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Sacituzumab govitecan — a new therapy for patients with triple-negative breast cancer

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ABSTRACT

Treatment outcomes in patients with metastatic triple-negative breast cancer (TNBC) have not improved significantly for many years. Modern treatments, including immune therapy and poly ADP-ribose polymerase (PARP) inhibitors, are available for a select group of TNBC patients. In many cases, classic chemotherapy remains the treatment of choice, which produces unsatisfactory response rates. The poor prognosis of patients with metastatic TNBC justifies intensive research on new drugs for this group of patients, including attempts to use conjugates. This article discusses the reports on sacituzumab govitecan (SG), which is composed of a monoclonal antibody targeting trophoblast-cell surface antigen 2 (Trop-2) expressed on many TNBC cells and linked to a payload (SN-38), the active metabolite of irinotecan. The structure and mechanism of action of this conjugate are presented. The available results of clinical trials with SG in breast cancer patients are summarized, including the results of the ASCENT registration study, which showed a significant improvement in the median progression-free survival, as well as overall survival, compared to classic chemotherapy in patients previously treated with advanced TNBC. The most common side effects of the drug are discussed, indicating principles of primary and secondary prophylaxis that allow for effective management of possible complications. Directions for further research in breast cancer patients on this very promising conjugate were also indicated.

Key words: sacituzumab govitecan, triple-negative breast cancer, conjugate, Trop-2

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Introduction

Treatment of patients with triple-negative breast cancer (TNBC) remains a challenge for oncologists. For cancers with either estrogen receptor (ER) expression or human epidermal growth factor receptor 2 (HER2) overexpression, modern therapies have been developed which allowed for a significant extension of median overall survival (OS) in patients with distant metastases [1, 2]. TNBC is associated with a much worse prognosis. The introduction of innovative drugs (e.g. immunotherapy) made it possible to achieve OS of 25 months in breast cancer patients with expression of programmed death ligand 1 (PD-L1) [3, 4]. While chemotherapy alone is

still a standard of care in the remaining patients, its effectiveness is limited [5, 6]. The median OS in patients with metastatic TNBC is up to 16–18 months [3, 4, 7]. The above data indicate that TNBC is currently the most aggressive breast cancer subtype. Intensive research is being conducted on new therapies that would improve the prognosis. As a result, new drugs (including conjugates) are being developed. One of the very promising ones is sacituzumab govitecan (SG).

This article discusses the structure and mechanism of action of SG, summarizes the results of available studies on using the drug in breast cancer patients, and presents the profile of side effects and practical guides for management during SG administration.

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Structure and mechanism of action of sacituzumab govitecan

Sacituzumab govitecan is a conjugate containing the monoclonal antibody sacituzumab that binds to the trophoblast-cell surface antigen 2 (Trop-2) on the surface of cancer cells, SN-38 active loading (govitecan), and a linker [8]. Approximately 7–8 molecules of SN-38 are attached to each antibody molecule (mean 7.6) (Fig. 1). SN-38 is a cytotoxic metabolite of irinotecan that inhibits topoisomerase I. It is 100–1000 times stronger than irinotecan. After SG administration, the monoclonal antibody binds to Trop-2 present on the cancer cell surface, then the receptor-conjugate complex is internalized, thanks to which SN-38 enters the cancer cells. SN-38 is released from the lysosomes and enters the cell nucleus, where it damages DNA by inhibiting topoisomerase I. The linker between antibody and payload has intermediate stability, which allows for the slow release of SN-38. Unbound SN-38 can cross cell membranes and reach and destroy the tumor microenvironment. This is due to the release of SN-38 from the tumor cells after internalization and splitting of SN-38 by linker hydrolysis before the conjugate internalization. This makes it possible to destroy Trop-2 negative cells (bystander effect) [9].

