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Sacituzumab govitecan: Antibody-drug conjugate in triple negative breast cancer and other solid tumors

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Summary:

Patients with metastatic triple negative breast cancer (mTNBC) that has progressed on first-line therapy have a poor prognosis with limited therapeutic options. Sacituzumab govitecan (SG) is a novel antibody-drug conjugate (ADC) that has shown promising efficacy in mTNBC. SG is comprised of SN-38, the active metabolite of irinotecan, conjugated via a hydrolyzable linker to a the humanized RS7 antibody targeting Trop-2, a glycoprotein that is expressed at high levels in many epithelial solid tumors. It has received breakthrough therapy status by the US Food and Drug Administration for the treatment of patients with pretreated mTNBC. In this review, we summarize available data regarding the pharmacology, pharmacokinetics, safety, and efficacy of SG and describe ongoing and future clinical studies investigating this agent.

Keywords

sacituzumab govitecan; metastatic triple negative breast cancer; antibody; drug conjugate; IMMU-132

Background:

Metastatic triple negative breast cancer (mTNBC) is associated with an aggressive clinical course and poorer prognosis compared to other breast cancer subtypes (1, 2). Recent data from the IMpassion130 trial provides evidence to support the use of an immunotherapy and taxane combination in the first-line setting for PD-L1 positive mTNBC (3). However, patients eventually experience disease progression on first-line therapy. Cytotoxic chemotherapy remains the standard of care in patients with relapsed or refractory disease. Unfortunately, response rates with chemotherapy are only around 10–15% in pretreated patients and the average progression-free survival is short. Therefore, there is an unmet need for newer, more effective, and less toxic therapies in this patient population.

Trop-2 as a therapeutic target

Trophoblast cell-surface antigen 2, or Trop-2, is a cell-surface glycoprotein also known as TACSTD2 (tumor-associated calcium signal transducer 2), GA733–1 (gastric antigen 733–

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1), and EGP-1 (epithelial glycoprotein-1) (4). It is encoded by the gene *TACSTD2* located on chromosome 1p32. Trop-2 is overexpressed in the majority of epithelial carcinomas, including breast, colon, prostate, pancreatic, urothelial, and lung cancers (5). It is also expressed in a variety of normal epithelial tissues including the heart, liver, kidney, and lung, but expression in these tissues is typically much lower than the level of expression seen in epithelial tumors, making it a promising therapeutic target (6). Trop-2 plays an important role in anchorage-independent cell growth and tumorigenesis by acting as a calcium signal transducer, leading to activation of various tumorigenic pathways including NF-κB, cyclin D1, and ERK (7–11). In several tumor types, Trop-2 expression is associated with more aggressive disease (4). In breast cancer, Trop-2 expression is associated with lymph node metastasis and poorer survival (12–14). Trop-2 is expressed in all breast cancer subtypes, including TNBC and luminal breast tumors (13).

Irinotecan and SN-38

Irinotecan is a prodrug of the camptothecin class. The active form of irinotecan is 7-ethyl-10-hydroxycamptothecin, or SN-38. SN-38 inhibits the enzyme topoisomerase-I, which induces reversible single-strand DNA breaks during replication in S phase. By inhibiting topoisomerase-I, SN-38 prevents the re-ligation of the DNA strand, resulting in double-strand DNA breakage and subsequent cell death (15). Irinotecan is active in multiple tumor types including colon cancer, pancreatic cancer, and small cell lung cancer and is FDA approved for first-line therapy in metastatic colorectal cancer in combination with 5-fluorouracil and leucovorin. Irinotecan has shown activity in metastatic breast cancer patients who have tumors that progressed on anthracyclines and taxanes, with objective response rates up to 23% (16). However, treatment with irinotecan can be challenging, as the drug is rapidly cleared in the blood and is converted to SN-38 at very low levels (<5%) *in vivo*. The degree of conversion to SN-38 is patient-dependent. Moreover, irinotecan is susceptible to inactivation through lactone ring hydrolysis and glucuronidation (17). SN-38 itself is a moderately toxic drug, with *in vitro* IC_{50} values in the nanomolar range compared to toxic drugs used in other ADCs such as auristatins or maytansines, which have IC_{50} values in the picomolar range. Recently, SN-38 has become a promising drug for use in antibody-drug conjugates (ADCs), allowing for targeted drug delivery to tumors while bypassing several of the pharmacokinetic issues associated with irinotecan.

