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Sacituzumab govitecan for hormone receptor-positive and triple-negative breast cancers

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Abstract

Sacituzumab govitecan is an antibody-drug conjugate. It is composed of a humanized monoclonal antibody raised against the trophoblast cell-surface antigen 2 (Trop-2), and linked to SN-38, which is an active metabolite of topoisomerase I inhibitor anticancer drug irinotecan. A hydrolyzable linker conjugates the antibody and the drug. Trop-2 is overexpressed in various tumors including the triple-negative breast cancers (TNBCs) that are more aggressive with limited therapeutic options. Sacituzumab govitecan has proven to be an important therapeutic modality to manage the TNBCs. It has shown progression-free survival (PFS) and overall survival (OS) benefits when compared to standard-of-care chemotherapeutics. Accordingly, it is approved for the treatment of TNBCs in the United States and the European Union. Sacituzumab govitecan has also shown PFS and OS benefits for hormone receptor-positive (HR+) and human epidermal growth factor receptor-2-negative (HER2-) metastatic breast cancers. Therefore, sacituzumab govitecan appears to be an option for HR+/HER2- metastatic breast cancers that are heavily pretreated and exhibit endocrine resistance. Although sacituzumab govitecan has shown promise, it also is toxic. Additional studies are therefore needed to further refine the use of sacituzumab govitecan in improving the management of metastatic breast cancer.

Keywords: Antibody-drug conjugate; Sacituzumab govitecan; Trop-2; SN-38; Progression-free survival; Overall survival

Breast cancer is one of the most frequently occurring cancers worldwide (1). In the United State 297,790 women are expected to be diagnosed with breast cancer in the year 2023 and 43,170 are estimated to die due to this disease (2). Thus, due to its high mortality rate, breast cancer remains a significant cause for concern. Breast cancer progression follows various pathologically defined stages. In the ductal type, there is flat epithelial atypia (FEA), atypical ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS), and invasive or infiltrating ductal carcinoma (IDC) (1, 3 and refs therein). In the lobular type, the stages include atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS) and invasive lobular carcinoma (ILC) (1, 3 and refs therein). Breast cancer also has four molecular subtypes, including Luminal A, Luminal B, Human epidermal growth factor receptor-2 (HER2) positive, and Triple negative (1, 4 and refs therein). Recent proposal of a fifth subtype namely normal-like has also been reported but remains debatable (3 and refs therein).

The triple-negative breast cancers (TNBCs) are deficient in estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (5). This subtype is more aggressive and associated with high metastatic potential and poor prognosis (1, 5). Patients diagnosed with TNBC have a mortality rate of about 40% within five years of diagnosis, and about 46% encounter distant metastases, most commonly in the brain and visceral organs. After metastasis, median survival time is about 13.3 months, with a post-surgical recurrence rate of about 25% (5). The most common population afflicted with TNBC is premenopausal women under 40 years old, who make up about 15% of all breast cancer patients (5). TNBC is generally diagnosed in younger women before they enter the population-based breast cancer screening programs. Among women who undergo periodic screening, TNBC is usually detected as an interval cancer that occurs between two mammograms. This subtype typically exhibits unfavorable histopathological characteristics, including a larger, higher-grade tumor size, and

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positive lymph nodes (6). However, the correlation between TNBC tumor size and lymph node status is not fully understood, as studies have shown mixed findings (6).

TNBCs are also different from the other subtypes because these have limited treatment options (5). For instance, these tumors tend not to respond to endocrine therapy or molecular targeted therapy (5). While chemotherapy remains the conventional form of treatment, its effectiveness is limited (5). Although retrospective data do show an association between chemotherapy guideline adherence and overall survival in some TNBC patients, newer treatments are also being investigated to improve TNBC patient outcomes (6).