Trop-2 is a cell-surface glycoprotein, reported to be overexpressed in breast cancer, lung cancer, gastric cancer, colorectal cancer, pancreatic cancer, prostate cancer, cervical cancer, ovarian cancer, as well as head and neck cancers [9]. Trop-2 overexpression in cancer cells stimulates their growth and metastasis through promotion of cell proliferation and motility. Trop-2 is also involved in the process known as epithelial-mesenchymal transition (EMT) [10]. There are limited studies on Trop-2 prognostic value in breast cancer. According to the current evidence, patients with high Trop-2 expression have more aggressive disease and a worse prognosis [11]. Importantly, Trop-2 expression is found in the vast majority of TNBCs, with a positive result rate of over 85% [9, 12, 13]. The above reports contributed to the attempts to use Trop-2 as a potentially attractive target of anti-cancer therapy.

Results of studies with sacituzumab govitecan in patients with triple-negative breast cancer

Phase I/II study

The first reports on the use of SG come from a phase-I trial, in which the treatment was used in 25 patients with various cancers (including 4 patients with TNBC). A clinical benefit was found in

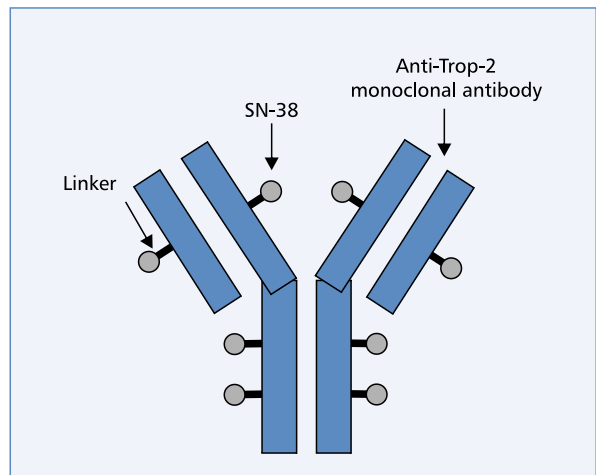


Figure 1. Structure of govitecan sacituzumab; Trop-2 — trophoblast-cell surface antigen 2

half of them [14]. The recommended SG dose for further studies was determined at 10 mg/kg body weight (BW).

Subsequently, the phase-I/II IMMU-132-01 basket trial was designed, which enrolled patients with various cancers (including patients previously receiving at least two lines of treatment for metastatic TNBCs). Patients were treated with SG administered intravenously on days 1 and 8 of the cycle, every 21 days, at the above-mentioned dose of 10 mg/kg BW. The general condition of the patients was good. The preliminary results of the study were published in 2017 [12]. After analyzing 69 patients with TNBC, the objective response rate (ORR) was 30%, and the clinical benefit rate (CBR) was 46%. The median progression-free survival (PFS) was 6 months, and the median OS was 16.6 months.

The final analysis of the phase-II study included data from 108 TNBC patients who underwent SG therapy (usually after 3 previous treatment lines; range 2–10) [15]. The vast majority of patients had previously received taxoids (98%) and anthracyclines (86%). Seventeen percent of patients had previously undergone immunotherapy. After 10 months of follow-up (median) ORR was 33%, CBR 45%, median PFS 5.5 months, and median OS 13.0 months.

ASCENT study

The obtained results contributed to the design of the phase-III clinical study ASCENT [13]. This open-label, randomized trial enrolled 529 patients with metastatic or inoperable locally advanced TNBC. Previously, at least 2 lines of systemic treatment were used (one of which could have been perioperative chemotherapy provided that relapse occurred within 12 months of completion). The study involved 61 patients with sta-

Table 1. Summary of the results of studies with sacituzumab govitecan in breast cancer patients

Indication	Study	Treatment schedule	Number of pts. (N)	ORR	CBR	Median PFS (months)	Median OS (months)
TNBC	IMMU-132-01 [15]	SG	108	33% (3% CR and 30% PR)	45%	5.5	13
	ASCENT (IMMU-132-05) [13]	SG vs. chemotherapy	235 vs. 233	35% (4% CR and 31% PR) vs. 5% (1% CR and 4% PR)	45% vs. 9%	5.6 vs. 1.7; HR = 0.41	12.1 vs. 6.7; HR = 0.48
ER+/HER2-	IMMU-132-01 [22]	SG	54	32%	44%	5.5	12

