

# First-in-Human Trial of a Novel Anti-Trop-2 Antibody-SN-38 Conjugate, Sacituzumab Govitecan, for the Treatment of Diverse Metastatic Solid Tumors

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## Abstract

**Purpose:** Sacituzumab govitecan (IMMU-132) is an antibody–drug conjugate (ADC) targeting Trop-2, a surface glycoprotein expressed on many epithelial tumors, for delivery of SN-38, the active metabolite of irinotecan. This phase I trial evaluated this ADC as a potential therapeutic for pretreated patients with a variety of metastatic solid cancers.

**Experimental Design:** Sacituzumab govitecan was administered on days 1 and 8 of 21-day cycles, with cycles repeated until dose-limiting toxicity or progression. Dose escalation followed a standard 3 + 3 scheme with 4 planned dose levels and dose delay or reduction allowed.

**Results:** Twenty-five patients (52–60 years old, 3 median prior chemotherapy regimens) were treated at dose levels of 8 ( $n = 7$ ), 10 ( $n = 6$ ), 12 ( $n = 9$ ), and 18 ( $n = 3$ ) mg/kg. Neutropenia was dose limiting, with 12 mg/kg the maximum

tolerated dose for cycle 1, but too toxic with repeated cycles. Lower doses were acceptable for extended treatment with no treatment-related grade 4 toxicities and grade 3 toxicities limited to fatigue ( $n = 3$ ), neutropenia ( $n = 2$ ), diarrhea ( $n = 1$ ), and leukopenia ( $n = 1$ ). Using CT-based RECIST 1.1, two patients achieved partial responses (triple-negative breast cancer, colon cancer) and 16 others had stable disease as best response. Twelve patients maintained disease control with continued treatment for 16 to 36 weeks; 6 survived 15 to 20+ months. No preselection of patients based on tumor Trop-2 expression was done.

**Conclusions:** Sacituzumab govitecan had acceptable toxicity and encouraging therapeutic activity in patients with difficult-to-treat cancers. The 8 and 10 mg/kg doses were selected for phase II studies. *Clin Cancer Res*; 21(17): 3870–8. ©2015 AACR.

## Introduction

Two new antibody–drug conjugates (ADC) incorporating different ultratoxic (picomolar potency) drugs have been approved, leading to further development of other ADCs based on similar principles, including use of ultratoxic drugs (1–3). Our group has taken an alternative approach, selecting a moderately toxic agent, SN-38, a topoisomerase-I inhibitor that is the active metabolite of irinotecan, an approved drug with well known but complex pharmacology (4–6). Several linkers for conjugating SN-38 were evaluated for release from

the IgG at varying rates, from several hours to days (4, 5, 7, 8). The linker selected, designated CL2A, resulting in an intermediate conjugate stability in serum, was attached to the hydroxyl group on SN-38's lactone ring, and contains a short polyethylene glycol moiety to enhance solubility (5,7). The active form of SN-38 was liberated when the carbonate bond between the linker and SN-38 was cleaved, which occurred at low pH, such as that found in lysosomes, as well as the tumor microenvironment, or possibly through enzymatic degradation.

The antibody chosen for this ADC targeted a tumor-associated antigen, Trop-2 (trophoblast cell-surface antigen; ref. 7), using the humanized RS7 monoclonal antibody that was shown previously to internalize (9). Trop-2 is overexpressed on many epithelial tumors, particularly more aggressive types (10–12), but is also present on a number of normal tissues. However, preclinical studies in monkeys that express the antigen observed only dose-limiting neutropenia and diarrhea with this new ADC, with no evidence of appreciable toxicity to the Trop-2–expressing normal tissues (7). Therefore, a phase I clinical trial was initiated to determine the maximum tolerated and optimal doses of this novel ADC in heavily pretreated patients with diverse, relapsed/refractory, metastatic epithelial tumors. This trial was registered at ClinicalTrials.gov (NCT01631552).

