# Sacituzumab Govitecan for Treatment of Refractory Triple-Negative Metastatic Breast Cancer

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Authors' disclosures of conflicts of interest are found at the end of this article.

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**Abstract**

Sacituzumab govitecan was initially approved in April 2020 under accelerated approval for the treatment of patients with metastatic triple-negative breast cancer who received at least two prior therapies for metastatic disease. A confirmatory phase III trial evaluating sacituzumab govitecan vs. chemotherapy of the provider's choice was published in April 2021. Based on this trial, the FDA granted sacituzumab govitecan full regulatory approval. This antibody-drug conjugate is composed of a monoclonal antibody targeted at Trop-2 and contains the active metabolite of irinotecan, SN-38, as a cytotoxic side moiety. In a phase III clinical trial, sacituzumab govitecan demonstrated a median progression-free survival of 5.7 months vs. 1.7 months with chemotherapy. It is now an additional option for patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for metastatic disease.

There was an estimated 276,480 new cases of breast cancer in the United States in 2020, making breast cancer the most common cancer in women (Siegel et al., 2020). While the rate of new cases has remained stable over the past decade, there has been a steady decline in the death rate. As women receive more treatments and live longer with refractory metastatic breast cancer, new agents continue to enter and shape the treatment landscape for this disease.

Sacituzumab govitecan (Trodelvy) was designated as a breakthrough therapy in 2016 for the treatment of metastatic triple-negative breast cancer (mTNBC). Triple-negative breast cancer lacks expression of estrogen receptors, progesterone receptors, and HER2 receptors, and is associated with poor patient outcomes (Anders et al., 2013). The majority of patient have disease progression after receiving first-line therapy, and subsequent options are limited. Patients often receive a series of single-agent chemotherapies. Despite a modest increase in the number of chemotherapeutic agents available, the overall survival has not changed in the past 20 years. Therapies tend to have low response rates, and patients will develop progression of disease (Zeichner et al., 2016).

Sacituzumab govitecan received accelerated approved by the FDA in April 2020 and subsequently full regulatory approval in April 2021 (Immunomedics Inc., 2021). This novel drug is approved for patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for metastatic disease. Also in April 2021, the FDA granted accelerated approval to sacituzumab govitecan for patients with locally advanced or metastatic urothelial cancer who previously received a platinum-containing chemotherapy and either a programmed cell death protein 1 or a programmed cell death ligand 1 inhibitor. Confirmatory phase III trails are ongoing for this indication.

The purpose of this article is to describe the use of sacituzumab govitecan in unresectable locally advanced and refractory mTNBC and the clinical implications for oncology advanced practitioners.

## PHARMACOLOGY AND MECHANISM OF ACTION

Sacituzumab govitecan is a novel antibody-drug conjugate (ADC). It is composed of a humanized monoclonal antibody that is connected to a modified active metabolite of irinotecan, SN-38 (Bardia et al., 2017; Fenn & Kalinsky, 2019). Modification of SN-38 allows for it to be less active from under physiologic conditions and prevents cross-reactivity during transport in the serum. Sacituzumab govitecan targets the glycoprotein Trop-2, which is a transmembrane calcium signal transducer. Trop-2 overexpression has been linked to various epithelial cancers, such as cervical, gastric, breast, and pancreatic cancer (Zaman et al., 2019) and plays an integral role in cell migration and anchorage-independent growth. It causes expression of NF-kB, cyclin D1, and ERK, leading to pro-growth signaling cascades (Cardillo et al., 2015). Once sacituzumab govitecan selectively binds Trop-2, it is internalized. SN-38 is released into the cell via pH-mediated release, where it functions as a topoisomerase-I (topo-I) inhibitor. It stabilizes the complex between topo-I and DNA, which eventually leads to double-stranded DNA breakage (Cardillo et al., 2015; Fenn & Kalinsky, 2019; Goldenberg et al., 2015; Govindan et al., 2012; Voigt et al., 1998). This then causes upregulation of proapoptotic protein signals p53 and p21, ultimately causing G1 cell cycle arrest and activating the intrinsic apoptotic pathway.

