Editorial Commentary

Sacituzumab govitecan and other antibody-drug conjugates targeting trophoblast cell-surface antigen 2 (Trop-2) in breast cancer

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Introduction

Triple-negative breast cancer (TNBC), defined as breast cancer that lacks expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor type 2 (HER2), accounts for approximately 10% to 15% of all breast cancers (1). TNBC has a worse prognosis than other types of breast cancer (2). Chemotherapy has been the mainstay of treatment for metastatic TNBC, but recent clinical trial results have led to U.S. Food and Drug Administration (FDA) approvals of targeted therapies for this disease, including poly (ADP-ribose) polymerase (PARP) inhibitors, checkpoint inhibitors, neurotrophic tyrosine kinase (NTRK) inhibitors, and antibody-drug conjugates (ADCs). The latter are novel therapies that allow for more targeted delivery of cytotoxic drugs and theoretically, they result in less systemic toxicities than would otherwise be observed with non-targeted cytotoxic treatments.

ADCs have made a significant impact in the treatment of breast cancer. In phase III trials, the HER2-targeted ADCs, ado-trastuzumab emtansine and trastuzumab deruxtecan, improved clinical efficacy over standard therapies in patients with metastatic HER2-positive breast cancer. This led to FDA drug approval of ado-trastuzumab emtansine in 2013 and the accelerated approval of trastuzumab deruxtecan in 2019 for advanced HER2-positive breast cancer (3,4). Trophoblast cell-surface antigen 2 (Trop-2), a transmembrane calcium signal transducer, is expressed in many solid tumors, including breast cancer (5). Several novel anti-Trop-2 ADCs are being studied in solid tumors. This editorial commentary will focus on the Trop-2-directed ADCs that have thus far been evaluated in phase III trials. Sacituzumab govitecan (SG) is an anti-Trop-2 monoclonal antibody (mAb) that is coupled to SN-38, a potent inhibitor of topoisomerase I and the active metabolite of irinotecan, via a hydrolysable linker (6). The ASCENT trial was the first phase III study to demonstrate that compared with standard chemotherapy, SG significantly improved median progression-free survival (PFS) and overall survival in patients with pre-treated metastatic TNBC (7).

Sacituzumab govitecan

SG is an intravenous ADC comprised of a humanized anti-Trop-2 mAb linked to SN-38 (6). In April 2020, it was granted accelerated approval by the FDA for the treatment of patients with metastatic TNBC who had received at least two prior lines of therapy in the advanced setting. The accelerated approval was based on efficacy results from the phase I/II trial (IMMU-132-01), which demonstrated that SG treatment resulted in an overall response rate (ORR) of 33.3% (8). In April 2021, the FDA granted full approval for the use of SG in patients with metastatic TNBC who have received at least two prior systemic therapies, with at least one of these received for treatment of metastatic disease. In 2021, SG was also granted marketing authorization by the European Medicines Agency. These approvals

were made on the basis of confirmatory results of the international, open-label, phase III ASCENT trial, which enrolled 468 patients with metastatic TNBC without baseline brain metastases (7). The primary endpoint was PFS. Patients were randomized 1:1 to treatment with either SG 10 mg/kg on days 1 and 8 on a 21-day cycle or chemotherapy of physician's choice (eribulin, vinorelbine, capecitabine, or gemcitabine). Most patients had visceral metastases. Approximately 70% of patients in each arm had received two or three lines of prior chemotherapy, with all patients having received a prior taxane and about 60% prior carboplatin; 30% in each arm had prior checkpoint inhibitors. In addition, less than 10% of patients in each arm had *BRCA1/BRCA2* mutations. Patients treated with SG had significant longer PFS (5.6 months) than those treated with chemotherapy [1.7 months; hazard ratio (HR) 0.41; 95% CI: 0.32–0.52; P<0.001] and longer overall survival; 12.1 months versus 6.7 months (HR 0.48; 95% CI: 0.38–0.59; P<0.001). The ORR on the SG arm was 35% whereas ORRs for the chemotherapy arms were 5%, 4%, 6% and 3% for eribulin, vinorelbine, capecitabine, and gemcitabine, respectively (9). Per recommendations from the data and safety monitoring committee, the trial was stopped early because of the demonstrated efficacy of SG.

