ 5 times ULN). No dose adjustment is required for patients with mild renal impairment, and there is no available data on SG use in cases of moderate renal impairment, severe renal impairment, or end-stage renal disease (creatinine clearance $\leq$ 15 mL/min) [29] [Fig. 1].

No dose adjustment is necessary for patients aged $\geq$ 65 years, despite a higher rate of dose reduction being observed in this population in the ASCENT study [20,30]. Data available for patients aged $\geq$ 75 years are limited.

Any role for biomarkers?

One of the focal points investigated in the ASCENT trial was the relation between efficacy outcomes and levels of the Trop-2 membrane protein. Patients were categorized into three groups according to immunohistochemistry (IHC) Trop-2 expression (OptiVIEW DAB detection kit; Roche Diagnostics, Indianapolis). These groups were classified as having high, medium, or low Trop-2 scores. The enrollment of participants in the trial was independent from Trop-2 score, although approximately 80 % of the tumor samples displayed high or medium Trop-2 values, as anticipated from earlier evaluations using tissue microarrays [32]. The observed absolute benefit was relatively smaller in tumors exhibiting low Trop-2 expression. Nonetheless, the Trop-2 low expression group had a limited sample size, which prevented drawing definitive conclusions. The advantages in terms of PFS, OS, and ORR over TPC were consistently present across all three Trop-2 score classes. The baseline germline BRCA1/2 mutational status was assessed in the entire study population. Efficacy outcomes were comparatively more favorable with SG as opposed to TPC, both for patients with and without

germline BRCA1/2 mutations. Once again, the superiority of SG over TPC seemed to be unaffected by the presence of mutations [32]. In summary, the current findings do not support the identification of a role for biomarkers in guiding the selection of SG prescriptions, as the therapeutic agent demonstrated efficacy regardless of the molecular characteristics of the tumors or the presence of germline mutations.

Quality of life

The recent advancements in survival outcomes have led to heightened emphasis on Health-Related Quality of Life (HRQoL), which has now become a pivotal endpoint in numerous clinical trials and an essential goal in daily clinical practice. Within the context of the ASCENT phase III trial, patients exhibited significantly greater improvements in all five primary-focused domains of HRQoL, as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. These domains encompass global health status, physical functioning, role functioning, fatigue, and pain. In comparison to TPC, the experimental treatment SG yielded superior results. Notably, while the difference was not statistically significant, SG showed inferiority to TPC in relation to nausea and vomiting. Nonetheless, this difference did not translate into a negative effect on global QoL score or functioning. Moreover, when compared to TPC, SG delayed worsening for four of the primary QoL domains [33]. When evaluated with the QLQ-C30 score, a significantly greater improvement in physical functioning and dyspnea was observed in the TROPiCS-02 study, and the only domain that got worse was diarrhea [34].

Efficacy outcomes in special populations

Additional data elucidating the efficacy of SG within specific populations have been provided through several post-hoc analyses.

Brain involvement frequently occurs in patients with advanced TNBC and HER2-positive BC. Following a median follow-up of approximately 2.5 years, it has been observed that 30–32 % of patients develop brain metastases (mts), in contrast to the 15 % incidence recorded in patients with luminal-like tumors. The incidence of central nervous system (CNS) mts increases with longer follow-up, exhibiting a 13 % incidence per patient-year in both TNBC and HER2-positive BC cases (compared to 5 % in luminal-like tumors). [35].

The presence of symptomatic brain mts is associated with a shorter OS [36]. Local treatment options encompass stereotactic radiosurgery when feasible, surgery in selected cases, and whole-brain radiation in scenarios where the number and the extension of brain lesions preclude the use of stereotactic radiosurgery [37]. Data pertaining to the activity of commonly used antitumor agents in BC patients harboring brain mts are scarce due to the omission of this population from most clinical trials, attributable to their grim prognosis and the uncertainty surrounding drug penetration through the blood–brain barrier. Furthermore, even when CNS involvement is not among the exclusion criteria, only patients with stable brain mts are selected, while patients with active lesions and/or leptomeningeal invasion are usually excluded.

