

Effects of Sacituzumab on Breast Cancer: Target Therapy

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Article History:

Received: November 30, 2023

Accepted: December 15, 2023

ePublished: December 29, 2023

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Abstract

Triple-negative breast cancer (TNBC) is considered one of the most aggressive forms of BC, which increases the risk of cancer-associated death. Despite the availability of specifically targeted medications for treating TNBC with HER2-positive or hormone receptor-positive cancers, chemotherapy is still the mainstay of treatment. Sacituzumab, an antibody-drug conjugate (ADC), targets tumor-associated calcium signal transducer 2 (Trop-2)-expressing cells and presents biologically active metabolites of irinotecan hydrochloride (SN-38). This review evaluates the effectiveness and safety of Sacituzumab in treating metastatic or previously treated TNBC in patients. According to the National Center for Biotechnology Information website, another epithelial metastasis has been included in data on clinical trials and sacituzumab. Sacituzumab has hopeful antitumor effects on patients with metastatic TNBC treated with at least two treatment lines, according to a clinical trial that is in phase I/II. Sacituzumab has a controllable adverse effect, with neutropenia, nausea, and diarrhea being the most frequent negative side effects. As a result of these promising early efficacy data, Sacituzumab's activity may develop in TNBC, as well as various other epithelial tumors, such as hormone receptor-positive BC.

Keywords: Metastatic breast cancer, Sacituzumab, TNBC, Trop-2, Antibody-drug conjugates

Introduction

Triple-negative breast cancer (TNBC) does not display any presence of estrogen or progesterone receptors, and the human epidermal growth factor receptor 2 does not appear to be amplified in this type of cancer.¹ Despite being more common in premenopausal women, adversary mutation carriers of the BC gene (*BRCA*), and African and American women, around 15% of BCs are classified as TNBC.^{2,3} BC promotion and malignant face can be associated with TNBC, with an elevated risk of recurrence and poor medical consequences.⁴ TNBC patients have an average total survival of less than 20 months, while the average improvement-free survival remains about 4–5 months with reasonable cytotoxic medications such as chemotherapy.^{5–9} Generally, Molecular sequencing results have improved the concept of homozygosity of molecular NBC in an approach to determining genomic types related to drug reactions.

There is an overlap between TNBC and intrinsic basal-like subtypes; nearly 60%–78% of TNBCs are basal-like, and about 82% of basal-like cancers are TNBCs.¹⁰ There are some genomic sets within TNBC, including BL1 and BL2 as basal-like 1 and 2, luminal androgen receptor (LAR), immunoregulatory, mesenchymal-stem-like, mesenchymal (M), and an unstable cluster.^{11,12} In some case studies, tumor-infiltrating lymphocytes

and mesenchymal cells serving tumors were detected in cancerous tissues, and expression templates were transformed into LAR, M, BL2, and BL1. The type of BL1 was related to an elevated pathologic perfect reaction level in individuals treated with taxane- and platinum-based neo-adjuvant medicine.^{13,14} The mRNA level profiling data of TNBC tumors has identified four TNBC subtypes, including mesenchymal, basal-like immunosuppressed, LAR, and basal-like immune-activated (BLIA).^{15,16} Importantly, BLIAs had positive results concerning cancer-free survival.¹⁵ More research must be undertaken to assess these types and determine genomic labels that predict reactions to medications. Multiple studies (clinical trials) are being conducted to evaluate medicines in the genomic subsets of TNBC, such as suppressors of androgen receptors in TNBC, which are favorable for AR.^{10,17} Programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) suppressors have been associated with lasting medical treatment in TNBC patients by targeting antitumor immunity.¹⁸ In TNBC, PD-L1 mRNA is found mainly in tumors filtered into immune cells other than cancerous cells.^{19,20} The Food and Drug Administration (FDA) has approved atezolizumab and nab-paclitaxel for patients with PD-L1-positive, malignant TNBC based on the Impassion 130 trial.^{21,22} In the Impassion 130 clinical trial, patients were randomly



assigned to receive either atezolizumab with nab-paclitaxel or a placebo with nab-paclitaxel. The study had two initial goals. Overall survival (OS in the ITT population and case of a significant finding in the PD-L1-positive subgroup), *progression-free survival* (PFS in the intention-to-treat [ITT] population and PD-L1 positive subgroup), and PD-L1 mRNA level were determined on tumor-infiltrating immune cells using immunohistochemistry. A PD-L1-positive result was determined by staining of $\geq 1\%$.