The longer median PFS, longer median overall survival, and higher ORR achieved with SG were compelling and clinically meaningful, especially in a population of patients who received a median of four prior anticancer regimens. This improvement in efficacy with SG was also observed in a subgroup analysis of patients who relapsed within 12 months of (neo)adjuvant therapy (10); this was notable because patients with early relapses (≤12 months) are likely to have more aggressive disease (11). A subgroup analysis of 61 patients with brain metastases was also conducted (12). Compared to chemotherapy, SG improved PFS [2.8 months (95% CI: 1.5–3.9) *vs.* 1.6 months (95% CI: 1.3–2.9)] and ORR (3% *vs.* 0%) but not overall survival [6.8 months (95% CI: 4.7–14.1) *vs.* 7.5 months (95% CI: 4.7–11.1)]. Evaluation of this subgroup bears importance as many patients with TNBC develop brain metastases. However, the small sample size for the analysis impedes conclusive determination of the effect of SG on outcomes for patients with brain metastases.

Overall, in the primary trial population, SG demonstrates robust efficacy in pre-treated and aggressive TNBCs. This is an exciting breakthrough, especially since SG has a manageable toxicity profile. Of note, the discontinuation rate due to adverse events from SG was low, at 5%. Treating providers must be prepared to support SG-treated patients with granulocyte colony-stimulating factors, dose reductions, and anti-diarrheal medications, as myelosuppression and diarrhea are common side effects. Neutropenia occurred in 63% of patients treated with SG versus 43% of those treated with chemotherapy, anemia in 34% versus 24%, and diarrhea in 59% versus 12%. The most frequent ≥ grade 3 adverse events with SG versus chemotherapy included neutropenia (51% *vs.* 33%), leukopenia (10% *vs.* 5%), diarrhea (10% *vs.* <1%), anemia (8% *vs.* 5%), and febrile neutropenia (6% *vs.* 2%). Additionally, an analysis of the effects of SG on health-related quality of life (HRQoL) in the ASCENT trial was conducted (13). HRQoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire, which was administered at baseline, on the first day of each cycle, and one month after therapy completion. The results showed that treatment with SG was associated with significantly better HRQoL outcomes than chemotherapy was, including improved global health status and extended time until quality of life deterioration. Although SG was more often associated with diarrhea, nausea, and vomiting, these outcomes did not significantly impact global health status, QoL, or functioning domains. As clinicians decide on treatment options for their patients, HRQoL improvements are important considerations and add to the appeal of prescribing SG for the treatment of incurable metastatic TNBC. Before the FDA approval of SG, the only option for the treatment of programmed cell death-ligand 1 (PD-L1)-negative metastatic TNBC without a germline *BRCA1/BRCA2* mutation, *NTRK* gene fusion, or high tumor mutational burden (defined as ≥10 mutations/megabase) was single-agent or doublet chemotherapy. Use of SG in the pre-treated metastatic TNBC setting is especially of value when a patient has significant pre-existing neuropathy as SG is not neurotoxic; no grade 2 or greater peripheral neuropathy was reported with SG on the ASCENT trial (7). Another common clinical scenario for use of SG is for treating a patient who has had recent neo(adjuvant) chemotherapy and experiences disease recurrence after first-line chemotherapy with or without a checkpoint inhibitor (14). In this instance, i.e., after disease progression on first-line therapy, SG would be a reasonable option. SG is a welcome addition to our armamentarium and is a new standard second-line treatment for metastatic TNBC.

