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New Drugs

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

Arianna Dri [a,b,*], Grazia Arpino [c], Giampaolo Bianchini [d,e], Giuseppe Curigliano [f,g], Romano Danesi [h], Michelino De Laurentiis [i], Lucia Del Mastro [j,k], Alessandra Fabi [l], Daniele Generali [m,n], Alessandra Gennari [o], Valentina Guarneri [p,q], Daniele Santini [r], Edda Simoncini [s], Claudio Zamagni [t], Fabio Puglisi [a,b]

[a] Department of Medicine, University of Udine, Udine, Italy
[b] Department of Medical Oncology, CRO Aviano, National Cancer Institute, IRCCS, Aviano (PN), Italy
[c] Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy
[d] Department of Medical Oncology, San Raffaele Hospital, Milan, Italy
[e] School of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy
[f] Division of New Drugs and Early Drug Development, European Institute of Oncology (IEO), IRCCS, Milan, Italy
[g] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
[h] Unit of Clinical Pharmacology and Pharmacogenetics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[i] Division of Breast Medical Oncology, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy
[j] Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy
[k] Department of Medical Oncology, Clinical Unit of Medical Oncology, IRCCS Hospital Policlinico San Martino, Genova, Italy
[l] Precision Medicine in Breast Cancer Unit, Department of Woman and Child Health and Public Health, IRCCS, Scientific Directorate, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy
[m] Department of Medicine, Surgery and Health Sciences, Cattinara Hospital, University of Trieste, Trieste, Italy
[n] Multidisciplinary Unit of Breast Pathology and Translational Research, Cremona Hospital, Cremona, Italy
[o] Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy, Ospedale Maggiore della Caritá, Novara, Italy
[p] Medical Oncology 2, Veneto Institute of Oncology (IOV), IRCCS, Padova, Italy
[q] Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy
[r] Oncologia Medica A, Policlinico Umberto 1, La Sapienza Università Di Roma, Rome, Italy
[s] Medical Oncology Unit, ASST Spedali Civili Di Brescia, Brescia, Italy
[t] Medical Oncology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

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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.

* Corresponding author at: Department of Medicine, University of Udine, Udine, Italy (A. Dri).
*E-mail address:* arianna.dri@gmail.com (A. Dri).

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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 Ca2 + 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 Ca2 +. 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 ~ 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 ± 3.816 μg/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 TNCB, 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. Approximatively 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