An exceptional case in point is demonstrated by the HER2CLIMB trial in HER2 positive metastatic breast cancer, which notably included patients with active brain metastases, thereby establishing a novel paradigm in the context of selection criteria [38]. Within the ASCENT trial, patients with stable CNS mts were eligible, comprising up to 15 % of the study population. The presence or absence of brain mts served as a key stratification factor. In terms of brain disease assessment through MRI, stability was defined by the absence of signs or symptoms for a minimum of 4 weeks overall, coupled with a span of at least 2 weeks without antiseizure medication, while the required corticosteroid dosage was $\leq$ 20 mg prednisone equivalent or exhibited a decreasing trend over the same timeframe preceding randomization. Consequently, adhering to these eligibility criteria, out of the 529 patients randomized for the trial, 61 (11.5 %) presented brain mts. As reported in preceding sections, the

ASCENT trial's primary endpoint was successfully met, with both PFS and OS demonstrating substantial extensions in the SG arm when compared to the TPC arm, even within the entire study population inclusive of patients with brain mts [21]. A post-hoc subgroup analysis focusing on patients with brain mts was presented at the San Antonio Breast Cancer Symposium in December 2020. The aim was to assess the efficacy and safety of SG in the subset of 61 patients who exhibited stable CNS mts at the time of randomization, with 32 assigned to the SG arm and 29 to the TPC arm. The findings indicated a low response rate, characterized by a single partial remission in the SG arm (3 %) and none in the TPC arm. Moreover, two additional patients in the SG arm sustained a stable disease for more than 6 months, as opposed to only one patient in the TPC arm (clinical benefit rate of 9 % vs 3 %). Outcomes were notably modest in both arms, as evidenced by a median PFS of 2.8 mo (range 1.5–3.9) in the SG arm compared to 1.6 mo (range 1.3–2.9) in the TPC arm, along with a median OS of 6.8 mo (range 4.7–14.1) and 7.5 mo (range 4.7–11.1) in the SG and TPC arms, respectively. Notably, the median PFS and OS in the SG arm were halved compared to the study population lacking brain mts. The safety profile paralleled that of the ASCENT population without CNS mts, with no treatment-related deaths occurring in either arm. In conclusion, the incidence of objective remission was minimal in both arms, and the overall prognosis was unfavorable for patients with CNS involvement. However, it is imperative to acknowledge that the interpretation of these findings is considerably hindered by the limited sample size. Therefore, definitive conclusions cannot be drawn, and the presence of brain mts should not be deemed a reason to preclude SG treatment for TNBC patients, provided that optimal local interventions are also offered [39].

In early-stage TNBC, experiencing a relapse within 12 mo after finishing (neo)adjuvant CT indicates an unfavorable prognosis, signifying an aggressive form of the disease resistant to traditional cytotoxic treatments. Within the ASCENT trial, 14 % of patients, both in the SG and in the TPC arm, encountered a recurrence within 12 mo of (neo)adjuvant treatment completion, subsequently receiving only a first-line regimen for advanced disease. In a dedicated subgroup analysis, SG demonstrated notable benefits in PFS (5.7 vs 1.5 mo, HR 0.41) and OS (10.9 vs 4.9 mo, HR 0.51) compared to TPC in second-line treatment. This advantage was obtained while still presenting a favorable tolerability profile [40].

Another subgroup analysis within the ASCENT trial focused on patients who initially did not exhibit the TNBC profile. Among these patients, 30 % received the SG treatment, while 33 % received the TPC. The clinical benefit obtained with SG persisted in this population as well. The median PFS was 4.6 versus 2.3 mo (HR 0.48), median OS was 12.4 versus 6.7 mo (HR 0.44), and ORR was 31 % versus 4 %. This ORR advantage was also evident in cases where prior CDK4/6 inhibitors were administered (21 % SG versus 5 % TPC).