Table 1 Components and characteristics of sacituzumab govitecan and datopotamab deruxtecan

Antibody-drug conjugate	Antibody	Target	Linker	Payload	Drug-to-antibody ratio
Sacituzumab govitecan	RS7	Trop-2	Hydrolysable	SN-38	7.6:1
Datopotamab deruxtecan	Datopotamab	Trop-2	Tetrapeptide-based, cleavable	Deruxtecan	4:1

Trop-2, trophoblast cell-surface antigen 2.

Trop-2 expression and ADCs

Trop-2 is a transmembrane calcium signal transducer. Its expression is increased in multiple solid tumors when compared to its expression in normal tissues, and therefore, Trop-2 is a reasonable drug target. Specifically, it has been shown that the majority of breast cancers express Trop-2, with increased levels associated with increased tumor growth and poor prognosis (5,15,16). Increasing evidence suggests that ADCs targeting Trop-2 can be efficacious; therefore, this antigen may prove to be a valuable target across a variety of solid tumors in the future (8,17,18). Thus far, clinical trials evaluating Trop-2–targeted ADCs in breast cancer have not limited enrollment based on elevated Trop-2 expression. In contrast, approval of ado-trastuzumab emtansine and trastuzumab deruxtecan was based on studies in which the eligibility criteria required the biomarker HER2 to be overexpressed (immunohistochemical score of 3+ or positive by *in situ* hybridization) (3,19,20). The role of trastuzumab deruxtecan in the treatment of tumors with lower HER2 expression has been evaluated, as these tumors may respond as well, possibly due to a "bystander effect," i.e., the chemotherapy payload kills cancer cells directly and also nearby cancer cells (21,22).

The manufacturer of SG does not recommend evaluating Trop-2 expression in the tumor tissue. In the phase III ASCENT trial, Trop-2 expression was not required for enrollment, but pre-specified analyses were planned to evaluate its expression and correlation with clinical outcomes. Of the 235 patients who received SG as part of the trial, 151 tumors were evaluable for Trop-2 expression level (64%); 56% of these tumors were categorized with high Trop-2 H-scores, 26% with medium and 18% with low (17). Across all three Trop-2 subgroups (high, medium, and low Trop-2 H-scores), ORR, median PFS, and median overall survival were numerically higher in the SG arm than in the chemotherapy arm. However, patients with high and medium Trop-2 expressing tumors treated with SG appeared to have numerically better ORR, PFS, and overall survival than tumors with low Trop-2 expression. In fact, ORR and PFS for the patients with high/medium Trop-2 expressing tumors were almost double that of the patients with low Trop-2 expressing tumors. The magnitude of benefit in patients with low Trop-2 H-scores is difficult to decipher given the low number of patients in this group. Further studies, specifically those that include patients with low Trop-2 expressing tumors, need to be conducted to evaluate whether Trop-2 levels can predict better response to SG. Until then, patients with metastatic TNBC should continue to receive SG regardless of Trop-2 expression in the tumor.

To date, SG has one other indication in solid tumors—for patients with previously treated, locally advanced or metastatic, urothelial cancer. Accelerated approval in this setting was granted based on its efficacy in the phase II trial TROPHY-U-01 (18). Determinating Trop-2 expression levels in the tumor was not required for eligibility in this trial and is also not required for patients to receive SG in this setting.

Datopotamab deruxtecan

Datopotamab deruxtecan (Dato-DXd) is another Trop-2–directed mAb that is gaining interest for the treatment of multiple solid tumor types, including breast cancer. The characteristics of Dato-DXd compared to SG are listed in *Table 1*. Dato-DXd is currently being investigated in the phase I trial, TROPION-PanTumor01 (NCT03401385). The dose escalation cohort included patients with either advanced TNBC or non-small cell lung cancer (NSCLC), whereas the expansion cohort included patients with various additional tumor types, including hormone receptor-positive (HR+) breast cancers. All patients were unselected for Trop-2 expression. The primary objectives were safety and tolerability. Data for the metastatic TNBC cohort (n=44) was reported at the 2021 San Antonio Breast Cancer Symposium by Krop *et al.* (23). Results demonstrated that patients treated with Dato-DXd had an ORR of 34% and a disease control rate of 77%. Patients could have received previous ADC therapy. After analyzing the subgroup that had not received any previous topoisomerase I inhibitor-