The use of atezolizumab elevated the average PFS from 4.9 to 6.8 months (hazard ratio [HR]=0.78, 92% CI=0.71–0.88, $P=0.003$) in patients with ITT and from 4.9 to 6.8 months (HR=0.59, 93% CI=0.51–0.81, $P<0.002$) in patients expressing PD-L1. By adding atezolizumab, the average OS increased from 18.1 months to 20.9 months (HR=0.79, 91% CI=0.71–1.13, $P=0.06$) in the patients with ITT and from 14.8 to 24.9 months in patients with PD-L1 expression (HR=0.59, 92% CI=0.42–0.83), but these findings were not considerably remarkable. Atezolizumab was the first immunotherapy approved for malignant TNBC. However, several clinical trials determined other medication therapies.¹⁸ In addition to the current confirmation of atezolizumab in combination with nab-paclitaxel, sequential chemotherapy remains the best option for malignant TNBC. Additionally, sequential single elements are chosen before combinations; however, combination medications could be utilized to treat metastatic cancer.²³ Medications such as eribulin, anthracyclines, taxanes, gemcitabine, capecitabine, and navelbine were recommended in this regard.^{24,25} Individuals with BRCA mutations, poly (ADP-ribose) polymerase (PARP) suppressors, and platinum salts are active.^{26,27} In the initial raw, the average PFS with palliative chemotherapy is 1.5–4 months without the applied agent.⁷ This describes the requirement for more systemic medications with better effectiveness in treating patients with malignant TNBC.^{25,28} In this article, the team of scientists attempts pharmacodynamics to explain the effect of Sacituzumab on malignant TNBC and other epithelial tumors by targeting trop-2 due to reducing the adverse effects of other drugs commonly used in the first line of therapy. The team also aims at investigating the pharmacodynamic, pharmacokinetic, and side effects of Sacituzumab.

Tumor-associated Calcium Signal Transducer 2 Targeting in Triple-negative Breast Cancer

Mode of Operation

A calcium transducer, “trophoblast cell-surface antigen 2 (Trop-2)”, acts as a transmission tract. Various epithelial tumors, such as BC, overexpress Trop-2 in comparison to joint tissues^{29,30}. Trop-2 has been reported to modulate some signaling pathways. Several signaling pathways are involved in cancer cells’ migration and proliferation.³¹ Trop-2 expression is observed in 82% of TNBC, and the highest expression is related to a more metastatic cancer period in multiple cancers. This includes breast

tumors.^{30,32} Therefore, the potential of Trop-2 and other epithelial tumors that express Trop-2 as a medical target for TNBC is quite promising. Specific antibody-drug conjugation is called Sacituzumab govitecan (IMMU-132) made of a humanized monoclonal RS7 IgG1κTrop-2 antibody with SN-38 as chemical linkage (Figure 1).³³⁻³⁵ An antibody–drug conjugate (ADC) adoptively confers cytotoxic chemotherapy agents on tumors while inhibiting the growth of healthy tissues³⁶. This results in an enhanced medical representative with increased intratumor concentrations of drugs and reduced toxicities that spread through the body. Recently, ADCs were confirmed for other types of cancer, such as brentuximab for lymphoma, gemtuzumab for acute myeloid leukemia, and other lymphoma types. In addition, inotuzumab is used for acute lymphoblastic leukemia and other diseases in medical development, and ado-trastuzumab has been used for malignant HER2-positive BC.^{36,37}

Sacituzumab leads to the internalization of the drug when it binds to Trop-2 within tumors. This, in turn, enables the intracellular delivery of SN-38 (Figure 2).^{38,39} The unique characteristics of this substance include a high ratio of drug to antibody and a linker known as CL2A, which can be easily broken down.^{33,40} Linkers with intermediate durability enable SN-38 secretion in Sacituzumab-bound and cancer cells. SN-38 concentrations at the site of action and conjugate binding may enhance the anticancer action of medications. Irinotecan, a topoisomerase-I suppressor, produces an active metabolite called SN-38 with an enhanced potency of about 1000-fold in inducing DNA breaks.^{41,42}

Pharmacokinetics, Pharmacodynamics, and Dosing of Sacituzumab

Sacituzumab has been assessed in the design of Phase I/II basket, multicenter, single-arm clinical trials in individuals whose malignant epithelial tumors had been treated previously.^{43,44} Based on recent reports of Trop-2 expression in epithelial tumors such as TNBC, monitoring the expression of Trop-2 was deemed unnecessary for determining trial competency.^{31,34} Twenty-five patients participated in the Phase I trial. Sacituzumab was intravenously injected on days 1 and 8 of a 21-day cycle, and the advised Phase II dose was 11 mg/kg.