The analysis reaffirms the effectiveness of the SG treatment irrespective of the biological subtype detected at the initial diagnosis. Additionally, it highlights the importance of performing a new tumor biopsy at the time of PD to reassess the biologic profile [41]. This practice is valuable as changes in the tumor subtype could expand the range of treatment options by incorporating the utilization of SG. In addition to its efficacy in treating TNBC, SG has also demonstrated interesting results in the treatment of other BC subtypes. In the phase III TROPICS-02 trial, patients diagnosed with hormone receptor positive and HER negative (HR + HER2-) mBC who had previously undergone endocrine therapy, cyclin-dependent kinase inhibitors (CDKi), and a minimum of two lines of systemic CT, including taxanes, were randomly assigned in a 1:1 ratio to receive either SG or the TPC. The results indicated that SG conferred a PFS advantage (5.5 vs 4.0 mo, HR 0.66) as well as an OS improvement (14.4 vs 11.2 mo, HR 0.79) when compared to TPC. Additionally, SG maintained a manageable safety profile [42,43]. Therefore, SG efficacy is confirmed also in endocrine-resistant disease settings. Post-hoc analyses were conducted on both TROPICS-02 and ASCENT trials to assess the efficacy of SG in HER2-low and in HER2

IHC score 0 mBC. These analyses revealed consistent benefits in terms of PFS, OS and ORR comparable to those observed in the overall study population [44,45].

In conclusion, the SG treatment has exhibited its efficacy not only in the context of TNBC but also across different biological profiles. The TROPICS-02 trial demonstrated its effectiveness in endocrine-resistant disease, while subsequent analyses confirmed positive outcomes in cases of HER2-low and HER2 IHC score 0 mBC, aligning with the results seen in the broader patient cohorts.

Future perspectives

Implemental strategies with sacituzumab govitecan

The phase II NEOSTAR trial (NCT04230109) investigated SG as an upfront strategy in 50 patients with localized TNBC. These patients were provided the option to receive additional neoadjuvant TPC in cases where biopsy-proven residual disease was present after completing 4 cycles of SG. The primary endpoint of the trial was the rate of pathological complete response (pCR) in both the breast and lymph nodes (ypT0/isN0). The results indicated that out of the entire cohort, 31 patients (62 %) achieved a radiological response solely with SG. Among this group, 26 patients directly proceeded to surgery, of which 15 (30 %) achieved a pCR. Notably, among the 8 patients harboring gBRCAm, 7 underwent surgery following SG, and of those, 6 attained a pCR. The trial hinted at the potential efficacy of SG in localized TNBC, with no emergence of new safety signals. However, the optimal timing, number of cycles, and combination with other treatments are aspects yet to be clarified [46].

In the ongoing SASCIA trial (NCT04595565), patients with either TNBC or HR-positive/HER2-negative (HR+/HER2-) BC presenting with residual invasive disease (>ypT1mi), or HR+/HER2- BC patients with a clinical and post-treatment pathological stage (CPS) along with an estrogen receptor status and grade (EG) score ≥ 3 , or EG score of 2 plus nodal involvement (ypN +), subsequent to taxane-based neoadjuvant CT (NACT), are randomly assigned to receive either SG or TPC for a total of 8 cycles. The primary endpoint of this trial is Invasive the disease-free survival (iDFS). The study is currently recruiting, and the projected of the primary phase is estimated to be in March 2027 [47].

Moving to first-line setting, the ongoing ASCENT-03 and ASCENT-04 trials are offering SG as a treatment possibility. Within the ASCENT-03 (NCT05382299), patients exhibiting either PD-L1- (CPS < 10) or PD-L1 + tumors (CPS ≥ 10), who have undergone immunotherapy as part of the curative therapy, are randomly assigned to receive either SG or TPC until PD or the occurrence of unacceptable toxicity. In cases of progression on the TPC arm, crossover to the SG is permitted. The primary endpoint is PFS, while secondary endpoints include OS, objective response rate, HRQoL, and safety [48].

Concurrently, the ASCENT-04 trial (NCT05382286) randomly assigns patients with PD-L1+ (CPS ≥ 10) TNBC to receive either SG plus pembrolizumab or TPC plus pembrolizumab, until PD or unacceptable toxicity. Patients with or without prior exposure to anti-PD-L1 agents in the (neo)adjuvant setting are eligible. Like ASCENT-03, the option for crossover from TPC arm to SG arm upon PD is permitted. Endpoints are the same of the already mentioned ASCENT-03 trial. A phase II trial is currently exploring the use of SG either as a single agent or in combination with pembrolizumab, specifically for PD-L1- TNBC (NCT04468061). Additionally, an early phase clinical trial is investigating the combination of SG with the anti PD-L1 agent avelumab (NCT03971409).