## CLINICAL TRIALS

A phase I/II, single-arm, multicenter, basket design, open-label trial showed sacituzumab govitecan to have an objective response rate (ORR) in one third of patients, with a median progression-free survival (PFS) of 5.5 months (Bardia et al., 2019). Other noteworthy outcomes from this trial were time to response (TTR), duration of response (DOR), and the clinical benefit rates, which were 2 months, 7.7 months, and 45.4%, respectively. However, 94% of patients experienced some degree of gastrointestinal toxicities. Neutropenia occurred in 64% of patients, 26% of which were grade 3 and 16% grade 4. Febrile neutropenia was reported in 9% of patients, including 8% grades 3 or 4 toxicity.

The phase III ASCENT trial for sacituzumab govitecan was published in April 2021 by Bardia and colleagues. The study was sponsored and designed by Immunomedics, the drug's manufacturer. The data were analyzed by both Immunomedics and Covance, a contract research organization.

The patients were enrolled between November 2017 and September 2019 for the phase III trial. The data cutoff was March 11, 2020. The ASCENT trial was a global, open-label, randomized trial. There were 529 patients enrolled and 61 had brain metastases at baseline; 488 patients were anticipated to enroll. The inclusion criteria included ECOG score of 0 or 1, age 18 years or older, mTNBC diagnosis, and previous treatment with two or more standard-of-care chemotherapies, including a taxane.

Chemotherapy agents selected in the physician's choice arm included eribulin, vinorelbine, capecitabine, or gemcitabine. The median age of patients was 54 years. The sacituzumab govitecan and chemotherapy groups had a majority of white patients, 80% and 78%, respectively.

Patients were randomized in a 1:1 fashion and stratified based on the number of previous chemotherapy regimens for advanced disease, presence/absence of brain metastases, and geographic area. The study group (235 patients) received 10 mg/kg of sacituzumab govitecan on days 1 and 8 every 21 days. The control arms received single-agent chemotherapy of physician's choice.

The primary endpoint was PFS in patients without brain metastases. The secondary endpoints included overall survival (OS), PFS, objective response, and safety. Imaging using CT and MRI was performed every 6 weeks for 36 weeks, and every 9 weeks after 36 weeks until disease progression was visualized or toxicity.

The primary endpoint of PFS in patients without brain metastases was 5.6 months for sacituzumab govitecan and 1.7 months for chemotherapy (hazard ratio [HR], 0.41; 95% confidence interval [CI] = 0.32–0.52; $p < .001$). Secondary endpoints of median OS were 12.1 months with sacituzumab govitecan and 6.7 months with chemotherapy (HR, 0.48; 95% CI = 0.38–0.59; $p < .001$). An objective response was observed in 35% of patients on sacituzumab govitecan and in 5% on chemotherapy.

The efficacy in patients with or without brain metastases differed slightly. The median PFS was 4.8 months with sacituzumab govitecan and 1.7 months with standard chemotherapy (HR, 0.43; 95% CI = 0.35–0.54). The median OS was 11.8 months with sacituzumab govitecan and 6.9 months with chemotherapy (HR, 0.51; 95% CI = 0.41–0.62).

## SAFETY

Safety was assessed throughout the trial and included 482 patients who received at least one dose of either treatment regimen (Table 1). Almost all (98%) patients experienced an adverse event while receiving either treatment. The most common adverse events in the sacituzumab govitecan arm