based ADC (n=27), it was found that the ORR was even greater, at 52%, with a disease control rate of 81%. Dato-DXd was deemed safe; the most common treatment-emergent adverse events were nausea and stomatitis. Treatment-emergent neutropenia, anemia, and diarrhea was low (<20% for each), which contrasts with the adverse events profile of SG (7). No drug-related interstitial lung disease (ILD) was observed in this TNBC cohort. However, during the dose analysis of 175 patients with metastatic NSCLC, 8% of patients experienced ILD, with three patients experiencing grade 5 ILD (24). The rates of ILD were higher in the 8 mg/kg group (15%) than in the 6 mg/kg group (2%) and the 4 mg/kg group (2%). In the TNBC cohort, 95% of the patients were treated at a dose of 6 mg/kg and only 5% were treated at a dose of 8 mg/kg.

An ongoing randomized phase III trial, TROPION-Breast02 (NCT05374512), is comparing Dato-DXd versus investigator's choice chemotherapy (either paclitaxel, nab-paclitaxel, carboplatin, capecitabine, or eribulin mesylate). This trial is being conducted in the first-line setting for patients with metastatic TNBC who are not candidates for treatment with immune checkpoint inhibitors. If results confirm efficacy, Dato-DXd could become another option for treating metastatic TNBC.

Looking to the future

Results of studies of the Trop-2–targeted ADCs have been clinically meaningful, and it remains to be seen whether using these agents as an earlier line of therapy or combining them with other drugs could broaden their applicability. Additionally, as Trop-2 is expressed in most solid epithelial cancers, a role for Trop-2–targeted agents may exist in treating other subtypes of breast cancer as well. Multiple ongoing trials are evaluating Trop-2–targeted agents in these settings.

Several trials (*Table 2*) in the metastatic TNBC setting are evaluating SG alone and in combination with other drugs, including immunotherapy agents and PARP inhibitors. In the randomized phase III trial, TROPiCS-02 (NCT03901339), SG was evaluated in patients with metastatic HR+/HER2-negative breast cancer. Patients must have progressed on at least two, but no more than four, prior chemotherapy regimens. Prior taxane, hormonal treatment, and cyclin-dependent kinase 4/6 inhibitors were all required for eligibility. Patients were randomized to either SG or physician's choice of chemotherapy (eribulin, capecitabine, gemcitabine, or vinorelbine). Primary results were presented at the 2022 American Society of Clinical Oncology Annual Meeting. Median follow-up was 10.2 months. PFS, the primary outcome, was longer in the SG arm than in the chemotherapy arm [5.5 versus 4.0 months (HR 0.66; 95% CI: 0.53–0.83; P=0.0003)] (25). Results of this first interim analysis showed that overall survival was longer with SG, albeit not significantly [13.9 versus 12.3 months (HR 0.84; 95% CI: 0.67–1.06; P=0.143)]. Results of subgroup analyses demonstrated improved benefit from SG across all subgroups, including older patients (>65 years), patients with visceral metastases, and those with ≥ three lines of chemotherapy in the metastatic setting. These are encouraging results, especially since patients with metastatic HR+/HER2-negative breast cancer who exhaust their oral treatment options often have less durable responses with each additional line of cytotoxic chemotherapy. On the basis of these primary results, SG could be considered another potential treatment option for patients with metastatic HR+/HER2-negative disease who have progressed through multiple lines of chemotherapy.