Immunotherapy has shown promising results as an antitumor approach to combat cancer. One broad category of immunotherapeutics includes targeted antibodies (1). In breast cancer, these targeted antibodies are primarily directed against tumor-associated antigens (TAA) (1). HER2 is a TAA that is overexpressed in about 20% of breast cancers and its presence is linked to an unfavorable prognosis (1). Due to its overexpression in breast cancer, HER2 is a target for antibody-drug conjugates (ADC). ADCs are composed of an antibody that targets a molecule expressed on cancer cell surface, a cytotoxic drug, and a cleavable linker molecule (1, 7). Some of the clinically relevant anti-HER2 ADCs are Ado-trastuzumab emtansine (T-DM1), approved in 2013, and trastuzumab deruxtecan, approved in 2019 (1). These ADCs are being used for the treatment of HER2-positive breast cancers.

Another ADC namely, sacituzumab govitecan has entered in the clinical use for the treatment of TNBC (8, 9). Sacituzumab govitecan is a humanized monoclonal IgG1 kappa antibody that targets the trophoblast cell-surface antigen 2 (Trop-2) (Fig. 1). It is conjugated to SN-38, which is an active metabolite of topoisomerase I inhibitor anticancer drug irinotecan (8, 9). A hydrolyzable CL2A linker is used for linking the antibody and the drug (8, 9) (Fig. 1). Once sacituzumab govitecan binds Trop-2, the payload i.e., SN-38 is released into the tumor cell through hydrolysis of the linker. There is a pH dependent cleavage site in the linker, which allows for drug release inside the cell (1). SN-38, due to its membrane permeable nature, may also mediate antitumor effects on the nearby non-Trop-2 expressing tumor cells. (1, 10). Sacituzumab govitecan appears to induce the intrinsic pathway of cell death in the tumor cells involving caspase

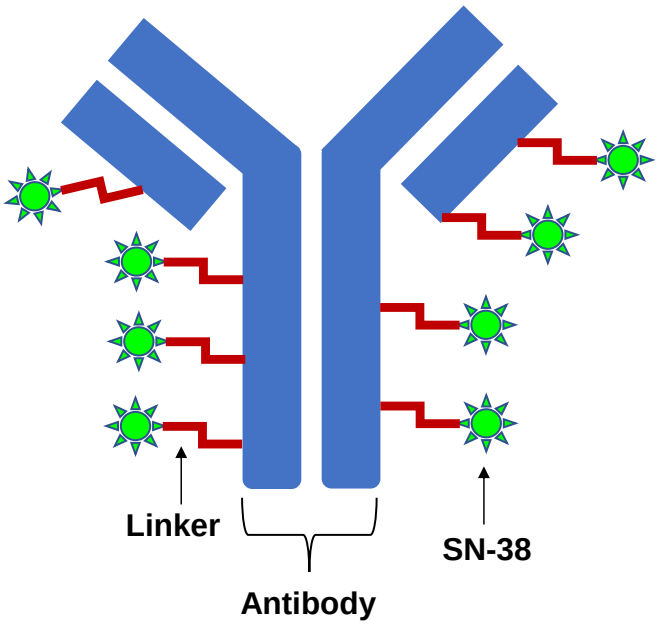

Figure 1. A schematic illustration of sacituzumab govitecan. Sacituzumab govitecan is a humanized monoclonal IgG1 kappa antibody that targets the trophoblast cell-surface antigen 2 (Trop-2). The antibody is conjugated to SN-38, which is an active metabolite of topoisomerase I inhibitor anticancer drug irinotecan via a hydrolysable linker. There is a high drug-to-antibody ratio of ~8 SN-38 molecules per one antibody.

activation and PARP cleavage (1). A notable property of sacituzumab govitecan is an augmented drug-to-antibody ratio of 7.6 SN-38 molecules to one antibody (11) (Fig. 1).