An intriguing phase Ib/II trial (NCT04039230) is assessing the combination of SG plus Talazoparib in the pretreated advanced TNBC. Despite the temporal separation of SG and PARPi exposure, preclinical models indicated that this dual therapy enhances DNA damage and selectively increases cytotoxicity within tumor cells, without causing similar effects in normal cells. No dose-limiting toxicities occurred

during the Ib phase, and further clinical results are expectedly awaited [49]. Relevant trials involving SG are summarized in table 1 [Table 1].

Emerging antigens targeted options

To date, ADCs are gaining increasing attention, and it is worth highlighting the landscape of non-anti-HER2 targeted molecules in this regard [50].

One such notable molecule is Datopotamab deruxtecan (Dato-DXd), which consists of a Trop-2 directed MoAb, a tetrapeptide-based linker and a topoisomerase 1 inhibitor. Dato-DXd is currently under investigation in the open-label, phase I basket trial TROPION-PanTumor01 (NCT03401385), which enrolls patients with advanced solid tumors of diverse histology. Encouraging results have been observed in terms of ORR, CBR, and disease control rate (DCR) among both HR+ and TNBC pretreated patients. Regarding the potential for cross-resistance, in TNBC subgroup, no significant outcome differences emerged among patients who previously received a topoisomerase 1 inhibitor-based ADC [51–53].

Ladiratuzumab vedotin (LV) is composed of a MoAb directed to LIV1 - an estrogen-regulated zinc transporter - conjugated to monomethyl auristatin E (MMAE) through a cleavable linker. Insights from preclinical models suggest that SGN-LIV1A, as it is also known, might enhance the effects of immunotherapy. At present, SGN-LIV1A is being investigated within a phase I clinical trial (NCT01969643) involving patients with LIV1-positive metastatic HR+/HER2- BC and TNBC [54,55]. The preliminary findings, combining data from both dose-escalation and expansion cohorts, have demonstrated promising ORR of 32 % and median PFS of 11.3 weeks in TNBC patients [56,57]. In the context of early-stage breast cancer, LV was incorporated as a neoadjuvant treatment in the I-SPY2 trial (NCT01042379). Regrettably, the experimental drug did not exhibit an increase in pCR rates in comparison to the control arm [58]. Ongoing trials are delving into the combination of LV with pembrolizumab (SGNLVA-002, NCT03310957) as first line-treatment, and with atezolizumab as second line-treatment (one arm of the Morpheus-TNBC, NCT03424005) in TNBC. Additionally, the exploration of LV combined with trastuzumab is being pursued in in HER2 + BC (SGNLVA-001, NCT01969643) [59].

Patritumab deruxtecan (P-DXd) consists of a MoAb targeting HER3, linked to deruxtecan via a peptide-based cleavable linker, featuring a DAR of 8. HER3 is a human growth factor receptor that plays a significant role in the emergence of resistance to therapies targeting EGFR, HER2, PI3K/AKT/mTOR, and in cancer progression [60,61]. P-DXd has been evaluated in a phase I/II clinical trial involving heavily pretreated patients with HER3-positive metastatic BC (NCT02980341), who were grouped in different cohorts based on their HER3 expression level (high or low), HR, and HER2 status. In an updated analysis presented at the 2022 American Society for Clinical Oncology (ASCO) Annual Meeting, an ORR of 30.1 % was reported across both HER3-high&low/HR+/HER2- subgroups. Specifically, the HER3-high/TNBC and HER3-high/HER2 + groups achieved ORRs of 22.6 % and 42.9 %, respectively. No complete responses were reported [62,63]. A window-of-opportunity trial evaluated the use of P-DXd within a 21-days pre-operative window in treatment-naïve patients with HR+/HER2- tumors (NCT04610528). This study revealed an association between P-DXd and clinical response, enhanced immune infiltration, and cell growth suppression [64].