Ongoing trials (*Table 2*) are assessing SG in patients with early-stage breast cancer in the neoadjuvant and adjuvant settings. NeoSTAR (NCT04230109) is a non-randomized, single arm phase II study enrolling patients with localized TNBC. The study will assess pathologic complete response (pCR) in patients receiving neoadjuvant SG with or without pembrolizumab. In clinical practice, treating TNBC with neoadjuvant therapy is a standard approach to improving resectability, downstaging the axilla, and increasing the likelihood of breast conservation (26). It also allows providers to evaluate the response to therapy at the time of surgery, which is important because patients with a pCR at the time of surgery have longer event-free survival and overall survival than those with residual disease (27-29). Recently, the importance of pCR was underscored by the approval of the addition of pembrolizumab to neoadjuvant chemotherapy (carboplatin, paclitaxel, doxorubicin, and cyclophosphamide) on the basis of the improved pCR rates and event-free survival reported in the KEYNOTE-522 trial (30,31). Another trial in the early-stage breast cancer setting, SASCIA (NCT04595565), will evaluate SG in the adjuvant setting. This phase III trial is enrolling patients with HER2-negative breast cancer with high risk of relapse. Eligible patients are those with TNBC and residual disease after neoadjuvant chemotherapy, defined as > ypT1mi, and patients with HR+ breast cancer and residual disease, defined as a CPS (clinical and post-treatment pathological stage) + EG (estrogen receptor status and grade) score ≥3

Table 2 Select ongoing trials with sacituzumab govitecan in breast cancer*

Trial title	NCT number	Phase	Population	Setting	Drug regimen
Response-guided Neoadjuvant Sacituzumab Govitecan (IMMU-132) in Patients with Localized TNBC (NeoSTAR)	04230109	II	Localized TNBC	Neoadjuvant	Experimental Arm A: sacituzumab govitecan. May be followed by standard chemotherapy Experimental Arm B: sacituzumab govitecan and pembrolizumab. May be followed by standard chemotherapy
Sacituzumab Govitecan in Patients with Primary HER2-negative BC with High Relapse Risk After Standard Neoadjuvant Treatment (SASCIA)	04595565	III	Localized HER2-negative BC at high risk of recurrence	Residual disease after neoadjuvant chemotherapy	Control Arm: capecitabine, platinum-based chemotherapy, or observation (physician's choice) Experimental Arm: sacituzumab govitecan For HR+ BC, endocrine therapy will be administered according to local guidelines
Atezolizumab and Sacituzumab Govitecan to Prevent Recurrence in TNBC (ASPRIA)	04434040	II	Localized TNBC with residual disease after neoadjuvant therapy	Adjuvant	Experimental Arm: sacituzumab govitecan and atezolizumab
Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy And Safety Of Multiple Immunotherapy-Based Treatment Combinations In Patients with Metastatic TNBC (Morpheus-TNBC)	03424005	Ib/II	Metastatic TNBC cohort: PD-L1-positive	First-line	Control Arm: atezolizumab and nab-paclitaxel Experimental Arm A: atezolizumab and sacituzumab govitecan Experimental Arm B: atezolizumab, nab-paclitaxel and tocilizumab
Saci-IO TNBC: Randomized Phase II Study of Sacituzumab Govitecan with or without Pembrolizumab in PD-L1-negative Metastatic TNBC	04468061	II	Metastatic TNBC PD-L1-negative	First-line	Experimental Arm A: pembrolizumab and sacituzumab govitecan Experimental Arm B: sacituzumab govitecan
Sacituzumab Govitecan and Pembrolizumab Versus Treatment of Physician's Choice and Pembrolizumab in Patients with Untreated Metastatic TNBC (ASCENT-04)	05382286	III	Metastatic TNBC PD-L1-positive	First-line	Control Arm: pembrolizumab and physician's choice chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin) Experimental Arm: pembrolizumab and sacituzumab govitecan
Phase 1b/2 Study to Evaluate Antibody-Drug Conjugate Sacituzumab Govitecan in Combination with PARP Inhibitor Talazoparib in Patients with Metastatic Breast Cancer	04039230	Ib/II	Metastatic TNBC	All treatment lines	Experimental: sacituzumab govitecan and talazoparib