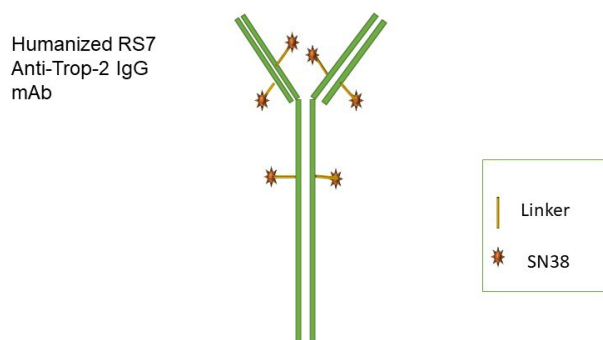


Figure 1. Sacituzumab Structure. mAb: monoclonal antibody

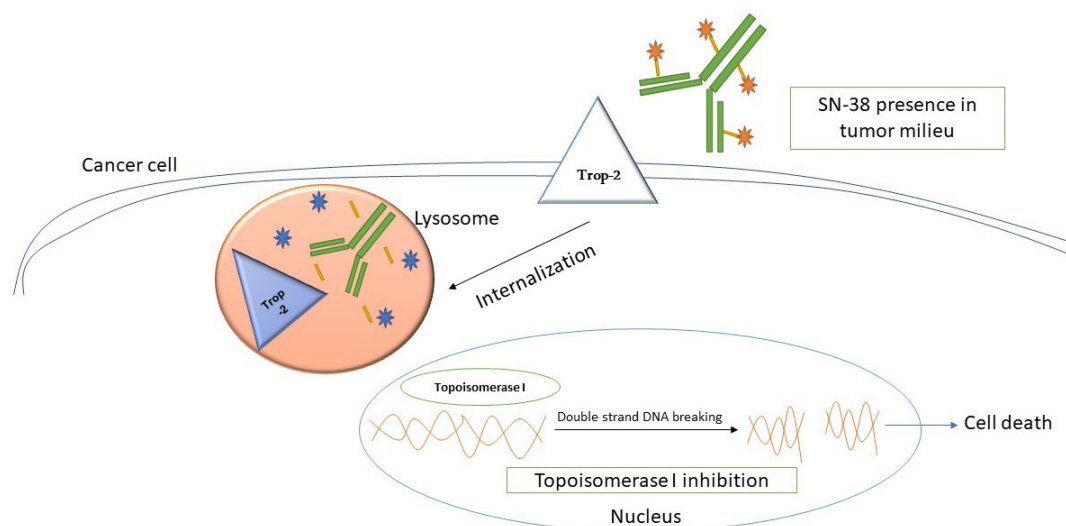


Figure 2. Mode of Action of Sacituzumab

Neutropenia was the essential dose-confined toxicity, and hopeful anticancer function was reported in individuals with lung, colorectal, and TNBC.^{35,43} Sacituzumab's pharmacokinetics, SN-38, IgG, and hRS7 IgG, were evaluated in some patients who participated in the Phase II section and received 9 mg/kg and 11 mg/kg.^{45,46} During the clinical study, the conjugate received 50% of the SN-38 payload every 24 hours. There were about 11–13 hours of durability for Sacituzumab and 99–108 hours for hRS7 immunoglobulin G (IgG). The area under the curve is about 6 mg-h/mL for Sacituzumab and 14 mg-h/mL for hRS7 IgG. Sacituzumab had a lower distribution volume, 33–37 mL/kg, compared to 57–60 mL/kg for hRS7 IgG. The Sacituzumab clearance rate was about 3 mL/h/kg compared to 0.6 mL/h/kg for hRS7 IgG. SN-38 in serum consists primarily of IgG, which accounts for less than 5% of the total. The SN-38 clearance rate was unaffected by tumor type, and its free serum level was unrelated to neutropenia.