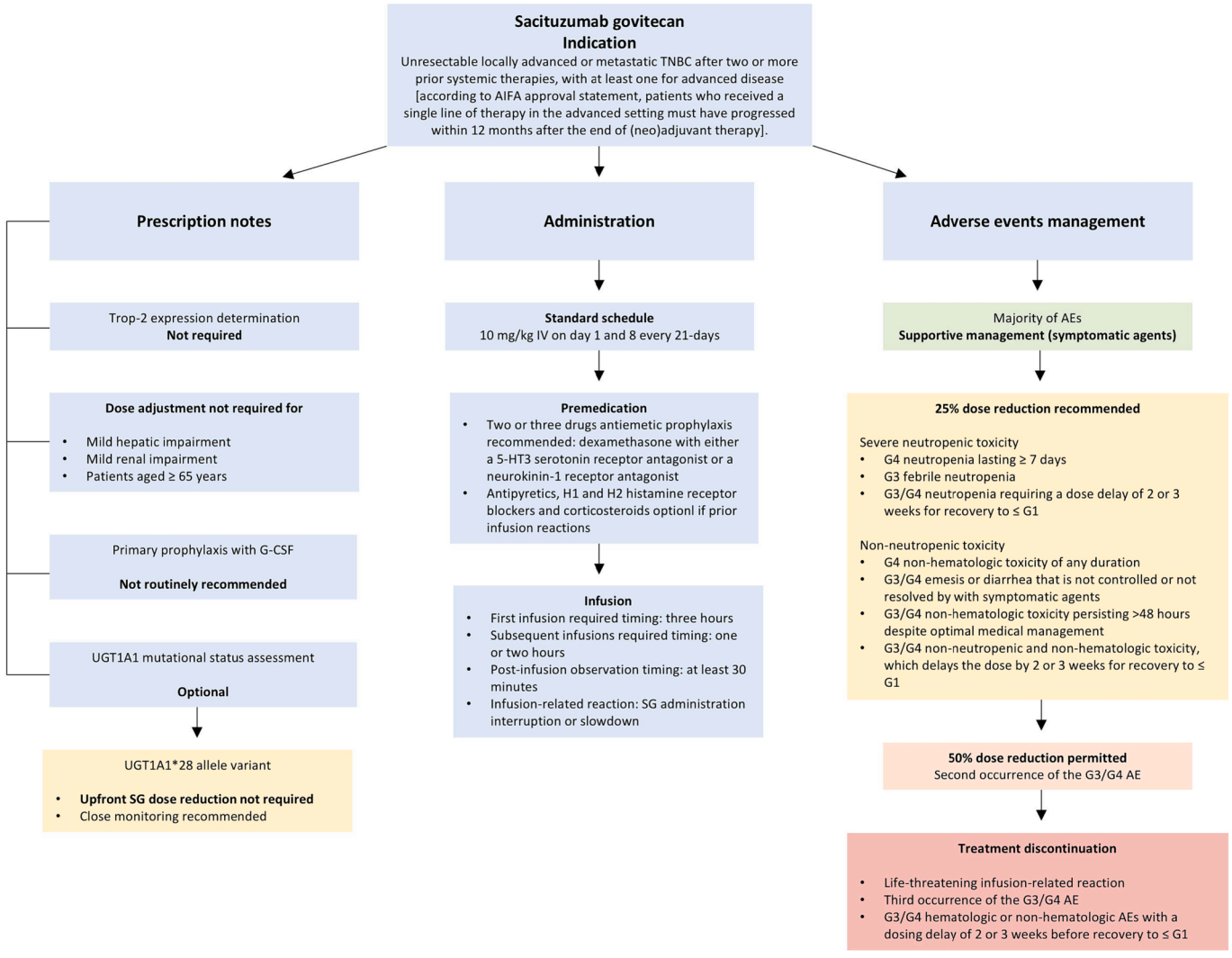


**Fig. 1.** Sacituzumab govitecan clinical practice notes: indications, prescribing information and adverse events management. AEs: adverse events; G1: grade 1; G3: grade 3; G4: grade 4; G-CSF: granulocyte colony stimulating factor; IV: intravenous; TNBC: triple negative breast cancer; UGT1A1: uridine 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 ≥ 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 ≥ 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 ≥ 7 days, G3 febrile neutropenia or G3/G4 neutropenia requiring a dose delay of 2 or 3 weeks for recovery to ≤ 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 ≤ 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 ≤ G1. No dose adjustment is required for patients with mild hepatic impairment (bilirubin ≤ 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 ≤ 15 mL/min) [29] [Fig. 1].

