Review

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Revolutionizing triple-negative metastatic breast cancer treatment: sacituzumab Govitecan's role in advancing chemotherapy

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Purpose: This review aims to discuss the role and efficacy of Sacituzumab Govitecan in the management of breast cancer.
Summary: Breast cancer is the most prevalent type of cancer among women worldwide. This comprehensive review delves into the advancements brought about by Sacituzumab Govitecan in the treatment of metastatic triple-negative breast cancer (TNBC). With a focus on its mode of action, efficacious role, clinical trials, and comparative advantages over conventional chemotherapy, the review highlights the therapy's precision in targeting cancer cells through monoclonal antibodies. Sacituzumab Govitecan's ability to deliver a chemotherapeutic payload specifically to cancer cells with the Trop-2 receptor sets it apart from traditional chemotherapy, minimizing collateral damage and reducing severe side effects. The impact of Sacituzumab Govitecan on improving progression-free survival, tumor response rates, and, significantly, the quality of life for patients is discussed. This article also sheds light on ongoing trials, FDA recognition, and the therapy's potential to transform breast cancer treatment.
Conclusion: In conclusion, Sacituzumab Govitecan shows potential as an innovative therapeutic option for breast cancer, particularly in metastatic breast cancer and triple-negative breast cancer, but it warrants additional research.

Keywords: antibody-drug conjugates, Sacituzumab Govitecan, Trop-2, breast cancer

Introduction

Each year, millions of women and, in some circumstances, men are affected by breast cancer, making it a serious global health concern. Significant improvements in chemotherapy regimens have been instrumental in the substantial success of treating breast cancer over the years[1,2]. Sacituzumab Govitecan, a new antibody-drug conjugate, is one of the most recent advancements in this area and can potentially enhance outcomes for patients with metastatic triple-negative breast cancer[3]. Triple-negative breast cancer (TNBC) is a rare type of breast cancer that lacks or has low levels of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) overexpression and gene amplification[4]. TNBC comprises 15–20% of all breast cancer cases[5]. They are the most challenging cancers to treat due to their rapid proliferation and aggressive nature due to the lack of hormone receptors and high risk of recurrence[6]. Hormone therapy, used for other types of breast cancer, does not work on TNBC[6]. Treating breast cancer with Sacituzumab Govitecan represents a paradigm change in precision medicine. This review aims to study this novel therapeutic strategy, its mode of action, and the recent clinical trials that proved its effectiveness. Additionally, it will examine how Sacituzumab Govitecan contrasts with conventional chemotherapy, illuminating the possible advantages and difficulties it brings to the forefront of managing breast cancer[7,8].

HIGHLIGHTS

- Each year, millions of women and, in some circumstances, men are affected by breast cancer, making it a serious global health concern.
- Triple-negative breast cancer (TNBC) is a rare type of breast cancer that lacks or has low levels of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) overexpression and gene amplification, hence given the name triple-negative.
- A humanized anti-trophoblast cell-surface antigen 2 (Trop-2) IgG1 kappa monoclonal antibody is combined with SN-38, the active metabolite of the topoisomerase inhibitor irinotecan, via a proprietary hydrolyzable linker to form Sacituzumab Govitecan, an antibody-drug conjugate.
- The significant improvement in progression-free survival and tumor response rate is one of the most critical outcomes of Sacituzumab Govitecan's clinical efficacy.

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Method

We searched online databases, including PubMed, Scopus, and Embase, for articles related to Sacituzumab Govitecan from inception until March 2024. We included clinical trials, meta-analyses, clinical trial extensions, subgroup analyses, post hoc analyses, cost-effectiveness analyses, and new human data. We excluded all articles in a language other than English.

Review

Conventional treatment modalities of TNBC

TNBC can be divided into early-stage and late-stage diseases. Traditionally, chemotherapy has been the sole effective systemic therapeutic choice for both early and late illness. Recent clinical trials have demonstrated that immunotherapy has a significant role in the treatment of this severe illness[9,10]. The standard treatment for early-stage disease is surgery with neoadjuvant or adjuvant chemotherapy and radiotherapy[9]. A trial investigated the efficacy of pembrolizumab in combination with chemotherapy, and a significantly higher complete response was observed[2]. Surgical options include lumpectomy or mastectomy[9]. Adjuvant chemotherapy options in early-stage disease include anthracycline, alkylating agents such as cisplatin and carboplatin, and taxanes[10]. Traditional Neoadjuvant regimes include a combination of anthracyclines and taxanes. In recent years, the addition of pembrolizumab to platinum-containing neoadjuvant chemotherapy has been the standard treatment[8–10]. Late-stage disease is also known as metastatic TNBC. Treatment options are limited, including whether the tumor tests positive for programmed death cell ligand 1 (PD-L1) protein or BRCA gene mutation[11].