An ADC is comprised of a monoclonal antibody attached to a cytotoxic drug via a chemical linker. Examples of ADCs that have been developed and are in current clinical use include trastuzumab emtansine (T-DM1) for the treatment of metastatic HER2-positive breast cancer and HER2-positive early stage breast cancer with residual disease after neoadjuvant chemotherapy, as well as brentuximab vedotin for the treatment of recurrent Hodgkin lymphoma and anaplastic large cell lymphoma (18–20). Sacituzumab govitecan (SG), originally known as IMMU-132, is a novel ADC combining the humanized RS7 antibody targeting Trop-2 coupled to a proprietary hydrolyzable linker that allows for a time-dependent release of the payload, SN-38. It is currently under clinical investigation in a variety of epithelial solid tumors, including in mTNBC.

Sacituzumab govitecan: Preclinical Development

Preclinical Pharmacology:

SG is comprised of an anti-Trop-2 IgG antibody (hRS7) connected to SN-38 via the CL2A linker moiety. The internalizing IgGκ antibody RS7–3G11 (RS7) was developed in mice to bind Trop-2 with nanomolar affinity and was later humanized for clinical use (21, 22). This antibody has the potential to be internalized after binding to Trop-2 expressing cells. Cardillo et al. covalently conjugated the topoisomerase I inhibitor SN-38 to humanized RS7 (hRS7) via a hydrolyzable linker to form an ADC (hRS7-SN-38) (23).

Several cleavable linkers of varying stability had previously been developed for the conjugation of SN-38, with rates of release from hours to days (24). The group ultimately utilized CL2, a linker with an intermediate serum stability, based on preclinical studies demonstrating that a SN-38 release rate of ~1 day conferred optimal efficacy (24, 25). The synthesis of the CL2 linker was simplified by removing its phenyalanine moiety, thus creating the final linker designated CL2A, with no significant effects on the stability, antigen binding, or *in vitro* cytotoxicity of the ADC. The linker contains a short polyethylene glycol moiety in order to increase aqueous solubility. The linker's intermediate stability is thought to contribute to the effectiveness of the ADC, as it allows for SN-38 release in the tumor microenvironment in addition to intracellular release after hRS7 internalization. The extracellular release of the free drug allows for targeting of adjacent tumor cells in a manner independent of Trop-2 expression.

The CL2A linker is attached to the lactone ring of SN-38. SN-38 is then conjugated site-specifically to 8 interchain thiols on the antibody. The substitution ratio is 7.6 drugs per antibody when accounting for a small amount of SN-38 that is disassociated from the linker during manufacturing (5). This ratio is higher when compared to those of previously developed ADCs, in which a ratio of 4:1 or lower is more typical. The higher substitution ratio does not affect pharmacokinetics but likely helps to compensate for the more moderate activity of SN-38 compared to ultratoxic drugs used in other ADCs. The cross-linker is attached to SN-38 at the 20-hydroxy position, thus maintaining SN-38 in its nonglucuronated form with a closed lactone ring, which is its active state. At low pH, SN-38 is cleaved from the linker at a benzylcarbonate site. Based on a drug-antibody ratio of 7.6 and a molecular weight of 150 KDa for SG, 100 mg of SG contains ~2mg SN-38.

In vitro studies—SG demonstrated activity against multiple solid tumor cell lines including Calu-3 (non-small cell lung carcinoma), SK-MES-1 (squamous cell lung carcinoma), COLO 205 (colonic adenocarcinoma), Capan-1 and BxPC-3 (pancreatic adenocarcinoma) and PC-3 (prostate adenocarcinoma) (23). In these studies, IC_{50} values were in the nmol/L range (1.95–23.14). Cells exposed to free SN-38 had a lower IC_{50} value compared to those exposed to SG but this difference decreased as Trop-2 expression increased. $T_{1/2}$ of the ADC was approximately 20 hours.