No dose adjustment is necessary for patients aged ≥ 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 ≥ 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 ≤ 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, 7underwent 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 $\geq$ 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 $\geq$ 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 $\geq$ 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 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-naive 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 (FRα). MORAb-202 consists of farletuzumab - a humanized IgG1 MoAb targeting FRα - 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 overcame 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; TTOR: 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 rectuiting. Estimated completion: october 2024. |
| SASCIA NCT04595565 | III | Open label RCT | Post-neoadjuvant (residual disease) | TNBC HR+/HER- | EXP arm: SG<br>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<br>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<br>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 +.<br>Cohort 2: TNBC ICI naïve.<br>Cohort 3: HR+/ HER2- mPIK3CA.<br>Cohort 4: HER2+/ HER2-low mPIK3CA. | CN arms: atezolizumab + nab-paclitaxel; capecitabine; atezolizumab + CT (gemcitabine + carboplatin or eribulin)<br>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.<br>EXP arm B: avelumab, SG<br>EXP arm C: avelumab, liposomal doxorubicin | 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 %<br>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; FRα: 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 | *MoAb*: datopotamab, anti-Trop2. *Payload*: topoisomerase I inhibitor (DXd). *Linker*: stable tetrapeptide-based cleavable. *DAR* ≈ 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 | *MoAb*: ladiratuzumab, anti-LIV1 (estrogen-regulated zinc transporter). *Payload*: monomethyl auristatin E (MMAE). *Linker*: cleavable. DAR ≈ 4. | Neutropenia Anemia | SGNLVA-001 NCT01969643 | I (SGN-LIV1A monotherapy; SGN-LIV1A + trastuzumab) | Metastatic HR+/HER2- BC, HER2+/HER2m BC and TNBC previously treated. | Completed. Actual completion: February 2023. | 54–59 |
| | | | | I-SPY2 NCT01042379 | II (SGN-LIV1A monotherapy as one of the arms, closed) | Early-stage, locally advanced HR+/HER2- BC, HER2 + BC and TNBC. | Recruiting. Estimated completion: December 2030. | |
| | | | | SGNLVA-002 NCT03310957 | Ib/II (SGN-LIV1A + pembrolizumab) | Unresectable locally-advanced or metastatic TNBC treatment naïve (first line) | Active, not recruiting. Estimated primary completion: March 2024. | |
| | | | | Morpheus-TNBC NCT03424005 | Ib/II (atezolizumab + SGN-LIV1A as one of the arms) | Unresectable, locally advanced or metastatic TNBC or HR+/HER2- mPIK3CA BC (first and subsequent line) | Active, not recruiting. Estimated primary completion: May 2026. | |
| Patritumab deruxtecan (U3-1402) | HER3 | *MoAb*: patritumab, anti-HER3. *Payload*: topoisomerase I inhibitor (DXd). *Linker*: peptide-based cleavable linker. *DAR* ≈ 7.8. | Nausea and vomiting Fatigue Alopecia Diarrhea Neutropenia | U31402-A-J101, JapicCTI-163401 NCT02980341 | I/II (U3-1402 monotherapy) | HER3 expressing metastatic BC | Not rectuiting. | 62–64 |
| | | | | SOLTI TOT-HER3 NCT04610528 | I (U3 1402 monotherapy) | Early-stage treatment naïve HR+/HER2- BC and TNBC. | Active, not recruiting. Actual completion: January 2022. | |
| Enfortumab vedotin (EV) | Nectin4 | *MoAb*: enfortumab, anti-nectin4. *Payload*: vedotin (microtubule inhibitor). *Linker*: cleavable. *DAR* ≈ 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 | FRα | *MoAb*: farletuzumab, anti-FRα. *Payload*: eribulin (microtubule inhibitor). *Linker*: protease-cleavable linker. *DAR* ≈ 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.

## CRediT authorship contribution statement

**Arianna Dri:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing. **Grazia Arpino:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Giampaolo Bianchini:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Giuseppe Curigliano:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Romano Danesi:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Michelino De Laurentiis:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Lucia Del Mastro:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Alessandra Fabi:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Daniele Generali:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Alessandra Gennari:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Valentina Guarneri:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Daniele Santini:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Edda Simoncini:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Claudio Zamagni:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Fabio Puglisi:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

## Declaration of competing interest

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## References

[1] Howlader N, Altekruse S, Li C, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106:5.
[2] Grinda T, Antoine A, Jacot W, et al. Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008–2017 ESME cohort. ESMO Open 2021;6(3):100114.
[3] Bianchini G, De Angelis C, Licata L, et al. Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. Nat Rev Clin Oncol 2022;19(2):91–113.
[4] Marmé F. Antibody-drug conjugates for breast cancer. Oncol Res Treat 2022;45(1–2):26–36.
[5] Tarantino P, Carmagnani Pestana R, Corti C, et al. Antibody–drug conjugates: Smart chemotherapy delivery across tumor histologies. CA Can J Clin 2022;72(2):165–82.
[6] von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380(7):617–28.
[7] Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. 2018;18(6):732-742.
[8] Krop I, Kim S, Martin A, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol 2017;18(6):743–54.
[9] Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med 2022;386(12):1143–54.
[10] Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2020;382(7):610–21.
[11] Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 2022;387(1):9–20.
[12] Goldenberg DM, Stein R, Sharkey RM. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. Oncotarget 2018;9(48):28989–9006.
[13] Pavšič M. Trop2 forms a stable dimer with significant structural differences within the membrane-distal region as compared to epcam. Int J Mol Sci 2021;22(19).
[14] Shvartsur A, Bonavida B. Trop2 and its overexpression in cancers: Regulation and clinical/therapeutic implications. Genes Cancer 2015;6(3–4):84–105.
[15] Zeng P, Chen MB, Zhou LN, et al. Impact of TROP2 expression on prognosis in solid tumors: a systematic review and meta-analysis. Sci Rep 2016 Sep;20(6):33658.
[16] Ocean AJ, Starodub AN, Bardia A, et al. Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: safety and pharmacokinetics. Cancer 2017;123(19):3843–54.
[17] Goldenberg DM, Cardillo TM, Govindan SV, et al. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). Oncotarget 2015 Sep 8;6(26):22496–512.
[18] Santi DV, Cabel L, Bidard F-C. Does sacituzumab-govitecan act as a conventional antibody drug conjugate (ADC), a prodrug of SN-38 or both? Ann Transl Med 2021;9(14):1113.
[19] Xie R, Mathijssen R, Sparreboom A, et al. Clinical pharmacokinetics of irinotecan and its metabolites in relation with diarrhea. Clin Pharmacol Ther 2002;72(3):265–75.
[20] Bardia A, Messersmith WA, Kio EA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and