Structure and mechanism of action of Sacituzumab Govitecan

A humanized anti-trophoblast cell-surface antigen 2 (Trop-2) IgG1 kappa monoclonal antibody is combined with SN-38, the active metabolite of the topoisomerase inhibitor irinotecan, via a proprietary hydrolyzable linker to form Sacituzumab Govitecan, an antibody-drug conjugate[12]. Trop-2 is a transmembrane calcium signal transducer highly expressed in breast cancers and associated with tumor progression[13,14]. The structure of Sacituzumab Govitecan is shown in Figure 1[15]. These antibodies have been specifically designed to seek and bind to a specific protein called Trop-2 in Sacituzumab Govitecan.

Trop-2 unlocks the therapy's targeted potential, which is only present on the surface of cancer cells[12]. Once the monoclonal antibodies of Sacituzumab Govitecan have successfully attached to the Trop-2 receptors, a transforming process starts. Irinotecan, the chemotherapeutic payload enclosed within the medication, is precisely released, as shown in Figure 2.

Irinotecan is an effective chemotherapy drug that can damage cancer cells' DNA, ultimately causing cancer cell death[16,17]. The monoclonal antibodies ensure that the chemotherapeutic medication is absorbed mainly by the cancerous cells with little impact on the healthy tissue around them since they specifically target these receptors. This is a significant difference from conventional chemotherapy, which usually affects both malignant and healthy cells, resulting in the severe side effects that patients frequently experience[17,18].

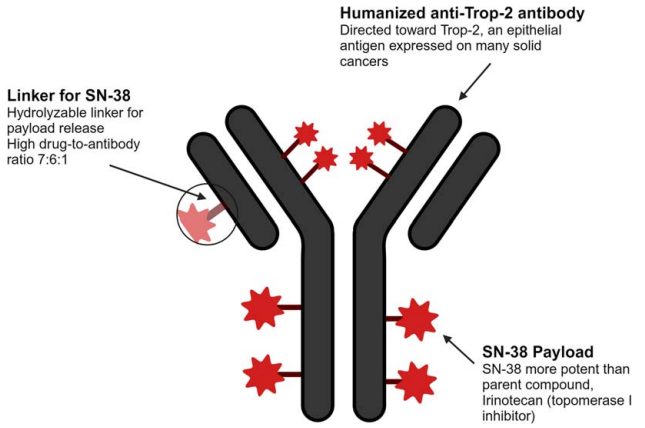

Figure 1. Structure of Sacituzumab Govitecan. Trop-2, anti-trophoblast cell-surface antigen 2.

Medical uses of Sacituzumab Govitecan

Sacituzumab Govitecan's tailored strategy significantly reduces collateral damage. The long-standing side effects of traditional chemotherapy, such as nausea, vomiting, hair loss, and other serious side effects, are greatly diminished. This improves the patient's quality of life overall while undergoing treatment and permits the continuation of routine daily activities that could otherwise be interrupted[19]. For individuals who have long struggled with advanced breast cancer, Sacituzumab Govitecan's efficacy, as seen in these trials, proves it to be a promising therapeutic intervention[15,19,20]. It can also be used in locally advanced or metastatic urothelial cancer treated with platinum-containing chemotherapy and a programmed death receptor-1 (PD-1)[21]. Its utility in HR + /HER2 – metastatic breast cancer has been underway. It has demonstrated significant progression-free survival benefits over chemotherapy in the TROPiCS-02 trial in endocrine-resistant HR + /HER2 – metastatic breast cancer[13].

Metastatic TNBC

One of breast cancer's most threatening forms is metastatic TNBC. It is distinguished by the absence of HER2, estrogen, and progesterone receptors and is well known for being aggressive and resistant to many conventional treatments. Patients with TNBC have frequently had many lines of therapy, including anthracyclines and taxanes[22].