CBR — clinical benefit rate; CR — complete response; ER — estrogen receptor; HR — hazard ratio; ORR — objective response rate; OS — overall survival; PFS — progression-free survival; PR — partial response; SG — sacituzumab govitecan; TNBC — triple-negative breast cancer

ble brain metastases. The study compared SG with single-drug chemotherapy (oral capecitabine at a dose of 2000–2500 mg/m² daily on days 1–14 every 3 weeks), or intravenous eribulin at a dose of 1.23–1.4 mg/m² on days 1 and 8 of the cycle every 21 days, or intravenous gemcitabine at a dose of 800–1000 mg/m² on day 1, 8, and 15 of the cycle every 28 days, or vinorelbine intravenously at a dose of 25 mg/m² every week) chosen by the investigator. The dosing of SG was standard (intravenous infusions of 10 mg/kg BW on days 1 and 8 of the cycle every 21 days). Treatment was continued until progression or unacceptable toxicity.

The primary endpoint of the study was median PFS in patients without brain metastases — the analysis included 235 patients in the experimental arm and 233 patients in the control group (468 patients in total). Secondary endpoints were OS in the cohort without brain metastases, PFS and OS in the overall population, ORR, safety, and quality of life.

The performance status according to the Eastern Cooperative Oncology Group scale (ECOG PS) was good (0-1). All patients had previously received taxoids, most of them also had anthracyclines (82%), and more than half had carboplatin (66%); 7% of patients had previously received therapy with PARP inhibitors, and 27% received immunotherapy.

After a median follow-up of 17.7 months, an improvement was achieved in the SG group. Median PFS in the population without brain metastasis, the primary endpoint, was 5.6 months in the SG arm and 1.7 months in the control arm [hazard ratio (HR) = 0.41; 95% confidence interval (CI): 0.32–0.52; p < 0.001]. PFS advantage in the SG arm was observed in all predefined subgroups, including patients ≥ 65 years of age, with more than 3 prior treatment lines, and after immunotherapy. The median OS was 12.1 months in the SG group and 6.7 months in patients undergoing chemotherapy (HR = 0.48; 95% CI 0.38–0.59; p < 0.001). The results of OS subgroup analyses were constantly more favorable for SG compared to chemotherapy. There was also a significant improvement in ORR in the experimental arm (35% compared with 5% in patients undergoing

standard chemotherapy). Similarly, CBR was greater in the SG group (45%) than in the control arm (9%).

Patients with brain metastases, most of whom had previously received 5 treatment lines, were analyzed separately [16]. There was numerically higher median PFS in the group treated with SG compared to chemotherapy (2.8 vs. 1.6 months) and similar results in terms of OS (6.8 and 7.5 months, respectively). On the other hand, ORR in both groups was 0% and 3%, and CBR was 9.4% and 3.4%, respectively. However, it should be highlighted that the analyzed subgroup with brain metastases was small, and the results regarding the effectiveness of the treatment require further studies.

The results of SG studies in breast cancer patients are summarized in Table 1.

Predictive biomarkers for sacituzumab govitecan efficacy

In the case of targeted therapies, response biomarkers are sought to more accurately qualify patients who have the best chance of obtaining benefits from the therapy. The Trop-2 expression seems to be the most promising biomarker of SG response [17]. In the above-mentioned study, the intensity of Trop-2 expression was determined by immunohistochemistry (IHC) in 290 patients, and three groups were distinguished, taking into account the percentage of stained cells and its intensity (H-score from 0 to 300). The most numerous was the group with high Trop-2 expression (H-score > 200–300) (54% of patients), while the group with intermediate expression (H-score 100–200) and low Trop-2 expression 2 (H-score from 0 to < 100) included 26% and 20% of patients, respectively.