The unconjugated hRS7 antibody demonstrated antibody-dependent cellular cytotoxicity against Trop-2 overexpressing high-grade ovarian carcinoma cell lines, though the unconjugated antibody did not show therapeutic activity against human-derived tumor

xenografts (22, 26). SG also showed mild antibody-dependent cellular cytotoxicity activity in gastric and pancreatic cancer cell lines, though the activity was reduced by about 60% compared to unconjugated hRS7 antibody (27). Increased expression of proteins involved in both early signaling events ($p21^{WAF1/Cip1}$, p53) and late apoptotic events (PARP cleavage) was observed upon treatment of cell lines with the ADC (23, 27). These effects were not seen when cells were exposed to an unconjugated antibody. When considered together, these studies suggest that SG's mechanism of action may be attributable to both SN-38 activity as well as antibody-dependent cellular cytotoxicity, though there are no *in vivo* preclinical data or clinical data to confirm the latter.

In vivo studies—Irinotecan is known to be effective in mouse tumor models, which is attributable to the fact that, unlike in humans, mouse plasma contains carboxylesterases that readily convert irinotecan to SN-38 (28). Studies in mice bearing human tumor xenografts have also supported the antitumor effects of SG (5, 23, 29). Cardillo et al. treated five different mouse tumor models with SG and observed reduction in tumor size across all groups (23). In all cases, SG was more effective than irinotecan except when irinotecan was administered at its maximum tolerated dose. In a mouse model of TNBC, mice bearing MDA-MB-468 xenografts who were treated with SG demonstrated significantly increased tumor regression compared to mice treated with saline, irinotecan, or a control anti-CD20 ADC given at the same dose levels (5). In mice that developed progression of disease after treatment with either irinotecan or control ADC, subsequent treatment of these animals with SG resulted in tumor regression. These studies suggest that the targeted delivery of SN-38 to tumor cells with SG provides the ADC with a therapeutic advantage over irinotecan.

In a study intended to test efficacy at various drug-antibody ratios (DARs), mice with Trop-2+ human gastric xenografts were treated with equal doses of SG with drug-antibody ratios (DAR) of 6.89, 3.28, or 1.64 (5). Those that were treated at the highest DAR had a significantly increased median survival time, thus supporting the use of a higher DAR in the final version of SG. In mice with gastric or pancreatic cancer xenografts, dosing schemes of every other week, weekly, or twice weekly all demonstrated similar efficacy (27).

Pharmacokinetics and Metabolism:

Preclinical data—SN-38 is released from its linker upon exposure to environments with low pH, including upon exposure to lysosomes after intracellular internalization of SG. SN-38 may also be slowly released in the tumor microenvironment by a similar mechanism. *In vitro* studies show that SG releases about 50% of its conjugated SN-38 daily (23, 25).

Mouse xenograft studies have shown substantially improved tumor delivery of SN-38 with SG in comparison to irinotecan. In a study of nude mice bearing human tumor Capan-1 xenografts, intratumoral concentrations of SN-38 after treatment with SG ranged from 20- to 136-fold higher than SN-38 concentrations after infusion with irinotecan (29). Furthermore, tumor:blood ratios were higher in mice treated with SG by 20- to 40-fold compared to those treated with irinotecan.

Clinical data—Based on preclinical studies, patients accrued to the phase I/II study of SG were treated on days 1 and 8 of a 21-day cycle in order to maximize exposure of tumor to

the ADC while minimizing toxicity. Safety analyses and PK studies were performed for patients who received SG at doses of 8 mg/kg (n=81) and 10 mg/kg (n=97) (30). SG cleared at a faster rate than hRS7 IgG, as expected from preclinical studies, since SN-38 is released from the ADC while in the serum. $T_{1/2}$ for the 10 mg/kg dose was 11.7 +/− 3.3 hours as measured by ELISA. V_D was 33.8 +/− 12.1 mL/kg and clearance was 2.0 +/− 0.6 mL/h/kg. Clearance rates did not vary considerably between patients. Similar to results from preclinical studies, SN-38 was released from the antibody at a rate of about 50% per day, and approximately 90% of the payload was dissociated from the ADC within 3 days.