Clinical data support Sacituzumab Govitecan's use in TNBC as a monotherapy, including milestone trials like IMMU-132-01 and ASCENT-05[3,7,23]. When this therapy was applied to patients who had previously tried numerous lines of treatment, they had reactions that had never been seen[23]. It is indicated for treating adults with metastatic TNBC who received at least two conventional therapies[24].

Improved progression-free survival and higher rate of tumor response

The significant improvement in progression-free survival and tumor response rate is one of the most critical outcomes of Sacituzumab Govitecan's clinical efficacy. These parameters are crucial for determining the effectiveness of a therapy

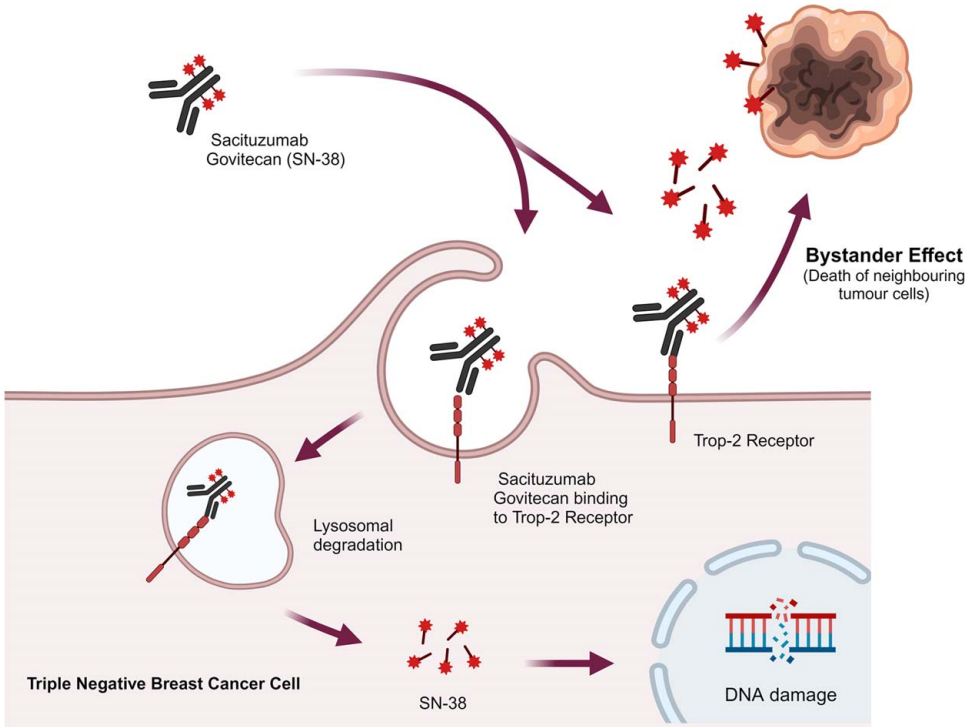

Figure 2. Mechanism of action of Sacituzumab Govitecan. Trop-2, anti-trophoblast cell-surface antigen 2.

because they are directly related to the patient's longevity and quality of life[25]. Additionally, Sacituzumab Govitecan has been shown to have a better tumor response rate in TNBC patients. The response rate in the IMMU-123 trial was 34.3%, and the median duration of response was 9.1 months[17]. This study shows that the medicine can drastically reduce or eliminate tumors in a hitherto unattainable way by attaching to the TROP-2 protein and stopping cancer cell growth[26]. In the ASCENT trial, Sacituzumab Govitecan extended the median PFS to 5.6 months compared to 1.7 months with standard chemotherapy, indicating a significant delay in disease progression[14]. The same trial reported a median overall survival (OS) of 12.1 months for patients treated with Sacituzumab Govitecan, compared to 6.7 months for those receiving standard treatment, almost doubling the expected survival time[14]. The objective response rate (ORR) in patients treated with Sacituzumab Govitecan was 33.3%, significantly higher than the 5.3% observed with standard chemotherapy[14,17].

Quality of life improvement with Sacituzumab Govitecan

Sacituzumab Govitecan impacts patient's quality of life by having a decrease in crippling side effects, such as vomiting, hair loss, and nausea, which is a critical benefit that improves the patient experience and enables people to preserve their self-respect and dignity throughout their difficult journey[26]. Quality of life assessments using tools like the EORTC QLQ-C30 questionnaire showed improved scores in patients treated with Sacituzumab Govitecan, with significant reductions in symptoms such as pain and fatigue, contributing to better daily functioning and well-being[14,17].