Table 2 (*continued*)

Table 2 (*continued*)

Trial title	NCT number	Phase	Population	Setting	Drug regimen
Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in Subjects with Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer Who Have Failed at Least Two Prior Chemotherapy Regimens (TROPiCS-02)	03901339	III	Metastatic HR+/ HER2–negative	≥2 prior lines of chemotherapy but no more than 4. At least 1 line must have involved a CDK4/6 inhibitor	Control Arm: eribulin, capecitabine, gemcitabine, or vinorelbine (physician's choice) Experimental Arm: sacituzumab govitecan
Trilaciclib Administered Prior to Sacituzumab Govitecan-hziy in Patients with Unresectable Locally Advanced or Metastatic Triple Negative Breast Cancer Who Received at Least Two Prior Treatments, at Least One in the Metastatic Setting	05113966	II	Metastatic TNBC	≥2 prior lines of chemotherapy. At least 1 in the metastatic setting	Experimental Arm: sacituzumab govitecan and trilaciclib

*, as of June 3rd, 2022 on clinicaltrials.gov. BC, breast cancer; CDK4/6 inhibitor, cyclin-dependent kinase 4/6 inhibitor; HR+, hormone receptor-positive; HER2, human epidermal growth factor receptor 2; PD-L1, programmed cell death-ligand 1; TNBC, triple-negative breast cancer.

or a score of 2 with a positive lymph node. Patients will be randomized to either eight cycles of SG or physician's choice therapy (capecitabine, platinum-based chemotherapy or observation with/without endocrine therapy). The primary endpoint is invasive disease-free survival. A clear need exists for improving outcomes in patients who are deemed high risk and do not attain pCR. If the results of SASCIA show that SG improves invasive disease-free survival, then SG is likely to become another option for treating residual disease in patients with high-risk primary HER2-negative breast cancer.

Dato-DXd is also being evaluated in multiple settings and with different drug combinations. *Table 3* lists the ongoing trials with Dato-DXd, including BEGONIA (NCT03742102), TROPION-Breast01 (NCT05104866), and the previously discussed TROPION-PanTumor01 study (NCT03401385). BEGONIA is a phase Ib/II multi-arm trial investigating durvalumab in combination with multiple different agents, including Dato-DXd, in the first line setting for patients with metastatic TNBC. At a median follow-up of 3.9 months, initial results for the 27 patients receiving Dato-DXd plus durvalumab demonstrated an ORR of 74% (7% CR and 67% PR), warranting further enrollment and analysis in the expansion phase (32).TROPION-Breast01 is a phase III trial assessing Dato-DXd versus investigator's choice chemotherapy (capecitabine, gemcitabine, eribulin, or vinorelbine) in patients with pre-treated (one or two previous lines) HR+/HER2-negative metastatic disease. The primary outcomes are PFS and overall survival. This trial is similar to TROPiCS-02 described above, although with the opportunity for less heavily pre-treated patients to be enrolled. Until now, ADCs have mostly been used to treat the TNBC and HER2-positive populations; however, these two trials highlight the unmet need for more effective therapies in later line settings for patients with HR+/HER2-negative metastatic disease.