Patients in the experimental arm with high, moderate, and low Trop-2 expression had median PFS of 6.9 months, 5.6 months, and 2.7 months, respectively. On the other hand, median PFS in the control arm in respective groups was considerably lower (2.5, 2.2, and 1.6 months, respectively). Patients in the group treated with SG with enhanced Trop-2 expression had also

improved OS outcomes. Median OS was 14.2 months, 14.9 months, and 9.3 months in the subgroups with high, intermediate, and low Trop-2 expression, respectively, and 6.9 months, 6.9 months, and 7.6 months in the respective subgroups in the chemotherapy arm. A similar association between ORR and intensity of Trop-2 expression was observed in the SG-treated group. The ORR in the experimental group was 44% vs. 1% in the group with high Trop-2 expression, 38% vs. 11% in the group with intermediate expression, and 22% vs. 6% in the group with low Trop-2 expression as compared to the control arm.

The mutation status of the *BRCA1/2* genes was known in 292 patients in the ASCENT study, and *BRCA* mutation was found in 12% of the analyzed patients. However, the conducted analyses did not show any differences in treatment outcomes depending on *BRCA* gene mutation status. SG therapy was significantly better compared to standard chemotherapy [17].

The analysis presented above is the basis for further research on the *predictive* biomarkers for SG efficacy. Currently, patients are eligible for SG treatment regardless of Trop-2 expression status. Further studies may allow for limiting the group of patients qualified for treatment. The authors of the analysis indicated that the size of the group of patients with low Trop-2 expression was small, which does not allow for formulating unequivocal recommendations limiting the use of SG in these patients.

Side effects of sacituzumab govitecan

All patients in the aforementioned phase-I/II study experienced adverse effects, with 66% and 19% experiencing grade 3 and grade 4 adverse effects (AEs), respectively. The most common adverse reactions were nausea (67%), diarrhea (62%), fatigue (55%), neutropenia (64%), anemia (50%), and the most common grade 3 or higher (with a frequency > 10%) were neutropenia (26%) and anemia (11%). Febrile neutropenia was diagnosed in 10 patients (9%). Adverse events leading to treatment withholding occurred in 48 of 108 patients (44%); the most common cause was neutropenia. Three patients (3%) discontinued treatment due to side effects of therapy [15].

A similar toxicity profile was observed in patients treated in the ASCENT study [13]. The most common treatment-related AEs (TRAEs) of all grades were neutropenia (63% in the SG group vs. 43% in the chemotherapy group), diarrhea (59% vs. 12%), nausea (57% vs. 26%), alopecia (46% vs. 16%), fatigue (45% vs. 30%), and anemia (34% vs. 24%). The most common grade 3 TRAE was neutropenia (51% in SG group vs. 33% in the chemotherapy arm), followed by leukopenia (10% vs. 5%), diarrhea (10% vs. 1%), anemia (8% vs. 5%), and febrile neutropenia (6% vs. 2%).

An additional analysis was performed to assess the effectiveness of SG and treatment complications in elderly patients [18]. The treatment outcomes in patients aged 65 and older were found to be similar to those in the overall population while the incidence of complications was slightly higher, indicating the need for closer monitoring.

In the ASCENT study, granulocyte colony-stimulating factor (G-CSF) was used in 49% of patients receiving SG and 23% of patients receiving chemotherapy. The percentage of patients with dose reduction due to AEs was also similar (22% in the SG group vs. 26% in the chemotherapy group). It has been shown that reducing the SG dose did not translate into a decreased treatment effectiveness [19]. Adverse events leading to treatment discontinuation were rare and occurred in 12 patients (5%) in each group. There were 3 deaths due to adverse events in each study arm, but neither was associated with SG use [13].

Patients' quality of life during treatment with sacituzumab govitecan

In the ASCENT study, patients' quality of life was assessed before starting the treatment, before each cycle, and after treatment discontinuation with the use of the EORTC QLQ-C30 questionnaire [20]. The analysis included all participants with available baseline data and at least one assessment following treatment initiation. The quality of life of patients actively treated from the 2nd to the 6th cycle of therapy was compared.