High-performance liquid chromatography (HPLC) was used to measure levels of total and free SN-38. The majority of SN-38 remained bound to IgG, with median free SN-38 levels in the 10 mg/kg group of only 2.3% at 30 minutes and 4.5% on day 1 (30, 31). Free SN-38 levels at 30 minutes did not correlate with a risk of neutropenia. The glucuronidated inactive form of SN-38 (SN-38G) comprised only a fraction of the total unbound SN-38 in these samples and never exceeded that of free SN-38. Serum samples were treated with acid, thus dissociating SN-38 from antibody via hydrolysis. SN-38G concentrations in these acid-hydrolyzed samples were similar to those seen in untreated samples, indicating that all antibody-bound SN-38 exists in its non-glucuronidated, active form (31).

Safety:

Preclinical data—Swiss-Webster mice were treated with two doses of either 4, 8, or 12 mg/kg SN-38 equivalents of SG over three days (23). SG was tolerated at all dose levels and no hematopoietic toxicity was observed. Elevated transaminases occurred in all groups by 7 days after treatment but began to resolve by day 15, with no evidence of hepatic damage on histologic evaluation. Besides the elevation in transaminases, no other significant gastrointestinal toxicity was noted in this study of mice treated with SG. Hyperglycemia and elevated chloride levels were observed at the two highest dose levels.

SG was also tested in Cynomolgus monkeys, which, unlike mouse models, express cross-reactive Trop-2 in similar tissues as humans (23). The monkey group received 2 doses of 0.96 mg SN-38/kg of SG. Transient decreases in neutrophil and platelet counts were observed but these values did not fall below the lower limit of normal. There were no perturbations in liver enzymes or serum chemistry values. In a group of monkeys who received 2 × 1.92 mg SN-38/kg of SG, there was one death due to gastrointestinal complications and bone marrow suppression, suggesting a toxicity profile that is similar to irinotecan. Necropsies at day 11 showed minimal to moderate microscopic changes in several organ systems, but these resolved entirely by the end of the recovery period at day 32, suggesting no significant damage to normal tissue. The maximum tolerated dose was determined to be between 0.96 and 1.92 mg/kg SN-38 in Cynomolgus monkeys, equivalent to 0.3 to 0.6 mg/kg SN-38 in humans. This is equivalent to a 40 mg/kg dose of total SG in humans, a much higher dose than the dose levels ultimately chosen for clinical trials (31).

Clinical data—In the first-in-human phase I study of SG in patients with pretreated solid tumors, dose escalation was performed according to a standard 3+3 design with a starting dose of 8mg/kg per injection on days 1 and 8 of a 21-day cycle with a plan for treatment

until unacceptable toxicity or progression (31). The drug was given by intravenous infusion; the initial infusion was usually completed within 3 hours and subsequent infusions were completed within ~ 1.5 to 2 hours. Investigators were permitted to prescribe pretreatment with medications including acetaminophen, antihistamines, and corticosteroids to reduce the risk of infusion reactions.

No dose limiting toxicities (DLTs) were observed within the first cycle among 3 patients treated at a dose level of 8mg/kg or among 9 patients treated at 12mg/kg, though in the latter group five patients experienced protocol-required delays and four experienced dose reductions, primarily due to hematologic toxicity. At 18 mg/kg, all three patients treated experienced dose delays after the first treatment, with two patients suffering grade 4 neutropenia, one of whom also had grade 2 diarrhea. Accordingly, the maximum tolerated dose for a single cycle was reported as 12 mg/kg (31).