efficacy results from the phase I/II IMMU-132-01 basket trial. Ann Oncol 2021;32(6):746–56.
[21] Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med 2021;384:1529–41.
[22] Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32(12):1475–95.
[23] NCCN Clinical Practice Guidelines in Oncology -Breast cancer (NCCN Guidelines). Version 2.2023 — February 7, 2023.
[24] Linee guida AIOM (Associazione Italiana Oncologia Medica) - Carcinoma mammario avanzato. Edizione 2023.
[25] Cortes J, Rugo HS, Cescon DW, et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. N Engl J Med 2022;387(3):217–26.
[26] Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379(22):2108–21.
[27] Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 2019;30(4):558–66.
[28] Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol 2020;31(11):1526–35.
[29] Trodelvy prescribing information. https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf.
[30] Spring LM, Nakajima E, Hutchinson J, Al E. Sacituzumab govitecan for metastatic triple-negative breast cancer: clinical overview and management of potential toxicities. Oncologist 2021;26(10):827–34.
[31] D'Arienzo A, Verrazzo A, Pagliuca M, et al. Toxicity profile of antibody-drug conjugates in breast cancer: practical considerations. *eClinicalMedicine*. 2023;62:102113.
[32] Bardia A, Tolaney SM, Punie K, et al. Biomarker analyses in the phase III ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. Ann Oncol 2021;32(9):1148–56.
[33] Loibl S, Loirat D, Tolaney SM, et al. Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer. Eur J Cancer 2023;178:23–33.
[34] Rugo H, Schmid P, Tolaney S, et al. 1553O Health-related quality of life (HRQoL) in the phase III TROPiCS-02 trial of sacituzumab govitecan (SG) vs chemotherapy in HR+/HER2- metastatic breast cancer (MBC). Annal Oncol 2022.
[35] Kuksis M, Gao Y, Tran W, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. Neuro Oncol 2021;23(6):894–904.
[36] Jung S, Rosenzweig M, Sereika S, et al. Factors associated with mortality after breast cancer metastasis. Cancer Causes Control 2012;23(1):103–12.
[37] Le Rhun E, Guckenberger M, Smits M, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol 2021;32(11):1332–47.
[38] Lin N, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. J Clin Oncol 2020;38(23):2610–9.
[39] Diéras V, Weaver R, Tolaney SM, et al. Abstract PD13-07: Subgroup analysis of patients with brain metastases from the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in metastatic triple-negative breast cancer. Can Res 2021.
[40] Carey LA, Loirat D, Punie K, et al. Sacituzumab govitecan as second-line treatment for metastatic triple-negative breast cancer-phase 3 ASCENT study subanalysis. NPJ Breast Can 2022;8(1):72.
[41] O'Shaughnessy J, Brufsky A, Rugo HS, et al. Analysis of patients without and with an initial triple-negative breast cancer diagnosis in the phase 3 randomized ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer. Breast Can Res Treat 2022;195(2):127–39.
[42] Rugo H, Bardia A, Marmé F, et al. Sacituzumab govitecan in hormone receptor–positive/human epidermal growth factor receptor 2–negative metastatic breast cancer. J Clin Oncol 2022;40(29):3365–76.
[43] Rugo H, Bardia A, Marmé F, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. Lancet 2023;Aug:23:S01.
[44] Hurvitz S, Bardia A, Punie K, et al. 168P - Sacituzumab govitecan (SG) efficacy in patients with metastatic triple-negative breast cancer (mTNBC) by HER2 immunohistochemistry (IHC) status: findings from the phase 3 ASCENT study. Ann Oncol 2022.