The quality-of-life analysis included a total of 419 patients. At baseline, the quality-of-life scores did not differ between the study groups. It was found that quality of life in the SG arm was improved compared to chemotherapy in the following subscales: general health (0.7 vs. -3.4), physical functioning (1.3 vs. -4.4), and emotional functioning (3.3 vs. -0.5), additionally indicating lower intensity of fatigue (2.0 vs. 7.1), pain (-8.9 vs. -1.9), dyspnea (-3.8 vs. 4.0) and insomnia (-4.7 vs. 0.3). Among all the symptoms reported by patients in the SG group, worse results were noted only for diarrhea (14.1 vs. -1.3).

In conclusion, the quality of life was maintained or improved in the SG group. Diarrhea was more frequently reported by patients in the experimental arm; however, this did not translate into an overall assessment of health or functioning.

Recommended supportive care

Based on observations conducted during studies with SG, it is recommended that the first infusion of the drug should last 3 hours, and subsequent infusions

from 1 to 2 hours, provided that the earlier ones were well tolerated [21]. Premedication (including antipyretics, histamine type 1 and type 2 receptor blockers, or corticosteroids, e.g. 50 mg of hydrocortisone or its equivalent, administered orally or intravenously) is recommended in patients treated with SG. In addition, prophylaxis of nausea and vomiting should be given in the form of two or three antiemetics (e.g. dexamethasone with serotonin receptor antagonist or neurokinin 1 receptor antagonist).

A complete blood count should be monitored during the treatment, and SG should not be administered if the absolute neutrophil count is less than $1500/\text{mm}^3$ on day 1 of the cycle or less than $1000/\text{mm}^3$ on day 8 of the cycle. The time to neutropenia onset is usually 15 days from treatment initiation, with median duration of 8 days. In patients with severe neutropenia or febrile neutropenia, G-CSF administration may be necessary, with SG dose adjustment after resolution.

The time to diarrhea onset is usually 13 days from treatment initiation, with median duration of 8 days. In addition, SG should not be administered in the case of grade ≥ 3 diarrhea, and treatment could only be restarted after resolution to grade ≤ 1 . After an infectious etiology has been ruled out, symptomatic treatment with loperamide, as well as fluids and electrolytes replacement should be started. In some patients who develop an excessive cholinergic response to SG treatment (e.g. in the form of stomach cramps, diarrhea, ptalism), appropriate treatment (e.g. atropine) may be given as part of premedication before subsequent SG cycles.

SN-38 is metabolized via uridine *diphosphate glucuronosyltransferase* 1A1 (UGT1A1). Genetic variations of the *UGT1A1* gene (e.g. UGT1A1*28 allele) lead to less UGT1A1 enzymatic activity. It has been observed that patients who are homozygous for the UGT1A1*28 allele are potentially at greater risk of developing complications (including neutropenia, febrile neutropenia, and anemia). Approximately 20% of the black population, 10% of the white population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Patients with lower UGT1A1 activity should be closely monitored for side effects. However, there are no indications for routine determining UGT1A1 activity in medical practice. The management of adverse effects, including recommended dose modification, is identical for all patients treated with SG [13, 21].

In addition, caution is required in all patients receiving SG with concomitant use of UGT1A1 inhibitors (e.g. ketoconazole or propofol) or inducers (e.g. carbamazepine or phenytoin), which may affect SN-38 activity.

Data on SG are summarized in Table 2.