**Table 1. Common Adverse Events Reported by Patients Receiving Sacituzumab Govitecan vs. Chemotherapy**

| | Sacituzumab govitecan (N = 258) | | | Chemotherapy (N = 224) | | |
|---|---|---|---|---|---|---|
| **Adverse event** | **Any grade** | **Grade 3** | **Grade 4** | **Any grade** | **Grade 3** | **Grade 4** |
| Any event | 252 (98) | 117 (45) | 48 (19) | 192 (86) | 71 (32) | 33 (15) |
| *Gastrointestinal disorders* | | | | | | |
| Diarrhea | 153 (59) | 27 (10) | 0 | 27 (12) | 1 (< 1) | 0 |
| Nausea | 147 (57) | 6 (2) | 1 (< 1) | 59 (26) | 1 (< 1) | 0 |
| Vomiting | 75 (29) | 2 (1) | 1 (< 1) | 23 (10) | 1 (< 1) | 0 |
| Constipation | 44 (17) | 0 | 0 | 32 (14) | 0 | 0 |
| Abdominal pain | 29 (11) | 3 (1) | 0 | 9 (4) | 1 (< 1) | 0 |
| *Blood and lymphatic system disorders* | | | | | | |
| Neutropenia | 163 (63) | 88 (34) | 44 (17) | 96 (43) | 45 (20) | 29 (13) |
| Febrile neutropenia | 15 (6) | 12 (5) | 3 (1) | 5 (2) | 4 (2) | 1 (< 1) |
| Anemia | 89 (34) | 20 (8) | 0 | 54 (24) | 11 (5) | 0 |
| *Skin and subcutaneous disorders* | | | | | | |
| Alopecia | 119 (46) | 0 | 0 | 35 (16) | 0 | 0 |
| Rash | 22 (9) | 1 (< 1) | 0 | 3 (1%) | 1 (< 1) | 0 |
| *General disorders and administration site conditions* | | | | | | |
| Fatigue | 115 (45) | 8 (3) | 0 | 68 (30) | 12 (5) | 0 |
| *Metabolism and nutrition disorders* | | | | | | |
| Decreased appetite | 51 (20) | 4 (2) | 0 | 32 (14) | 1 (< 1) | 0 |

*Note*. Information from Bardia et al. (2021).

were neutropenia, anemia, diarrhea, nausea, alopecia (46%), and fatigue (45%). Neutropenia was the most common adverse event with sacituzumab govitecan, with 63% of patients experiencing any grade, 34% with grade 3, and 17% with grade 4. In comparison, 43% of patients on chemotherapy experienced neutropenia of any grade. Anemia occurred in 34% of patients receiving sacituzumab govitecan, 8% being grade 3. Anemia was seen in 24% of patients in the chemotherapy arm. Gastrointestinal adverse events were also common. Diarrhea was the most common, with 59% of patients on sacituzumab govitecan experiencing any grade and 10% with grade 3. In the chemotherapy group, 12% of patients experienced diarrhea. Nausea was seen in 57% of sacituzumab govitecan patients compared with 26% of chemotherapy patients. Another notable toxicity was one case of grade 3 pneumonitis in the sacituzumab govitecan group while no one experienced this in the chemotherapy group.

## DOSING AND ADMINISTRATION

Sacituzumab is to be administered intravenously at 10 mg/kg on days 1 and 8 of a 21-day treatment cycle (Immunomedics Inc., 2021). A solution of 0.9% sodium chloride for injection resulting in a final concentration of 1.1 to 3.4 mg/mL is required at final dilution. The volume of the finished product should not exceed 500 mL. If patients exceed 170 kg, infusions should be split equally between two 500-mL infusion bags and infused sequentially. The first infusion should be administered over 3 hours. If the first infusion is tolerated then subsequent infusions may be administered over 1 to 2 hours. Patients should be observed for 30 minutes after each infusion.

In order to reduce infusion-related reactions (IRR), premedications are recommended. Acetaminophen, $H_1$, and $H_2$ blockers should be used prior to each infusion. If a patient has had a previous IRR, then corticosteroids may be added.

In the case of an IRR, the infusion rate should be slowed or interrupted. If the reaction is life threatening, then the sacituzumab should be permanently discontinued.

If grade 4 neutropenia lasts 7 or more days, there is grade 3 febrile neutropenia, or if grade 3 to 4 neutropenia delays treatment by greater than 2 to 3 weeks before recovery to grade 1 occurs, then a dose reduction of 25% is recommended (Table 2). With the second occurrence, a 50% dose reduction is allowed. Treatment should be discontinued after a third occurrence.