Enfortumab vedotin (EV) is an ADC composed of a MoAb targeting anti-nectin 4 - an adhesion protein involved in oncogenesis - and by the anti-microtubule agent monomethyl auristatin E joined by a protease cleavable linker. Its efficacy has already well established in patients with locally advanced or metastatic urothelial carcinoma who have received both platinum-based CT and an ICI, or are ineligible for cisplatin, based on the data from the phase II clinical trial EV-301 [65]. In vivo studies on nectin-4-positive xenograft TNBC showed rapid, complete, and durable responses to EV [66]. An ongoing histology-agnostic phase II basket trial

(EV-202, NCT04225117) is investigating the activity of EV across neoplasms displaying high nectin-4 expression, and it includes a HR+/HER2- BC and a TNBC cohort [67]. Another promising target under investigation is the folate receptor alpha (FR α). MORAb-202 consists of farletuzumab - a humanized IgG1 MoAb targeting FR α - combined with the microtubule inhibitor eribulin, conjugated through a protease-cleavable linker. It showed promising anti-tumor activity in *in vitro* studies, along with a reassuring safety profile in a phase I clinical trial in various solid tumors. Currently, MORAb-202 is being investigated in a phase I/II clinical trial encompassing different tumor types, including TNBC (NCT04300556) [68,69]. The characteristics of the cited emerging ADCs are summed up in table 2 [Table 2].

Challenges and open questions

To date, PD-L1 and BRCA status remain the sole reliable predictive markers aiding in the definition of treatment strategies for TNBC. In this context, the potential benefit of ICI in combination with CT within the first-line setting is limited to patients harboring PD-L1 + tumors. As previously discussed, ADCs could serve as a strategy to broaden the spectrum of patients who could derive benefit from immunotherapy. The exposure to ADCs has been associated with an increase in functional T cells within the tumor microenvironment, suggesting the possibility of a synergistic effect [70]. Several trials are currently underway, including those involving SG treatment as mentioned earlier. The Phase Ib/II BEGONIA (NCT03742102) represents a platform study evaluating the safety and efficacy of durvalumab in combination with innovative agents as a first-line treatment for TNBC within a biomarker-unselected population. Available data report a confirmed ORR of 57 % with durvalumab plus T-DXd and 74 % with durvalumab plus Dato-DXd, regardless of PD-L1 status [71–74]. The concept of combining ICI with ADCs has been further explored in the Phase Ib DS8201-A-U105 trial, which evaluated T-DXd plus nivolumab in patients with pretreated HER2-expressing advanced BC. The ORR was 65.6 % in the HER2 + cohort and 50 % in the HER2-low cohort, defined as IHC 2+/*in situ* hybridization (ISH) negative or IHC 1 +. An exploratory analysis of PD-L1 status revealed no discernible predictive value [75].

One of the open questions concerning the ADCs pertains to the subsequent treatment strategy once their efficacy wanes. A post-hoc subgroup analysis of the ASCENT trial delved into the outcomes of patients for whom SG was discontinued due to PD. In these cases, 73 % of patients received post-PD therapy, which remarkably improved median OS (13.4 vs 7.3 mo; HR 0.46) when compared to those who did not receive such therapy. These data suggest that ADCs do not preclude the administration of further systemic treatments, even after their effectivity diminishes [76].

Drawing from the experience in HER2 + disease, it is evident that an ADC could be a great option in patients who have progressed on another ADC. In the randomized trial DESTINY-Breast02, T-DXd showed PFS advantage over TPC (17.8 versus 6.9 mo; HR 0.36) in patients with HER2 + BC resistant to T-DM1, thereby showing that an ADC can overcome the resistance acquired to a previous one [77]. Building on this premise, treatment sequences involving ADCs may indeed offer a viable option, especially when employing ADCs with different payloads.

Currently, the selection of patients eligible for ADC treatment is guided by clinical factors, including patients' general conditions, performance status, comorbidities, extent of organ function impairment, prior therapies, and the tumor's biological profile as defined by receptor status (HR and HER2). One of the forthcoming challenges revolves around identifying predictive biomarkers for each ADC, aimed at elucidating whether the magnitude of expression of the target sAg expression plays a decisive role. Furthermore, additional studies are needed to discern whether ADCs can replace traditional CT as first-line treatment in TNBC.