In order to find a dose level that would allow administration of multiple cycles with minimal delays, four more patients were treated at 8 mg/kg and six more were treated at a new intermediate dose level of 10 mg/kg (31). One patient in the 8 mg/kg group required a dose reduction due to grade 2 rash and neutropenia. One patient in the 10 mg/kg group developed grade 3 febrile neutropenia and grade 4 hemoglobin and ultimately died four weeks after the first dose; however, the hemoglobin drop was deemed related to a gastric perforation and was not considered to be drug-associated. The rest of the patients continued on therapy at the assigned dose level until disease progression. Grade 3 or 4 neutropenia occurred in 2 of 14 patients (14.3%) treated at either dose level, compared to historical rates of 14% to 26% in patients receiving irinotecan monotherapy (32).

Since doses of 8 to 10 mg/kg were found to be generally better tolerated initially and allowed for ongoing treatment with minimal dose delays, these two dose levels were chosen for subsequent phase II studies. In the dose expansion phase II cohort, 178 patients with various solid tumor malignancies were treated at either 8 mg/kg (n=81) or 10 mg/kg (n=97) (30). Dose delays in the first cycle occurred in 29% in the 8 mg/kg group and in 34% in the 10 mg/kg group, primarily due to grade 3 or 4 neutropenia. Dose reductions occurred in 19% of patients at 8 mg/kg and for 28% at 10 mg/kg. Investigators were permitted to use growth factors for neutropenia prophylaxis; 22% of patients in the 8 mg/kg group and 26% in the 10 mg/kg group received at least one dose of growth factor. Diarrhea was common, with 62% experiencing any grade of diarrhea and 10% with ≥ grade 3 diarrhea in the 10mg/kg group. However, the rates of diarrhea were considerably lower when compared with historical rates associated with irinotecan monotherapy (32–34). Delayed-onset diarrhea is a frequent toxicity in humans treated with irinotecan, likely due to the conversion of SN-38 to its inactive glucuronidated product SN-38G, followed by reconversion to active SN-38 by bacteria in the intestine. In a mouse xenograft study, mice treated with SG had up to 20 times lower intestinal uptake compared to those treated with irinotecan, which may explain the lower incidence of diarrhea seen in humans treated with SG (29).

Adverse events, particularly diarrhea, neutropenia, and febrile neutropenia, were slightly more common in the 10 mg/kg group but the differences were not appreciable enough to reduce the starting dose for subsequent trials to 8 mg/kg (30). With data showing a trend

toward better objective response rate (ORR) and clinical benefit rate, 10 mg/kg was selected as the starting dose chosen for subsequent trials.

In the expanded mTNBC cohort of the phase I/II IMMU-132–01 study, 108 patients with mTNBC were treated with SG at 10 mg/kg after receiving at least two prior anticancer therapies for their metastatic disease (35). In this group, toxicities were similar to those seen in the phase I study; the most common adverse events were nausea (67%), neutropenia (64%), fatigue (55%), anemia (50%), and vomiting (49%) (35). Grade 3 toxicities occurred in 66% of patients; those occurring in 5% of patients or higher included neutropenia (26%), anemia (11%), hypophosphatemia (9%), fatigue (8%), diarrhea (8%), nausea (6%), and vomiting (6%). Febrile neutropenia occurred in 7% of patients. Grade 3 or higher infusion-related hypersensitivity events occurred in 3 (3%). No neuropathy of grade 3 or higher was observed. Treatment interruptions due to toxicity occurred in 44%; neutropenia was the most common reason for dose delay. Three patients (3%) discontinued the study drug due to adverse events. Four patients (4%) had adverse events leading to death, but all were attributed to disease progression.

Among the overall safety population consisting of 420 patients with multiple tumor subtypes who were treated on the phase I/II study at doses of 8, 10, 12, or 18 mg/kg, the most common adverse events were nausea (67%), diarrhea (62%), fatigue (57%), neutropenia (55%), vomiting (44%), and alopecia (42%). Grade 3 toxicities occurred in 69% of patients and included neutropenia (25%), anemia (11%), diarrhea (9%), hypophosphatemia (5%), and nausea (5%). Grade 4 neutropenia was noted in 13%. Adverse events prompted study discontinuation in 7.4% of patients.