Side effects profile of Sacituzumab Govitecan

Patients' physical and mental health might suffer significantly from the debilitating side effects frequently associated with traditional chemotherapy. Particularly severe bouts of nausea and vomiting can cause loss of appetite and a general decrease in health. The most damaging visible side effect of hair loss, which affects self-esteem and body image, is hair loss. In many cases, these side effects add to the already tremendous physical and mental toll of living with cancer[27]. The most common side effects include neutropenia, nausea, diarrhea, anemia, vomiting, alopecia, rash, and abdominal pain[28]. It may cause harm to a developing fetus or newborn baby. It has a boxed warning regarding the risk of severe neutropenia and diarrhea[28,29]. Patients treated with Sacituzumab Govitecan experienced lower rates of severe adverse effects like neutropenia (10% vs. 50%) and diarrhea (10% vs. 18%) compared to those on traditional chemotherapy, leading to better overall patient tolerance and fewer hospitalizations[14,28]. Managing critical side effects of Sacituzumab Govitecan is crucial for optimizing its efficacy and patient quality of life. Neutropenia, a common and significant side effect, requires regular complete blood count (CBC) monitoring and using granulocyte-colony stimulating factors (G-CSFs) prophylactically for high-risk patients[14,30]. Dose adjustments are necessary based on the severity of neutropenia, with delays and reductions implemented as needed. Early intervention with anti-diarrheal agents like loperamide and adequate hydration and electrolyte management is essential for diarrhea[17]. Persistent cases may require dose reduction or treatment interruption. Collectively, these strategies ensure that Sacituzumab Govitecan's benefits are maximized while minimizing adverse effects.

Maintaining daily functioning with dignity and self-respect

Here, the emphasis should be on how Sacituzumab Govitecan significantly lessens the burden of adverse effects of chemotherapy by targeting cancer cells specifically with the chemotherapeutic payload. Patients who receive this therapy report far less severe nausea, vomiting, and hair loss. The impact of cancer treatment on daily life is one of the frequently disregarded components of the disease. The most routine daily tasks can seem impossible due to persistent nausea, vomiting, and exhaustion. Patients have reported retaining a noticeably more significant level of daily functioning due to the medication's reduced adverse effects. This entails participating in ordinary activities, completing obligations to one's family and job, and leading a more routine life[30]. Cancer therapies can significantly impact a person's feelings of dignity and self-respect. In comparison, the minor side effects of Sacituzumab Govitecan not only lessen these emotional burdens but also help patients maintain a stronger sense of identity and normalcy during their treatment[30,31].

FDA recognition and fast-track designation

The acknowledgement and approval of innovative medicines by regulatory bodies are crucial milestones that denote a fundamental shift in the paradigm of patient care in the dynamic world of pharmaceuticals and healthcare. The FDA has given Sacituzumab Govitecan both Fast Track and Breakthrough Medication Designation by the US Food and Drug Administration (FDA), providing a critical acceleration in its development and making it more quickly available to patients in need than ever before. The FDA's fast-track designation is coveted for drugs that meet unmet medical requirements. This classification speeds up a drug's research and review, enabling a quicker path to market and ensuring treatments are quickly available to those needing them[32].

IMMU-123 trial

Sacituzumab Govitecan's first milestone trial was IMMU-123, published in 2017 and 2019[7,17]. This study involves Sacituzumab-Govitecan-hziy in refractory metastatic TNBC. The trial was performed on 108 patients who had received a median of 3 previous therapies. The most common side effects were anemia and thrombocytopenia. The response rate was 34.3%, and the median duration of response was 9.1 months[17]. The clinical benefit rate was 45.4%, median progression-free survival was 5.5 months, and overall survival was 13 months[7,17]. As a result of this trial, Sacituzumab-Govitecan-hziy was associated with durable objective response in patients with heavily pretreated metastatic TNBC.