Table 1
Relevant selected clinical trials with sacituzumab govitecan. BC: breast cancer; BORR: best overall response rate; CBR: clinical benefit rate; CN: control; CT: chemotherapy; DDFS distant-disease free survival; DFS: disease free survival; DLT: dose limiting toxicity; DOR: duration of response; ET: endocrine therapy; EXP: experimental; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iBCFS: invasive breast cancer-free survival; iDFS: invasive disease free survival; LRRFI: locoregional recurrences-free interval; mo: months; mPIK3CA: mutation of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; NTC: national clinical trial; ORR: objective response rate; OS: overall survival; pCR:pathologic complete response; PD-L1: programmed death-ligand 1; PFS: progression free survival; PK: pharmacokinetics; PROs: patient reported outcomes; QoL: quality of life; RCT: randomized clinical trial; rRR: radiological response rate; SG: Sacituzumab govitecan; TNBC: triple negative breast cancer; TPC: Treatment of Physician's Choice; TTD: time to deterioration; TTR: time-to-objective response; TTR: time to response.

Trial	Phase	Trial design	BC Setting	BC Population	Treatment	Key Endpoints	Key Results with SG	Status
IMMU-132-01 NCT01631552	I/II	Open label non RCT, sequential assignment	Metastatic (subsequent line)	TNBC	EXP arm: SG	Primary: safety, ORR. Secondary: DOR, TTR, CBR, PFS, OS, PK.	ORR: 33.3 %; DOR: 7.7 mo; PFS: 5.6 mo; OS: 13 mo. ¹⁸	Recruitment completed.
ASCENT NCT02574455	III	Open label RCT	Unresectable, locally advanced or metastatic (subsequent line)	TNBC	EXP arm: SGCN arm: TPC (eribuline, capecitabine, gemcitabine, vinorelbine)	Primary: PFS. Secondary: OS.	PFS 5.6 mo; OS 12.1 mo; ORR 35 %. ¹⁹	Recruitment completed.
TROPICS-02 NCT03901339	III	Open label RCT	Metastatic (subsequent line)	HR+/HER2-	EXP arm: SGCN arm TPC (eribuline, capecitabine, gemcitabine, vinorelbine)	Primary: PFS. Secondary: OS, ORR, DOR, CBR, TTD, safety.	PFS 5.5 mo; OS 13.9 mo; ORR 21 %; CBR 34 %. ⁴²	Active, not recruiting. Estimated completion: october 2024.
SASCIA NCT04595565	III	Open label RCT	Post-neoadjuvant (residual disease)	TNBC HR+/HER-	EXP arm: SG CN arm: capecitabine, carboplatin or cisplatin	Primary: iDFS. Secondary: OS, DDFS, iBCFS, LRRFI, safety, PROs.	Not available.	Recruiting. Estimated primary completion: March 2027.
Saci-IO TNBC NCT04468061	II	Open label RCT	Metastatic treatment naïve (first line)	TNBC, PD-L1 -	EXP arm A: SG + pembrolizumab EXP arm B: SG	Primary: PFS. Secondary: OS, ORR, DOR, TTOR, CBR, safety.	Not available.	Recruiting. Estimated primary completion: April 2024.