Patients did not develop conjugated antibody responses. SN-38 levels were higher than SN-38G levels due to liver glucuronidation protection by UGT1A1 when RS7 IgG was bound. Over time, the conjugate may release SN-38, resulting in decreased levels of SN-38G in the intestines. Bacterial beta-glucuronidase can then convert it to active SN-38.⁴⁷ In patients receiving irinotecan, elevated levels of SN-38G may be linked to severe diarrhea.^{48,49} The in vivo exclusion of Sacituzumab has not been documented in any solemn research. Simplified SN-38 is expected to be removed from Sacituzumab similarly to SN-38 which is expected to be removed from irinotecan.⁵⁰ During 24 hours of irinotecan injection, only 0.17–0.39% of the drug is recovered in urine as a result of SN-38. Individuals have different biliary excretions, and SN-38 results in 0.1%–0.9%, while SN-38G results in 0.6%–1.1%. Fecal samples were found to contain SN-38 and a small number of SN-38G concentrations. Initially, SN-38G is excluded from the urine based on glucuronic acid 50's polar nature. High

toxicity with irinotecan is related to ACU1G1 haplotype status, and homozygosity of ACU1G1*28 was assessed in participants in Phase II section.^{45,51} Regarding statistical data, no significant association was reported between ACU1G1*28 homozygosity and grade more than 3 neutropenia or diarrhea, but these reports showed a slight increase.

Sacituzumab Effects in Metastatic Triple-Negative Breast Cancer

Sacituzumab's safety and efficacy were assessed in people with progressive TNBC who had previously received at least two medications for malignancy.

Part of Phase I/II Clinical Trial 46

The trial included 110 patients with these conditions who were administered Sacituzumab at a dose of 10 mg/kg intravenously on the first and eighth days of every 21-day cycle. These people were treated with an average of 3 lines of general medication⁵²⁻⁵⁷; accordingly, 97% were treated with taxanes and 87% with anthracyclines. The reaction rate to Sacituzumab was 34.6% (95% CI=23.7–41.8) and included three complete and 29 partial reactions. The average response duration was 8.1 months (95% CI=5.1–11.2), and the clinical advantage level was 51.3%. The average PFS was 5.2 months (95% CI=3.9–5.8), and the average total survival was 12.8 months (95% CI=10.8–14.2).

The quality and efficacy were higher than in previously managed patients with malignant TNBC receiving common treatments after their first line.^{7,58} Tissue samples from malignant TNBC subtype patients who received Sacituzumab were evaluated for Trop-2 expression.⁵⁹ Moderate staining was observed in 87% of samples. The PFS of people with mild to significant staining was attempted in some studies, but no significant improvements were observed. The adversary effect profile of Sacituzumab in people who experienced

TNBC in metastasis demonstrated similarity to people with other types of cancer.^{45,46} The highest usual side effects were hematologic and gastrointestinal (Table 1). The most common side effects were neutropenia (59% of all scores, 28% score 3, 15% score 4), nausea (71% of all scores, 5% score 3), and diarrhea (59% of all scores, 7% score 3).³³ Although febrile neutropenia is rare, it was reported in 9 patients (8.8%). Deleterious effects, particularly neutropenia, interrupted treatment in 39% of patients. Three patients (3.2%) terminated treatment because of treatment-associated deleterious effects. Sacituzumab has a side effect profile similar to other medications used for TNBC treatment (Table 1).^{46,60-62} Most patients (93%) received chemotherapy treatments before administration. Particular drugs varied in inpatients, including antihistamines, H₂ antagonists, acetaminophen, glucocorticoids, antiemetics, atropine, and anxiolytics.⁴⁶ Growth factors are commonly utilized to manage treatment-induced neutropenia. It compares Sacituzumab's efficacy to single-agent medication adoption in a randomized and open-label trial now. Patients with progressive TNBC who have undergone at least two previous treatments are randomly assigned to receive Sacituzumab or the physician's choice of chemotherapy with eribulin, capecitabine, or gemcitabine in a 1:1 ratio. Independent factors and classification parameters determined the early termination status of the ASCENT trial. These factors include several prior therapy lines, the absence or presence of specified brain metastases, and geographical regions. The second endpoint is OS. Additionally, Sacituzumab showed promising efficacy in treating metastatic TNBC in Phase I/II clinical trials⁶³⁻⁶⁶ in HER2-negative hormone receptor-positive BC, urothelial cancer, small cell lung carcinoma, and non-small cell carcinoma.