Since irinotecan toxicity is associated with homozygosity for UGT1A1*28, investigators examined adverse events by UGT1A1 status (35, 36). In the total dose expansion cohort, 333 patient samples were analyzed for UGT1A1 status; 144 (43%) had a *1/*1 genotype, 152 (46%) had a *1/*28 genotype, and 37 (11%) had a *28/*28 genotype. The incidence of neutropenia was numerically increased in *28 homozygous patients (64.9%) compared to those with *1/*28 (37.5%) or *1/*1 (34.7%) genotypes. There was no trend toward an increase in the incidence of diarrhea in *28 homozygous patients, though this analysis was limited by the small number of patients who were found to have *28 homozygosity. Ultimately, the degree of difference between these groups was not felt to be large enough to recommend screening for *UGT1A1* genotypes (30).

Clinical Efficacy:

In a first-in-human phase I study (IMMU-132–01; NCT01631552), IMMU-132 was administered to 25 patients with a variety of metastatic epithelial solid tumors who were relapsed or refractory to at least one prior line of chemotherapy (31). The study drug was dosed on days 1 and 8 of 21-day cycles at starting doses of 8 (n=7), 10 (n=6), 12 (n=9) or 18 (n=3) mg/kg. Using RECIST 1.1 criteria, there were two partial responses in a patient with mTNBC and colon cancer, respectively. Stable disease was the best response in 16 other patients. The median time to progression (TTP) among 24 patients (excluding a patient who withdrew after 1 treatment) was 3.6 months (range, 1–12.8). For patients with stable disease or partial response (PR: n=18), TTP was 4.1 months (range, 2.6–12.8). Notably, among 9

patients who had received prior topoisomerase-I inhibitors, two had a significant decrease in target lesions and 5 achieved stable disease. No infusion reactions were noted, and no patients developed antibodies to the IgG antibody or to SN-38 at any point during the study (30, 31).

Triple negative breast cancer—Based on the promising phase I results reported by Starodub et al., the phase II portion of the IMMU-132–01 study expanded accrual to patients with select tumor types, including mTNBC. Bardia et al. reported preliminary results for 69 patients treated in the mTNBC cohort in the *Journal of Clinical Oncology* in 2017 (37). Updated data were published in *The New England Journal of Medicine* in 2019, reporting results for 108 patients with mTNBC who had progressed on at least two prior lines of anticancer therapies and were treated with SG at a dose of 10 mg/kg on days 1 and 8 of a 21-day cycle (35). The median number of prior treatments was 3 (range, 2 to 10) and most had received prior taxanes (98%) and anthracyclines (86%). The primary efficacy endpoint was the objective response rate (ORR) per RECIST 1.1 criteria. Other efficacy endpoints were time to response, duration of response, clinical benefit rate (CBR; defined as a complete or partial response or stable disease for at least 6 months), progression-free survival, and overall survival. The ORR was 33.3% and the CBR was 45.4%, with a median duration of response of 7.7 months (95% CI, 4.9 to 10.8). Three patients (2.8%) had a complete response. Median progression-free survival (PFS) was 5.5 months (95% CI, 4.1 to 6.3) and median overall survival was 13.0 months (95% CI, 11.2 to 13.7). The median duration of treatment with SG was 5.1 months, more than double the median time on the previous line of therapy. Responses were seen in patients who had previously received checkpoint inhibitors, with 8 of 18 patients (44%) achieving a clinical response. Subgroup analyses did not show differences in outcomes based on demographic and clinical factors such as age, number of prior therapies, or presence of visceral metastases, though the analysis was limited by the relatively small number of patients on study.

Hormone receptor-positive breast cancer—Patients with HR-positive (HR+), HER2-negative breast cancer who had tumors that progressed on at least one prior hormonal therapy were also enrolled in the SG phase I/II basket study. As of April 2018, 54 patients with HR+/HER2- disease had been enrolled and received at least one dose of SG; in this group, the ORR was 31% and the CBR was 48% (38). Median PFS was 6.8 months (95% CI, 4.6 to 8.9). Among patients who had previously received CDK 4/6 inhibitors (n=37), the ORR was 24%.