Saci-IO HR + NCT04448886	II	Open label RCT	Metastatic, after previous ET	HR+/HER2 -	EXP arm A: SG + pembrolizumab EXP arm B: SG	Primary: PFS. Secondary: CBR, DOR, ORR, OS, TTP, safety.	Not available.	Recruiting. Estimated primary completion: July 2025.
Morpheus-TNBC NCT03424005	Ib/II	Open label, umbrella RCT	Unresectable, locally advanced or metastatic (first and subsequent line)	Cohort 1: TNBC, PD-L1 +. Cohort 2: TNBC ICI naïve. Cohort 3: HR+/HER2- mPIK3CA. Cohort 4: HER2+/HER2-low mPIK3CA.	CN arms: atezolizumab + nab-paclitaxel; capecitabine; atezolizumab + CT (gemcitabine + carboplatin or eribulin) EXP arms: tocilizumab; atezolizumab + SG; atezolizumab + ipatasertib; atezolizumab + SGN-LIV1A; atezolizumab + selicrelumab + bevacizumab; inavolisib + abemaciclib + fulvestrant; inavolisib + ribociclib + fulvestrant; inavolisib + trastuzumab deruxtecan.	Primary: ORR; safety. Secondary: PFS, DCR, OS, DOR.	Not available.	Active, not recruiting. Estimated primary completion: May 2026.
ASCENT-03 NCT05382299	III	Open label RCT	Unresectable, locally advanced or metastatic treatment naïve (first line)	TNBC, PD-L1 - and PD-L1 +	EXP arm:SGCN arm: TPC (paclitaxel, nab-paclitaxel, gemcitabine + carboplatin)	Primary: PFS. Secondary: OS, ORR, DOR, TTR, safety, QoL.	Not available.	Recruiting. Estimated primary completion: May 2027.
ASCENT-04 NCT05382286	III	Open label RCT	Unresectable, locally advanced or metastatic treatment naïve (first line)	TNBC, PD-L1+	EXP arm: SG + pembrolizumabCN arm: TPC (paclitaxel, nab-paclitaxel, gemcitabine + carboplatin) + pembrolizumab	Primary: PFS. Secondary: OS, ORR, DOR, TTR, safety, QoL.	Not available.	Recruiting. Estimated primary completion: February 2027.
InCITe NCT03971409	II	Open label, RCT	Unresectable, locally advanced or metastatic (subsequent line)	TNBC	EXP arm A: avelumab, binimetinib, liposomal doxorubicin. EXP arm B: avelumab, SG EXP arm C: avelumab, liposomal doxorubicin EXParm: SG (after the SG cohort completion, SG + pembrolizumab cohort will open)	Primary: BORR. Secondary: ORR, CBR, PFS, OS, safety, QoL.	Not available.	Recruiting. Estimated primary completion: June 2024.
NeoSTAR NCT04230109	II	Open label, non RCT	Early or locally advanced treatment naïve (neoadjuvant)	TNBC	EXParm: SG (after the SG cohort completion, SG + pembrolizumab cohort will open)	Primary: pCR rate with SG. Secondary: rRR, EFS, safety, QoL.	pCR rate 30 % rRR 62 % ⁴⁵	Recruiting. Estimated primary completion: October 2025.
NCT04039230	I/II	Open label, non RCT	Metastatic (subsequent line)	TNBC	EXP arm: SG + talazoparib.	Primary: DLT. Secondary: TTR, DOR, PFS, OS.	Not available.	Recruiting. Estimated primary completion: December 2023.