Trop-2 is a type-1 transmembrane glycoprotein containing an extracellular region on the cell surface and short cytoplasmic region (Fig. 2) (12). Upon initial discovery, it was characterized as a cell surface marker of trophoblast cells, however, it was rediscovered in the ensuing years as a tumor-associated calcium signal transducer 2 (TACSTD2), membrane component chromosome 1 surface marker 1 (M1S1), gastrointestinal antigen 733-1 (GA733-1), and epithelial glycoprotein-1 (EGP-1) (1, 8, 13). The *TROP-2* gene does not contain any introns and codes for a protein containing 323 amino acids, weighing 35-46 kDa, subject to the glycosylation status (1, 13). The N-terminal 30 amino acids of Trop-2 protein correspond to a signal peptide; the extracellular region harbors various motifs (12) (Fig. 2). For example, a cystine-rich domain resides within amino acids 27-73, a thyroglobulin type 1 domain is present within amino acids 73-146, and a cystine-poor domain resides within residues 146-274. Amino acid residues 275-297 form the transmembrane domain and amino acids 275-323 correspond to the cytoplasmic region (12) (Fig. 2). The cytoplasmic

region interacts with phosphatidyl-inositol 4,5-bisphosphate (PIP2) and harbors a serine residing at position 303 that is phosphorylated by PKC (12) (Fig. 2).

Trop-2 is implicated in the regulation of various molecular pathways such as cellular self-renewal, proliferation, invasion, and survival. These pathways are generally linked to cancer cell growth (1, 7, 11) (Fig. 3). Trop-2 is overexpressed in several tumor types, including colon, breast, lung, pancreatic, prostate, and urothelial cancers (11). It has been reported that overexpression of Trop-2 is associated with elevated tumor growth, increased cell proliferation, enhanced migration, greater anchorage-independent growth, and poor overall survival outcomes among several tumors (14, 10). In the case of TNBCs, Trop-2 is highly expressed in about 80-90% of such tumors, and is associated with a poor prognosis, thus, making it an attractive target for TNBC treatments (1).

The United States Food and Drug Administration (FDA) granted regular approval to sacituzumab govitecan for the treatment of TNBC in April 2021. Prior to that, it had received accelerated approval for TNBC treatment in 2020, which was based on the results from the phase I/II basket trial namely, IMMU-132-01. This trial evaluated sacituzumab govitecan as a monotherapy in 108 TNBC patients. An objective response rate of 33% was noted with a median progression-free survival (PFS) of 5.5 months and a median overall survival (OS) of 13 months (9).

The phase 3 ASCENT trial was a global, open-label, randomized confirmatory trial (9). It was meant to evaluate the safety and efficacy of sacituzumab govitecan in patients with relapsed or refractory metastatic TNBCs. Sacituzumab govitecan was compared with the physician's choice chemotherapy such as eribulin, vinorelbine, capecitabine, or gemcitabine. PFS was the primary endpoint. Four hundred and sixty-eight patients without brain metastases had undergone randomization such that 235 received sacituzumab govitecan and 233 received chemotherapy. Their median age was 54 years, and all had prior history of taxanes use. The median PFS was noted to be 5.6 months on the sacituzumab govitecan arm, and 1.7 months on the chemotherapy arm. The median OS was also evaluated, and it was 12.1 months with sacituzumab govitecan and 6.7 months with chemotherapy. Sacituzumab govitecan gave 35% objective response, which was 5% with

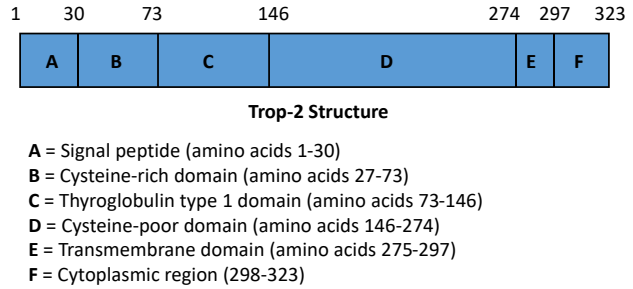

Figure 2. Structure of Trop-2 protein. Trop-2 is composed of 323 amino acids; has various motifs as indicated. The signal peptide is reported to correspond to amino acids 1-30 (12) or 1-26 (15).