Other tumor types—Reported efficacy data of SG by tumor type is summarized in Table I. Early responses were seen in patients with metastatic urothelial cancer (mUC) enrolled in the SG phase I/II basket study (39). In February 2019, updated results of the expansion cohort were reported; 45 patients with mUC were treated with an ORR of 31%, including 2 complete responses and 12 partial responses (40). Median duration of response was 12.9 months, with two patients continuing on drug for over two years.

SG has also demonstrated activity in both small cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) patients who were treated on the phase I/II protocol. In this study, 50 patients with metastatic small cell lung cancer were treated with either 8 mg/kg or 10 mg/kg

SG with an ORR of 14%, CBR of 34%, and a median response duration of 5.7 months (41). Similarly, 54 patients with metastatic NSCLC were treated, with an ORR of 17%, CBR of 43%, and median response duration of 6.0 months (42). The NSCLC population was heavily pretreated, with a median of three prior therapies.

Given the high rate of Trop-2 overexpression in epithelial cancers, patients enrolled in the phase I/II study were not preselected for Trop-2 expression. Assessment for Trop-2 expression was performed retrospectively in a subset of enrolled patients and demonstrated consistently high expression across tumor subtypes: in 150 samples, 93% stained positively for Trop-2 and 82% had moderate to strong (2–3+) Trop-2 expression by immunohistochemistry (30). In the mTNBC cohort, among patients with Trop-2 assessment (n=48) there was a trend toward higher PFS in patients with moderate to strong Trop-2 expression (88%) versus those with weak or no staining (12%) (37). Similarly, in patients with SCLC there was a trend toward higher response rates in patients with stronger staining, but no significant differences in PFS or OS (41). These analyses, however, were limited by small sample sizes, and in general no definitive association between degree of Trop-2 expression and clinical outcome has been observed (35). While there are high rates of Trop-2 expression across tumor types, larger studies are required to clarify the relationship between expression and response to treatment. Trop-2 expression was not required as an entry criterion for the current ongoing randomized trials of SG.

Indications:

Based on efficacy signals seen in mTNBC patients treated on the expansion phase I/II study, SG received breakthrough therapy designation by the FDA on February 5, 2016 for the treatment of patients with mTNBC who have progressed on at least two prior therapies.

Drug Interactions:

Since SG remains an investigational drug, there is little information available regarding specific drug interactions. However, since SN-38 is processed by CYP3A4, drugs that induce or inhibit CYP3A should be used with caution in patients receiving SG.

Ongoing Trials:

Based on the promising results of the mTNBC cohort in the phase I/II IMMU-132–01 study, a confirmatory multicenter randomized phase III trial is ongoing. This study, known as the ASCENT trial (NCT02574455), will enroll 488 mTNBC patients who have failed at least two prior lines of chemotherapy, including a taxane. Patients will be randomized to SG or physician’s choice of one of four chemotherapeutic agents (capecitabine, gemcitabine, vinorelbine, or eribulin). Given the presence of high levels of Trop-2 expression across all breast cancer subtypes, SG also has potential therapeutic value in hormone receptor (HR)-positive metastatic breast cancer. The TROPiCS-02 study (NCT03901339) is an open-label, randomized, multicenter registrational phase III study currently recruiting patients with HR-positive HER2-negative metastatic breast cancer who have progressed on at least one prior hormonal treatment, at least one CDK4/6 inhibitor, and at least 2 prior systemic chemotherapy regimens in the metastatic setting. Patients will be randomized to SG or physician’s choice chemotherapy (capecitabine, gemcitabine, vinorelbine, or eribulin).

Based on responses seen in the phase I/II basket study in patients with metastatic urothelial cancer, the phase II TROPHY-U-01 study is currently recruiting with plans to enroll 140 mUC patients in total (43). The main cohort will consist of 100 patients who have progressed after both platinum chemotherapy and an immune checkpoint inhibitor, and an exploratory cohort of 40 patients will be comprised of patients who are platinum-ineligible but have progressed on an immune checkpoint inhibitor. The primary outcome is ORR.