## IMPLICATIONS FOR THE ADVANCED PRACTITIONER

When treating with sacituzumab govitecan, patients should undergo routine monitoring for complications. Patients should have a complete blood count with differential drawn prior to each dose on days 1 and 8 of their cycles as neutropenia is a boxed warning for sacituzumab govitecan. Dose reduction are recommended for neutropenic episodes (Table 2). Therapy should be held for patients with absolute neutrophil count (ANC) less than 500 cells/$mm^3$ lasting 7 or more days and resumed when the ANC is greater than 1,500 cells/$mm^3$ on day 1 of a cycle or greater than 1,000 cells/$mm^3$ on day 8 of a cycle. Practitioners should consider granulocyte colony-stimulating factors in patients who demonstrate neutropenia during treatment and follow recommended dose reductions. In patients with prolonged or severe neutropenia not responsive to treatment, practitioners should suspect patients to have homozygous UGT1A1*28 alleles. This genetic polymorphism would confer a greater risk of toxicity to sacituzumab govitecan; however, no dose recommendations exist for these patients, and individual tolerance should determine dosing. If an episode of neutropenia lasts longer than 3 weeks and has not resolved to grade 1, treatment should be discontinued.

Sacituzumab govitecan has an additional boxed warning of diarrhea. Early diarrhea can be managed by the administration of atropine. Late-onset diarrhea can be managed by loperamide after ruling out infectious causes. Patients should be counseled on how to manage diarrhea with loperamide prior to their first dose. Sacituzumab govitecan should be held if grade 3 or greater diarrhea is present and should not be resumed until diarrhea returns to a grade 1 toxicity.

Due to the risk of IRR, patients should be premedicated with $H_1$ and $H_2$ antagonists as well as acetaminophen prior to each dose. Patients should be monitored for IRR during infusions and for 30 minutes after each infusion.

In addition, females of child-bearing potential should be evaluated for pregnancy status throughout treatment.

Lastly, sacituzumab govitecan is highly emetogenic, and patients should receive prophylaxis for nausea and vomiting. Acceptable regimens should contain 5-$HT_3$ antagonists, dexamethasone, and NK1 antagonists with or without olanzapine. Patients should receive dexamethasone or olanzapine for 3 days following each dose of sacituzumab govitecan, and a prescription for breakthrough nausea and vomiting should be provided.

## ONGOING CLINICAL TRIALS

Currently, there are three phase I clinical trials evaluating sacituzumab govitecan in glioblastoma, advanced or metastatic solid tumor, and liver failure. There are currently 13 phase II clinical trials underway further investigating triple-negative breast cancer, invasive and metastatic breast cancer, invasive breast carcinoma, ER-negative breast cancer, HER2-negative breast cancer, PR-negative breast cancer, PD-L1–negative, HER2-positive breast cancer, anatomic stage IV breast cancer, endometrial carcinoma, glioblastoma, urothelial carcinoma, ovarian cancer, and non–small cell lung carcinoma. There are also five phase III clinical trials investigating use in metastatic breast cancer, HER2-negative breast cancer, triple-negative breast cancer, urothelial carcinoma, bladder cancer, metastatic urothelial carcinoma, locally advanced urothelial cancer, and transitional cell carcinoma. Two clinical trials were recently suspended, one temporarily to mitigate the impact of the COVID-19 pandemic and the other for reasons not provided.

## SUMMARY

With phase III clinical trial data demonstrating a PFS of 5.6 months and OS of 12.1 months with sacituzumab govitecan compared with 1.7 months and 6.7 months with chemotherapy, respectively, sacituzumab govitecan represents a new option for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for metastatic disease. This ADC combines the antibody target of Trop-2 and a cytotoxic side moiety of SN-38 to exert its effect. However, the monitoring and management of diarrhea, nausea and vomiting, and myelosuppression remain critical components in caring for patients receiving sacituzumab govitecan.

**Table 2. Dose Levels**

| Grade 3 or 4 adverse events | Dose levels |
|---|---|
| Starting dose | 10 mg/kg |
| First occurrence | 7.5 mg/kg |
| Second occurrence | 5 mg/kg |
| Third occurrence | Discontinue |

### Disclosure

The authors have no conflicts of interest to disclose.

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