Table 2

Main non anti-HER2 targeted antibody drug conjugates and related key trials. BC: breast cancer; DAR: drug antibody ratio; FR α : Folate receptor alpha; HER2: human epidermal growth factor receptor 2; HER2m: human epidermal growth factor receptor 2 mutation; HER3: human epidermal growth factor receptor 3; HR: hormone receptor; MoAb: monoclonal antibody; TNBC: triple negative breast cancer; Trop2: trophoblast cell surface antigen.

Molecule name	Target antigen	Biochemical structure	Key Adverse Events	Key Trials	Phase	BC Population	Status	References
Datopotamab deruxtecan (Dato-DXd)	Trop2	<i>MoAb</i> : datopotamab, anti-Trop2. <i>Payload</i> : topoisomerase I inhibitor (DXd). <i>Linker</i> : stable tetrapeptide-based cleavable. DAR $\approx$ 4.	Nausea Vomiting Stomatitis Fatigue	TROPION-Pan-Tumor01 NCT03401385	I (Dato-DXd monotherapy)	Metastatic TNBC previously treated.	Recruiting. Estimated completion: January 2025.	51–53
Ladiratuzumab vedotin (SGN-LIV1a)	LIV1	<i>MoAb</i> : ladiratuzumab, anti-LIV1 (estrogen-regulated zinc transporter). <i>Payload</i> : monomethyl auristatin E (MMAE). <i>Linker</i> : cleavable. DAR $\approx$ 4.	Neutropenia Anemia	SGNLVA-001 NCT01969643 I-SPY2 NCT01042379 SGNLVA-002 NCT03310957 Morpheus-TNBC NCT03424005	I (SGN-LIV1A monotherapy; SGN-LIV1A + trastuzumab) II (SGN-LIV1A monotherapy as one of the arms, closed) Ib/II (SGN-LIV1A + pembrolizumab) Ib/II (atezolizumab + SGN-LIV1A as one of the arms)	Metastatic HR+/HER2- BC, HER2+/HER2m BC and TNBC previously treated. Early-stage, locally advanced HR+/HER2- BC, HER2 + BC and TNBC. Unresectable locally-advanced or metastatic TNBC treatment naïve (first line) Unresectable, locally advanced or metastatic TNBC or HR+/HER2-mPIK3CA BC (first and subsequent line)	Completed. Actual completion: February 2023. Recruiting. Estimated completion: December 2030. Active, not recruiting. Estimated primary completion: March 2024. Active, not recruiting. Estimated primary completion: May 2026. Not recruiting.	54–59
Patritumab deruxtecan (U3-1402)	HER3	<i>MoAb</i> : patritumab, anti-HER3. <i>Payload</i> : topoisomerase I inhibitor (DXd). <i>Linker</i> : peptide-based cleavable linker. DAR $\approx$ 7.8.	Nausea and vomiting Fatigue Alopecia Diarrhea Neutropenia	U31402-A-J101, JapicCTI-163401 NCT02980341 SOLTI TOT-HER3 NCT04610528	I/II (U3-1402 monotherapy) I (U3 1402 monotherapy)	HER3 expressing metastatic BC Early-stage treatment naïve HR+/HER2- BC and TNBC.	Active, not recruiting. Actual completion: January 2022.	62–64
Enfortumab vedotin (EV)	Nectin4	<i>MoAb</i> : enfortumab, anti-nectin4. <i>Payload</i> : vedotin (microtubule inhibitor). <i>Linker</i> : cleavable. DAR $\approx$ 3.8.	Alopecia Peripheral sensory neuropathy Pruritus Fatigue Decreased appetite	EV-202 NCT04225117	II (EV monotherapy in BC cohorts)	Locally advanced or metastatic HR+/HER2- BC and TNBC previously treated.	Active, not recruiting. Estimated primary completion: September 2026.	65–67
MORAb-202	FR α	<i>MoAb</i> : farletuzumab, anti-FR α . <i>Payload</i> : eribulin (microtubule inhibitor). <i>Linker</i> : protease-cleavable linker. DAR $\approx$ 3.8.	Leukopenia Neutropenia ALT increase Anemia Nausea	NCT04300556	I/II (MORAb-202 monotherapy)	Metastatic TNBC previously treated.	Recruiting. Estimated primary completion: March 2025.	68–69

Conclusions

ADCs are increasingly gaining momentum within the therapeutic landscape for BC. They have already become a cornerstone in the treatment of HER2 + BC, and the introduction of SG is opening new horizons in TNBC. In this subtype, SG could emerge as a preferred therapeutic option, surpassing conventional CT both in the second- and first-line settings, particularly in cases of early relapse after (neo)adjuvant therapy. Notably, SG has exhibited comparable advantageous

outcomes across all patient subgroups, displaying a lack of discernible cross-resistance with prior CT regimens. To this end, the option of undergoing a new biopsy to redefine the biologic profile of BC upon disease progression holds merit, as it might unveil a change in receptor status that could potentially facilitate access to the drug. Importantly, SG has demonstrated a manageable safety profile, even furnishing a HRQoL benefit. Most of the AEs associated with SG are of G1 or G2 severity, and they can be effectively managed through symptomatic interventions as per clinical practice. Notably, dose reductions do not appear to

compromise the treatment's efficacy.

The landscape of ADCs is enriched with numerous other compounds currently undergoing investigation in diverse contexts. Pertinent challenges on the horizon encompass the judicious selection of patients, the establishment of optimal treatment sequences, the further exploration of combination strategies, and the identification of predictive biomarkers that can significantly contribute to informed clinical decision-making.

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Declaration of competing interest

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