ASCENT-05 trial

Sacituzumab Govitecan's second milestone trial was published in 2021 and named ASCENT-05 Trial[3,14]. It compared the effectiveness and safety of Sacituzumab Govitecan in combination with Pembrolizumab after surgery to either Pembrolizumab or Pembrolizumab plus Capecitabine in people with relapsed or refractory metastatic TNBC. This trial was performed on 468 patients with metastatic TNBC who had already completed two or more standard chemotherapy treatments. Standard chemotherapy included eribulin, vinorelbine, capecitabine, or gemcitabine. The median progression-free survival was 5.6 months with Sacituzumab Govitecan compared to 1.7 months with chemotherapy[3,14]. The median overall survival was 12.1 months with Sacituzumab Govitecan compared to 6.7 months. The tumor shrank in more patients who took Sacituzumab Govitecan than in chemotherapy patients. The most common side effects were neutropenia and diarrhea[14].

Dosing and administration schedule of Sacituzumab Govitecan

Sacituzumab Govitecan is administered intravenously at a recommended dose of 10 mg/kg[12,14]. The administration schedule follows a 21-day cycle, with infusions given on Days 1 and 8. Pre-medication with antipyretics, antihistamines, and corticosteroids is often required to minimize the risk of infusion-related reactions. The initial injection is typically administered over 3 h, with the infusion rate potentially shortened for subsequent treatments if well tolerated. Regular monitoring of vital signs during and after the infusion is essential to detect any immediate adverse reactions. In case of side effects, dose adjustments are necessary; the dose can be reduced to 7.5 mg/kg or further to 5 mg/kg, depending on the patient's tolerance[16,20]. Treatment cycles are repeated every 21 days and continue until disease progression or unacceptable toxicity is observed. This structured approach ensures the optimal balance between efficacy and safety when administering Sacituzumab Govitecan[17,19].

Ongoing trials and future research directions on Sacituzumab Govitecan

Sacituzumab Govitecan's FDA recognitions help it advance toward establishing a standard of care for the treatment of breast cancer. Patients and their families can anticipate a better, more hopeful future in the fight against this persistent disease as the medical community, pharmaceutical companies, and regulatory agencies work together to offer this promising medication to those in need[33]. The EVOKE-01 trial is a phase 3 study of Sacituzumab Govitecan versus docetaxel in patients with non-small cell lung cancer (NSCLC)[34]. The TROPiCS-02 trial includes Sacituzumab Govitecan in HR + /HER2 – metastatic breast cancer[15]. Ongoing research on Sacituzumab Govitecan focuses on enhancing its efficacy, expanding its use through combination therapies, and identifying biomarkers for patient selection[34]. Studies are investigating its combination with immune checkpoint inhibitors, PARP inhibitors, and other targeted therapies to improve outcomes in breast cancer patients[33]. These combinations aim to exploit synergistic effects and overcome resistance mechanisms.

Additionally, future research is exploring the use of Sacituzumab Govitecan in other cancer types, such as urothelial and non-small cell lung cancer, broadening its therapeutic potential. Biomarker-driven trials are crucial to identify patients who would benefit most from this therapy[30]. A summary of ongoing trials studying the role of Sacituzumab Govitecan is presented in Table 1. These trials study outcomes like disease-free progression, overall survival, number of patients with treatment-related adverse events, assessment of the quality of life, etc., to investigate the efficacy of Sacituzumab Govitecan therapy.

Limitations and challenges

Sacituzumab Govitecan, a promising therapeutic agent for breast cancer, faces severe significant challenges that impact its public availability. Regulatory hurdles, such as obtaining approvals

Table 1

Ongoing clinical trials of Sacituzumab Govitecan in breast cancer.