chemotherapy. Neutropenia was among the treatment-related grade 3 or higher adverse events, the incidence of which was higher in the sacituzumab govitecan arm. The other grade 3 or higher adverse events included leukopenia, diarrhea, anemia, and febrile neutropenia. Deaths due to sacituzumab govitecan use were not reported (9). Regarding PFS and OS, it was noted that among all patients with or without brain metastases, the median PFS was 4.8 months on sacituzumab govitecan arm and 1.7 months with chemotherapy. The median OS was 11.8 months with sacituzumab govitecan and 6.9 months with chemotherapy (9). Based on the results from the ASCENT trial, the FDA granted regular approval to sacituzumab govitecan. It is approved for patients with unresectable locally advanced or metastatic TNBCs that have undergone prior treatments with systemic therapies, one of which is for the metastatic condition.

In addition to TNBCs, sacituzumab govitecan has also been evaluated in hormone receptor-positive (HR+) breast cancers (8, 7). In the IMMU-132-01 trial, the efficacy of sacituzumab govitecan was also investigated in 54 patients having HR+ and HER2- metastatic breast cancers. Those patients had undergone at least one previous endocrine therapy and one chemotherapy for the metastatic disease. The median PFS was 5.5 months, and the OS was 12 months with an objective response rate of 31.5%. These were encouraging results for sacituzumab govitecan use in patients with HR+/HER2- metastatic breast cancers (8).

Recently, the results of TROPiCS-02 trial were reported (8). TROPiCS-02 is a phase III, open-label, global, randomized trial. In this trial, HR+/HER2– locally recurrent and inoperable or metastatic breast cancers were studied (8). These tumors had exhibited resistance to endocrine therapy and the patients had previously received