Meanwhile, SG remains under investigation in a variety of other solid tumors (e.g. advanced non-small cell lung cancer) in the phase II open label TROPiCS-03 study (NCT03964727). Recruitment is anticipated to begin in the summer of 2019. Additionally, a phase II study investigating the safety and efficacy of SG in patients with metastatic castration-resistant prostate cancer who have progressed on abiraterone or enzalutamide is now open (NCT0372561).

Future Directions:

Given the initial studies of SG which show promising response rates in patients with pretreated metastatic breast cancer, results from the registrational randomized phase III studies ASCENT and TROPiCS-02 are eagerly awaited. These studies are anticipated to provide more robust data on the efficacy and safety of SG compared to single agent chemotherapy in patients with triple negative and hormone receptor-positive HER2-negative tumors, respectively.

Additionally, there is interest in combining SG with other therapeutic agents in order to overcome mechanisms of resistance and to enhance efficacy. Since topoisomerase inhibitors are known to induce multidrug resistance, the concurrent use of drug efflux inhibitors may be effective to counteract drug resistance. In one preclinical study, the addition of an ABCG2 inhibitor in combination with SG restored the efficacy of SG in cell lines that were previously resistant to SN-38 (44). In another study, the addition of PARP inhibitors to SG resulted in synergistic growth inhibition in human TNBC cell lines, suggesting PARP inhibition as a potential strategy to enhance the DNA damaging effects of SG (45). Finally, the high response rate seen in patients with various solid tumor types who had prior immune checkpoint inhibitor exposure raises the question of whether the combination of SG with immune checkpoint inhibition could increase therapeutic efficacy.

Conclusions:

Sacituzumab govitecan (IMMU-132) is a novel ADC consisting of an IgG antibody targeting Trop-2, a glycoprotein expressed at high levels in epithelial cancers, coupled to a proprietary hydrolyzable linker that allows for time-dependent release of the payload SN-38, the active metabolite of irinotecan. SG has several unique properties that contribute to its favorable safety and efficacy profile. Unlike other ADCs that employ ultratoxic drugs, SN-38 is a moderately cytotoxic drug. However, the efficacy of SG is enhanced by the use of a high drug substitution ratio and a moderately stable linker. These modifications allow for a substantial amount of SN-38 to be localized to the area of the tumor. Subsequently, SN-38 is released intracellularly following drug binding to Trop-2 and is also released in the tumor microenvironment, allowing for targeting of adjacent tumor cells through a bystander effect.

A phase I/II basket trial of SG in patients with a variety of pretreated metastatic epithelial cancers demonstrated a manageable safety profile at the chosen dose of 10 mg/kg administered on days 1 and 8 of a 21-day cycle. The most common adverse event was neutropenia. While diarrhea was also commonly seen, the rates of diarrhea and the severity of symptoms were less than those associated with irinotecan, likely because of reduced conversion of SN-38 to its glucuronidated form.

SG has shown promising efficacy signals in a variety of epithelial solid tumor subtypes, including breast cancer, urothelial cancer, and lung cancer. In the subgroup of patients with pretreated mTNBC, the objective response rate with SG was 33.3%, which compares favorably to historical controls with single-agent cytotoxic chemotherapy. SG thus presents a promising therapeutic option for patients with refractory mTNBC, who have a poor prognosis and limited therapeutic options. A separate registrational phase III study of SG versus physician's choice of chemotherapy is underway for pretreated patients with metastatic triple negative breast cancer.

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Table I:

Summary of efficacy data for SG by cancer type.

Cancer type	N	ORR (%)	Median DoR (months)	Median PFS (months)	Median OS (months)
TNBC (35)	108	33	7.7	5.5	13.0
HR+ BC (38)	54	31	7.4	6.8	NR
UC (39, 40)	45	31	12.9	7.3	16.3
NSCLC (42)	54	17	6.0	5.2	9.5
SCLC[1] (41)	50	14	5.7	3.7	7.5

DoR = duration of response, PFS = progression-free survival, OS = overall survival, NR = not reported, TNBC = triple negative breast cancer, BC = breast cancer, UC = urothelial carcinoma, NSCLC = non-small cell lung cancer, SCLC = small cell lung cancer

[1]Patients with SCLC received either 8 or 10 mg/kg SG.