[45] Schmid P, Cortés J, Marmé F, Al E. 214MO - Sacituzumab govitecan (SG) efficacy in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer (MBC) by HER2 immunohistochemistry (IHC) status in the phase III TROPiCS-02 study. Ann Oncol 2022.
[46] Spring L, Tolaney S, Vijay Desai N, et al. Phase 2 study of response-guided neoadjuvant sacituzumab govitecan (IMMU-132) in patients with localized triple-negative breast cancer: results from the NeoSTAR trial. J Clin Oncol 2022.
[47] Marmé F, Hanusch C, Furlanetto J, et al. 199TiP Phase III post-neoadjuvant study evaluating sacituzumab govitecan (SG), an antibody drug conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment: SASCIA. Ann Oncol 2021.
[48] Bardia A, Punie K, Barrios C, et al. 275TiP ASCENT-03: Phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in first-line (1L) metastatic triple-negative breast cancer (mTNBC). Ann Oncol 2022;33(supp7):S88–121.
[49] Bardia A, Coates J, Spring L, et al. Abstract 2638: Sacituzumab Govitecan, combination with PARP inhibitor, Talazoparib, in metastatic triple-negative breast cancer (TNBC): Translational investigation. Cancer Res 2022;82:2638.
[50] Zardavas D. Clinical development of antibody-drug conjugates in triple negative breast cancer: can we jump higher? Expert Opin Invest Drugs 2022;31(6):633–44.
[51] Bardia A, Juric D, Shimizu T, et al. LBA4 Datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody-drug conjugate (ADC), for triple-negative breast cancer (TNBC): Preliminary results from an ongoing phase I trial. Ann Oncol 2021;32:S60.
[52] Meric-Bernstam F, Krop I, Juric D, et al. Abstract PD13-08: phase 1 TROPION-PanTumor01 study evaluating datopotamab deruxtecan (Dato-DXd) in unresectable or metastatic hormone receptor–positive/HER2–negative breast cancer (BC). Cancer Res 2023.
[53] Bardia A, Jhaveri K, Kalinsky K, et al. TROPION-Breast01: Datopotamab deruxtecan vs chemotherapy in pre-treated inoperable or metastatic HR + / HER2 – breast cancer. Fut Oncol 2023. Jun 30.
[54] Taylor K, Morgan H, Smart K, Al E. The emerging role of the LIV-1 subfamily of zinc transporters in breast cancer. Mol Med 2007;13(7):396–406.
[55] Sussman D, Smith L, Anderson M, Al E. SGN-LIV1A: a novel antibody-drug conjugate targeting LIV-1 for the treatment of metastatic breast cancer. Mol Can Ther 2014;13(12):2991–3000.
[56] Modi S, Pusztai L, Forero A, Al E. Abstract PD3-14: Phase 1 study of the antibody–drug conjugate SGN-LIV1A in patients with heavily pretreated triple-negative metastatic breast cancer. Cancer Res 2018.
[57] Tsai M, Han H, Montero A, Al E. 259P Weekly ladiratuzumab vedotin monotherapy for metastatic triple-negative breast cancer. Ann Oncol 2021..
[58] Koster K-L, Huober J, Joerger M. New antibody-drug conjugates (ADCs) in breast cancer—an overview of ADCs recently approved and in later stages of development. Explor Target Anti-tumor Ther 2022:27–36.
[59] Meisel J, Pluard T, Vinayak S, Stringer-Reasor E, Al E. Phase 1b/2 study of ladiratuzumab vedotin (LV) in combination with pembrolizumab for first-line treatment of triple-negative breast cancer (SGNLVA-002, trial in progress). J Clin Oncol 2022.
[60] Grinda T, Rassy E, Pistilli B. Antibody-drug conjugate revolution in breast cancer: the road ahead. Curr Treat Options Oncol 2023.
[61] Uliano J, Corvaja C, Curigliano G, et al. Targeting HER3 for cancer treatment: a new horizon for an old target. ESMO Open 2023;8(1):100790.