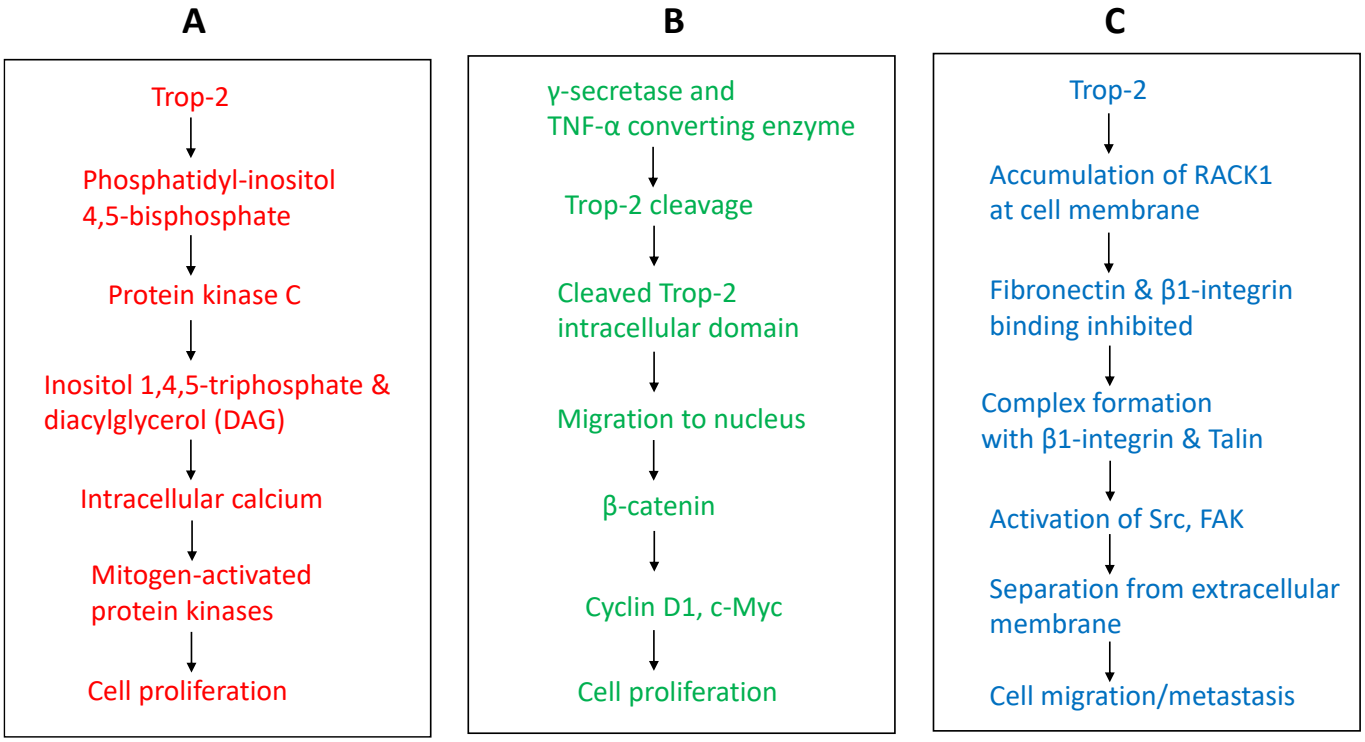

Figure 3. Trop-2 regulation of various signaling events. (A) The cytoplasmic region of Trop-2 harbors a PIP2-binding site. Trop-2 interactions with PIP2 result in PKC phosphorylation. PIP2 is cleaved into IP3 and DAG. IP3 mediates intracellular calcium accumulation, which promotes activation of MAPKs and eventual cell proliferation. (B) γ-secretase and TNF-α converting enzyme cleave Trop-2 such that the cleaved intracellular domain translocates to nucleus and interacts with b-catenin and other molecules to regulate cyclin D1 and c-Myc regulation and eventual cell proliferation. (C) Trop-2 promotes accumulation of RACK1 at cell membrane, which affects fibronectin & β1-integrin binding. Complex formation with β1-integrin and talin occurs, which leads to activation of Src and FAK, and cell migration/metastasis.

chemotherapy. Sacituzumab govitecan was compared with the physician's choice single-drug chemotherapy such as eribulin, vinorelbine, capecitabine, or gemcitabine. PFS was the primary endpoint. Five hundred forty-three patients had undergone randomization such that 272 received sacituzumab govitecan and 271 received chemotherapy. A total of 268 patients in the sacituzumab govitecan arm and 249 in the chemotherapy arm remained in the study. Their median age was 56 years. These patients had visceral metastases and history of chemotherapy and cyclin-dependent kinase 4/6 (CDK4/6) inhibitor use. The noteworthy findings were, a median PFS of 5.6 months on the sacituzumab govitecan arm, and 4.0 months on the chemotherapy arm. There was a 34% reduced risk of disease progression or death. The first interim analysis indicated that median OS was not mature. The grade 3 or higher adverse events included neutropenia and diarrhea; their incidences were higher in the sacituzumab govitecan arm compared to the chemotherapy arm (8). Thus, sacituzumab govitecan offered a PFS benefit that was statistically significant, although modest, compared to chemotherapy in patients that were previously treated and had endocrine-resistant HR+/HER2- disease.

Clearly, sacituzumab govitecan, a first-in-class, has proven to be an important therapeutic modality to manage TNBCs. It has shown PFS and OS benefits when compared to standard-of-care chemotherapeutics. Accordingly, it is now approved for the treatment of TNBCs in the United States and the European Union. In the case of HR+/HER2- metastatic breast cancers, sacituzumab govitecan has also shown PFS benefit over standard-of-care chemotherapeutics. As for the OS in patients with such tumors, first interim analysis was not mature in the recently published study (8). A second interim analysis reported in a subsequent scientific meeting revealed OS improvement of 3.2 months over the standard-of-care chemotherapeutics (7). Thus, sacituzumab govitecan also offers PFS and OS benefits for HR+/HER2- metastatic breast cancers. Although these benefits are modest, such patients have limited options. Therefore, sacituzumab

govitecan appears to be an option for metastatic HR+/HER2- breast cancers that are heavily pretreated and exhibit endocrine resistance. Additional clinical trials are currently underway, and the outcomes are expected to further refine the use of sacituzumab govitecan in better management of metastatic breast cancer.

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Conflicts of Interest

The authors have no relevant conflicts of interest to declare.

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