Conclusion

Sacituzumab is developed as an ADC targeting Trop-2 with suitable function in malignant TNBC, such as other epithelial tumors. Metastasized TNBC is a malignant breast tumor with confined effects from medications other than first-line therapy. Sacituzumab has a controllable

adversary effect profile regarding hematologic and gastrointestinal toxicities.

TNBC is defined as cancer without active HER2-directed or hormonal medications. There are no positive adoption parameters that may impact the weak clinical prognosis reported with cytotoxic treatment as a singular treatment for the metastatic option. Atezolizumab in a mixture with nab-paclitaxel for PD-L1.

It is an essential medication for patients with positive TNBC, leading to other immunotherapy combinations for palliative and curative treatments. Active, targeted therapies are essential for 50% of TNBC patients who are negative for PD-L1 and show immunotherapy resistance. Sacituzumab is an excellent ADC due to its unstable connector, which allows for slow secretion of the SN-38 payload over a period of about 49% every 24 hours. The primary form of SN-38 in the blood is IgG, while SN-38G is secreted in the gastrointestinal tract for several days.

It is probable that the antibody will gradually release SN-38, which is the main parameter resulting in Sacituzumab's efficacy and tolerability in malignant TNBC. Since the success of this approach, the hypothesized future use of this technology is to target other surface markers on various cancer cells. The therapeutic quality of Sacituzumab reported in Phase I/II clinical trials is hopeful compared to the clinical trials of single-element chemotherapy in patients with previous treatments.

Patients with metastatic TNBC demonstrated a poor response (10–15%) to treatment, while Sacituzumab showed a 32.7% response rate⁴⁶. The administration of Sacituzumab in these patients, a phase II clinical trial, revealed 5.5 months as the average of PFS. The patients had undergone three rounds of chemotherapy previously, with a range of 2–10.^{34,63-67} It is better to interpret this cautiously regarding the adoption bias toward healthier patients. Although the ASCENT trial is still ongoing to confirm its effectiveness, we plan to include Sacituzumab in upcoming trials as a neo-adjuvant therapy for patients who did not respond completely to neoadjuvant chemotherapy and are at a high risk of metastatic recurrence. The toxicity profile of Sacituzumab is manageable, and hematologic and gastrointestinal toxicities are the most common high-grade events.^{46,68,69} Diarrhea rates in TNBC patients were about 8%. This rate is significantly lower than that observed with irinotecan monotherapy, which is reported in 22–29% of patients.⁴⁷ Four of the 110 patients passed up from the clinical trial because of the deleterious effects associated with Sacituzumab.⁴⁶ In this trial, most patients were prescribed pre-therapeutics to suppress antiemetics, and the patient's diarrhea was managed using standard protective measures. Furthermore, growth factors were applied to some patients to treat neutropenic disease. This should be evaluated in future research. The mode of action of Sacituzumab in TNBC was quickly understood due to the updated design of the Phase I/II clinical trial. This design resulted in multiple Phase II clinical trials specific to cancer due to the marked clinical activity

Table 1. Most Usual Deleterious Complications Observed in 110 Patients With TNBC (in the Form of Metastasis) Who Received Sacituzumab⁴⁶

Event	All Grades (%)	Grade 3–4 (%)
Neutropenia	59	28-15
Nausea	71	5
Fatigue	57	9
Diarrhea	59	7
Infections	55	10
Vomiting	50	8
Anemia	49	9
Constipation	33	2
Alopecia	40	1

Note. TNBC: Triple-negative breast cancer.

observed across various cancer types. According to the primary expression of Trop-2 in epithelial metastatic cancer, Sacituzumab may play a role in treating various types of cancer with TNBC. Sacituzumab is an FDA-approved therapy for metastatic TNBC. This element is used in TNBC in several ways, including concurrent immunotherapy and neoadjuvant therapy for high-risk patients.⁷⁰ Various medications are being evaluated for treating metastatic BC, including inhibitors of androgen receptors, immunotherapy, phosphatidylinositol-3-kinase/mammalian target of rapamycin pathway suppressors, and PARP suppressors.^{24,71,72}

Acknowledgments

All authors were involved in all stages of the article writing, and they will share all possible material and intellectual rights for this article.

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Competing Interests

All of the authors declare that they have no conflict of interests.

Ethical Approval

Not applicable.

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