The treatment paradigm for metastatic TNBC has evolved since 2020 when the first checkpoint inhibitor was approved and when PARP and NTRK inhibitors became treatment options for patients harboring the appropriate biomarkers. ADCs represent the latest treatment advancement. ASCENT was the first trial to show that treatment with an ADC improved overall survival for metastatic TNBC in a patient population unselected for biomarkers. With the approval of SG in the second line setting and beyond, an effective treatment option now exists for patients, regardless of their biomarkers. Patients with PD-L1–positive tumors can receive SG after progression on their first line chemoimmunotherapy. In the ASCENT trial, 29% of patients had previous exposure to a PD-1/PD-L1 inhibitor. A subgroup analysis of PFS showed that regardless of previous exposure to PD-1/PD-L1

Table 3 Select ongoing trials with datopotamab deruxtecan (Dato-Dxd) in breast cancer*

Trial name	NCT number	Phase	Population	Setting	Drug regimen
Phase 1, Two-part, Multicenter, Open-label, Multiple Dose, First-in-human Study of DS-1062a in Subjects with Advanced Solid Tumors (TROPION-PanTumor01)	03401385	I	Multiple metastatic tumor types including TNBC and HR+/HER2-negative BC	After relapse or progression following local standard treatment(s)	Experimental Arm: Dato-DXd
A Phase IB/II, 2-stage, Open-label, Multicenter Study to Determine the Efficacy and Safety of Durvalumab (MEDI4736) + Paclitaxel and Durvalumab (MEDI4736) in Combination with Novel Oncology Therapies with or without Paclitaxel for First-line Metastatic Triple-Negative Breast Cancer (BEGONIA)	03742102	Ib/II	Metastatic TNBC	First-line	Experimental Arm A: durvalumab and Dato-DXd Experimental Arm B: durvalumab and trastuzumab deruxtecan Experimental Arm C: durvalumab, paclitaxel and oleclumab Experimental Arm D: durvalumab, paclitaxel and capivasertib Experimental Arm E: durvalumab and paclitaxel
A Phase-3, Open-Label, Randomized Study of Dato-DXd Versus Investigator's Choice of Chemotherapy in Participants with Inoperable or Metastatic HR-Positive, HER2-Negative Breast Cancer Who Have Been Treated with One or Two Prior Lines of Systemic Chemotherapy (TROPION-Breast01)	05104866	III	Metastatic HR+/HER2-negative	1-2 prior lines of therapy	Control Arm: eribulin, capecitabine, gemcitabine or vinorelbine (investigator's choice) Experimental Arm: Dato-DXd
A phase 3, Open-label, Randomized Study of Dato-DXd Versus Investigator's Choice of Chemotherapy in Patients Who Are Not Candidates for PD-1/PD-L1 Inhibitor Therapy in First-line Metastatic TNBC (TROPION-Breast02)	05374512	III	Metastatic TNBC	First-line	Control Arm: paclitaxel, nab-paclitaxel, carboplatin, capecitabine or eribulin mesylate (investigator's choce) Experimental Arm: Dato-DXd

*, as of June 3rd, 2022 on clinicaltrials.gov. BC, breast cancer; Dato-DXd, datopotamab deruxtecan; HR+, hormone receptor-positive; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

inhibitors, PFS was longer in patients receiving SG than for those receiving chemotherapy. For patients with BRCA mutations, it is reasonable to sequence SG after a PARP inhibitor, as PARP inhibitors are effective in this population, and since these drugs are administered orally, treatment is less cumbersome. Patients with BRCA mutations who had received prior PARP inhibitors comprised 7% of the ASCENT population.

With the compelling overall survival results from the ASCENT trial and initial response rates from results of the TROPION-PanTumor01 trial, Trop-2-targeted ADCs appear to be not only efficacious but appropriate for a broad patient population, as they do not require expression of a specific biomarker (based on the current data). It is possible that moving ADCs to the front-line, as monotherapy or in combination, could result in greater benefit. As previously described, efforts are underway to investigate ADCs in the metastatic setting in earlier lines and in

combination with other agents. Furthermore, multiple trials are now investigating the incorporation of ADCs into the neoadjuvant/adjuvant setting for early-stage HER2-negative breast cancer. As these trials and other ADC trials in breast cancer continue to accrue and report results, more information will be available to guide further incorporation of Trop-2-targeted ADCs into our treatment algorithms.

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