Clinical trial number	Clinical trial name	Phase	Intervention/experiment	Disease
NCT05143229	Phase I Trial Of Alpelisib Plus Sacituzumab Govitecan In Patients With Metastatic Or Locally Recurrent HER2-Negative Breast Cancer	I	Alpelisib Plus Sacituzumab Govitecan	Breast cancer
NCT05006794	Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of GS-9716 as Monotherapy and in Combination With Anticancer Therapies in Adults With Solid Malignancies	Ia/b (multi-arm)	GS-9716, Docetaxel, Sacituzumab-Govitecan-hziy	Triple-negative breast cancer, NSCLC
NCT04039230	Phase 1b/2 Study to Evaluate Antibody-Drug Conjugate Sacituzumab Govitecan in Combination With PARP Inhibitor Talazoparib in Patients With Metastatic Breast Cancer	I/II	Sacituzumab Govitecan, Talazoparib	Triple-negative breast cancer
NCT05101096	A Phase 1/2 Open-Label Study of Sacituzumab Govitecan in Japanese Patients With Advanced Solid Tumors (ASCENT-J02)	I/II	Sacituzumab Govitecan-hziy	Solid tumors or triple-negative breast cancer
NCT03424005	A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating The Efficacy And Safety Of Multiple Treatment Combinations In Patients With Metastatic Breast Cancer (Morpheus-panBC)	Ib/II (multi-arm)	Sacituzumab Govitecan, Bevacizumab, Atezolizumab, Tocilizumab & 13 other interventions	Triple-negative breast cancer
NCT04230109	A Phase 2 Study of Response-guided Neoadjuvant Sacituzumab Govitecan (IMMU-132) in Patients With Localized Triple-Negative Breast Cancer (NeoSTAR)	II	Sacituzumab Govitecan (monotherapy) and with Pembrolizumab	Localized triple-negative breast cancer
NCT04468061	Saci-IO TNBC: Randomized Phase II Study of Sacituzumab Govitecan With or Without Pembrolizumab in PD-L1-negative Metastatic Triple Negative Breast Cancer (TNBC)	II	Sacituzumab Govitecan (monotherapy) and with Pembrolizumab	Triple-negative breast cancer
NCT04448886	Saci-IO HR+: Randomized Phase II Study of Sacituzumab Govitecan With or Without Pembrolizumab in Hormone Receptor-positive (HR+) / HER2-Metastatic Breast Cancer (MBC)	II	Sacituzumab Govitecan (monotherapy) and with Pembrolizumab	HR+/HER2− metastatic breast cancer
NCT03901339	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 (MBC) Who Have Failed at Least Two Prior Chemotherapy Regimens	III	Sacituzumab Govitecan, Eribulin, Gemcitabine, Capecitabine, Vinorelbine	HR+/HER2− metastatic breast cancer

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSCLC, non-small cell lung cancer.

from the FDA and EMA, can delay its widespread use. The high cost of the drug, coupled with varying reimbursement policies, further limits patient access[1,6,10]. Supple chain issues can also impede the consistent availability of the medication[10]. Clinically, there is variability in patient response, with some individuals experiencing limited efficacy or developing resistance to the treatment over time[15,20]. Efficacy concerns arise from the variability in patient responses and the potential for tumors to develop resistance over time[25]. Determining the optimal dosage and managing side effects like neutropenia and diarrhea require careful attention to treatment protocols.

Additionally, integrating Sacituzuman Govitecan with other therapies introduces complexities in clinical trial designs, and accumulating long-term safety data are crucial to maximizing the drug's benefits[34]. This necessitates ongoing research to identify biomarkers to predict response and tailor treatments accordingly. Overcoming these challenges is essential to ensure that Sacituzumab Govitecan can effectively and reliably improve outcomes for breast cancer patients.

Conclusion

Sacituzumab Govitecan ushers in a new era of precise and effective interventions against the formidable challenge of breast cancer. This novel antibody-drug conjugate offers renewed hope, precisely targeting cancer cells while minimizing damage to healthy tissues. Its impressive clinical performance, particularly in metastatic triple-negative breast cancer, has delivered remarkable response rates, prolonged survival, and a significantly reduced toxicity burden. As research progresses, optimizing treatment protocols, exploring synergistic combinations, and harnessing biomarker-driven patient selection strategies hold immense promise. Sacituzumab Govitecan is a testament to scientific innovation, offering hope to those battling this persistent disease.

Ethical approval

Our study was a narrative review and therefore, did not involve patients. Thus, ethical approval from the ethics committee was not applicable.

Consent

Our study was a narrative review and therefore, did not involve patients. Thus, taking consent was not applicable.

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Not applicable.

Author contribution

Z.Q.: data curation, conceptualization, methodology, supervision; A.J.: writing—original draft; writing—reviewing and editing; F.A.: writing—reviewing and editing, supervision; R.S.:

writing—original draft; E.F.: writing—original draft; S.D.: writing—reviewing and editing; R.S.Z.: writing—reviewing and editing; S.S.: writing—original draft.

Conflicts of interest disclosure

The authors declare no conflict of interest.

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Data availability statement

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Our paper was not invited.

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