Table 2. Summary of data for sacituzumab govitecan

Sacituzumab govitecan

Conjugate composed of anti-Trop2 monoclonal antibody combined with SN-38 (active metabolite of irinotecan — topoisomerase I inhibitor)

Dosage: 10 mg/kg body weight, intravenously on days 1 and 8, cycles every 21 days

Side effects: most common neutropenia, diarrhea, nausea, alopecia, weakness

Recommended primary prophylaxis of infusion reactions and nausea/vomiting, secondary prophylaxis in severe neutropenia

Symptomatic treatment of diarrhea: loperamide; in the case of severe early cholinergic symptoms, additionally atropine before subsequent infusions

Improvement or maintenance of quality of life in patients treated with SG compared with chemotherapy

Significant improvement in median PFS and OS as well as ORR and CBR rates

EMA registration: advanced or metastatic TNBC after prior treatment

CBR — clinical benefit rate; EMA — European Medicines Agency; ORR — objective response rate; OS — overall survival; PFS — progression-free survival; SG — sacituzumab govitecan; TNBC — triple-negative breast cancer

Future perspectives

There are numerous clinical trials with SG in patients with TNBC, including preoperative treatment (the NeoSTAR study), adjuvant treatment in patients with residual disease (the SASCIA study in HER2-negative cancers), and palliative treatment [monotherapy or in combination with pembrolizumab (the Saci-IO study), atezolizumab, or talazoparib]. In addition, a clinical study for patients with brain metastases has been planned.

SG is also assessed in patients with ER+/HER2- breast cancer. The first data are from the phase-I/II IMMU-132-01 basket study, presented above [22]. Patients who previously received at least one line of hormone therapy and one line of chemotherapy due to metastatic breast cancer were eligible for the study. The results of 54 patients in whom SG was used at the recommended dose of 10 mg/kg BW on days 1 and 8 of the cycle every 21 days are already presented. All patients had previously received hormone therapy, 85% used taxoids, 67% anthracyclines, 65% capecitabine, 61% CDK 4/6 inhibitor, and 44% mTOR inhibitor. ORR was 32%, while CBR was 44%. Median PFS was 5.5 months and median OS was 12 months. The toxicity profile of SG was similar to that seen in the studies in TNBC patients. The most common grade 3 adverse reactions were neutropenia (50% of patients), anemia (11.1%), and diarrhea (7.4%). Two patients discontinued treatment due to adverse events. No deaths related to SG therapy have been reported.

Further clinical trials are currently ongoing in patients with ER+/HER2- breast cancer treated with SG in monotherapy compared with chemotherapy (the TROPiCS-02 study), as well as SG in combination with pembrolizumab (the Saci-IO HR+ study).

The results of the above-mentioned studies will allow us to determine the optimal setting in which SG should be used in breast cancer patients in a few years and possibly extend the current indications for using this promising drug.

Conclusions

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved SG as the first conjugate for the treatment of patients with advanced inoperable or metastatic TNBC who have been previously treated [21]. SG is made of an anti-Trop-2 antibody combined with SN-38 molecules (topoisomerase I inhibitor — the active metabolite of irinotecan). The pivotal ASCENT study showed a significantly greater benefit in terms of median PFS (5.6 months) and OS (12.1 months), as well as ORR (35%) and CBR (45%) with SG compared to standard chemotherapy [13]. Predictive factors for response to SG treatment are being sought, and preliminary observations indicate a promising role of Trop-2 expression. The most common side effects of SG are diarrhea and hematological complications (including neutropenia). The principles have been developed that allow for efficient management of complications [21]. The quality of life of patients in the studies was maintained or better in the SG group despite higher diarrhea incidence. Based on the results of the ASCENT study, SG is recommended for use in the 2nd line treatment in patients with metastatic TNBC [6].

There are multiple clinical trials on SG in patients with TNBC and ER+/HER2- breast cancer. The outcomes will provide a better understanding of indications for SG treatment.

Conflict of Interest

KP: Fees for consultations/lectures/training/clinical trials and fees for scientific congresses: Roche, Novartis, Eli Lilly, Pfizer, MSD, AstraZeneca, Gilead, Teva, Egis, and Vipharm.

AJG: Fees for consultations/lectures/training/clinical trials: AstraZeneca, Novartis, Roche, Gilead, Eli Lilly, Amgen, Pfizer, and MSD.

AN: Fees for consultations/lectures/training/fees for scientific congresses: Pfizer, Novartis, and Roche.

ZN: Fees for consultations/lectures/training/clinical trials: Roche.

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