[62] Yonemori K, Masuda N, Takahashi S, et al. Abstract 1510 - Single agent activity of U3–1402, a HER3-targeting antibody-drug conjugate, in HER3-overexpressing metastatic breast cancer: updated results from a phase I/II trial. Ann Oncol 2019;30(suppl_3):III48.
[63] Krop I, Masuda N, Mukohara T, et al. Results from the phase 1/2 study of patritumab deruxtecan, a HER3-directed antibody-drug conjugate (ADC), in patients with HER3-expressing metastatic breast cancer (MBC). J Clin Oncol 2022;40.
[64] Oliveira M, Falato C, Cejalvo JM, et al. Patritumab deruxtecan in untreated hormone receptor-positive/HER2-negative early breast cancer: final results from Part A of the window-of-opportunity SOLTI TOT-HER3 pre-operative study. Ann Oncol 2023;34(8):670–80.
[65] Powles T, Rosenberg J, Sonpavde G, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021;384(12):1125–35.
[66] M-Rabet M, Cabaud O, Josselin E, Al. E. Nectin-4: a new prognostic biomarker for efficient therapeutic targeting of primary and metastatic triple-negative breast cancer. Ann Oncol. 2017;28(4):769-776.
[67] Ono M, Bruce J, Feinstein T, et al. Abstract OT1-02-04 - Enfortumab vedotin 202: Phase 2 study of enfortumab vedotin for previously treated advanced solid tumors, including breast cancer. Cancer Res 2022;82.
[68] Shimizu T, Fujiwara Y, Yonemori K, et al. First-in-human phase 1 study of MORAb-202, an antibody–Drug conjugate comprising farletuzumab linked to Eribulin Mesylate, in patients with folate receptor-a–Positive advanced solid tumors. Clin Cancer Res 2021;27(14):3905–15.
[69] Matsunaga Y, Yamaoka T, Ohba M. Novel anti-FOLR1 antibody-drug conjugate MORAb-202 in Breast cancer and non-small cell lung cancer cells. Antibodies (Basel) 2021;10(1):6.
[70] Nicolò E, Giugliano F, Ascione L, et al. Combining antibody-drug conjugates with immunotherapy in solid tumors: current landscape and future perspectives. Cancer Treat Rev 2022;106:102395.
[71] Schmid P, Im S-A, Armstrong A, et al. BEGONIA: Phase 1b/2 study of durvalumab (D) combinations in locally advanced/metastatic triple-negative breast cancer (TNBC)—Initial results from arm 1, d+paclitaxel (P), and arm 6, d+trastuzumab deruxtecan (T-DXd). J Clin Oncol. 2021;39(suppl_15):1023-1023.
[72] Schmid P, Jung K, Wysocki P, et al. 166MO - Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): initial results from BEGONIA, a phase 1b/2 study. Ann Oncol 2022;33.
[73] Schmid P, Wysocki P, Park YH, et al. PD11-08 Trastuzumab deruxtecan (T-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic hormone receptor-negative (HR−), HER2-low breast cancer: updated results from BEGONIA, a phase 1b/2 study. Cancer Res 2023;83.
[74] Schmid P, Im S, Armstrong A, et al. BEGONIA: Phase 1b/2 study of durvalumab (D) combinations in locally advanced/metastatic triple-negative breast cancer (TNBC)-Initial results from arm 1, d+paclitaxel (P), and arm 6, d+trastuzumab deruxtecan (T-DXd).J Clin Oncol 2021;39(15_suppl):1023-1023.
[75] Hamilton E, Shapiro C, Boni V, Martin Jimenez M, Del Conte G. 162O Primary analysis from DS8201-A-U105: A 2-part, open label, phase Ib trial assessing

trastuzumab deruxtecan (T-DXd) with nivolumab (nivo) in patients (pts) with HER2-expressing advanced breast cancer. Ann Oncol 2022;33:S196.

[76] Cortés J, Bardia A, Loirat D, et al. Abstract P5-16-15 - Post-Progression Therapy Outcomes in Patients From the Phase 3 ASCENT Study of Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *Cancer Res*. 2022;82(supp4):P5-16-15.

[77] André F, Park H, Kim S, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2023;401(10390):1773–85.