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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### Translational Relevance

Sacituzumab govitecan is an antibody–drug conjugate (ADC) targeting Trop-2, a surface glycoprotein increased in many epithelial tumors, for delivery of SN-38, which is the active metabolite of the camptothecin, irinotecan. The use of this moderately toxic payload (nanomolar potency) challenges the paradigm that successful ADCs must use an ultra-toxic drug that is bound tightly to the IgG. Preclinical studies indicate the best linker for SN-38 with an intermediate stability and a high drug substitution ratio of approximately 7.6:1 did not impact its binding, clearance, or pharmacokinetics. Furthermore, SN-38 is retained in its most potent form, nonglucuronidated and with a closed lactone ring until released, thereby maximizing the therapeutic benefit when localized in the tumor. This phase I clinical study confirms that this ADC is therapeutically active in patients with diverse metastatic epithelial tumors, with manageable neutropenia as the major toxicity, and establishes the phase II dose for repeated courses of therapy.

## Materials and Methods

### Entry criteria

Patients were enrolled after approval from the Institutional Review Boards and obtaining written informed consent from the patients. The primary objective was to determine the safety and tolerability of sacituzumab govitecan (IMMU-132) as a single agent. The trial was designed as a standard 3 + 3 phase I design, starting at a dose of 8 mg/kg per injection, with dosages given weekly for 2 weeks in a 3-week treatment cycle.

Male and nonpregnant, nonlactating females  $\geq 18$  years of age were eligible if they had a diagnosis of one of 13 different types of epithelial tumors. Although no preselection based on Trop-2 expression was required, Trop-2 expression in  $>75\%$  of the cases based on immunohistology studies on archival specimens was found. Patients were required to have measurable metastatic disease (no single lesions  $\geq 5$  cm) and had relapsed or were refractory to at least one approved standard chemotherapeutic regimen for that indication. Other key criteria included adequate (grade  $\leq 1$ ) hematology, liver, and renal function, and no known history of anaphylactic reactions to irinotecan, or grade  $\geq 3$  gastrointestinal toxicity to prior irinotecan or other topoisomerase-I treatments. As patients with such diverse diseases were allowed, prior irinotecan therapy was not a prerequisite. Patients with Gilbert disease or those who had not tolerated previously administered irinotecan or with known CNS metastatic disease were excluded. Additional details are included in Supplementary Information online.

### Study design

Baseline evaluations were performed within 4 weeks of the start of treatment (see Supplementary Information online for studies performed), with regular monitoring of blood counts, serum chemistries, vital signs, and adverse events. Anti-antibody and anti-SN-38 antibody reactions were measured by ELISA by the sponsor, with samples taken at baseline and then before the start of every even-numbered treatment cycle. The first CT examination was obtained 6 to 8 weeks from the start of

treatment and then continued at 8- to 12-week intervals until progression. Additional follow-up was required only to monitor any ongoing treatment-related toxicity. Toxicities were graded using the NCI CTCAE version 4.0, and efficacy assessed by RECIST 1.1.

An ELISA to detect Trop-2 in serum was developed that has a sensitivity of 2 ng/mL, but after testing 12 patients and finding no evidence of circulating Trop-2, no further screening was performed. Although not an eligibility criterion, specimens of previously archived tumors were requested for Trop-2 determination by immunohistology, using a goat polyclonal antibody anti-human Trop-2 (R&D Systems), since the epitope recognized by the ADC's antibody, hRS7, is not preserved in formalin-fixed, paraffin-embedded sections (9). Staining is described in Supplementary Information online.

### Therapeutic regimen

Reconstituted sacituzumab govitecan was infused over 2 to 3 hours [100 mg of antibody contained approximately 1.6 mg of SN-38, with a mean drug:antibody ratio (DAR) of 7.6:1]. Before the start of each infusion, most patients received acetaminophen, antihistamines (H1 and H2 blockers), and dexamethasone. Prophylactic use of antiemetics or anti-diarrheal medications was prohibited. Therapy consisted of two consecutive doses given on days 1 and 8 of a 3-week treatment cycle, with the intent to allow patients to continue treatment for up to 8 cycles (i.e., 16 treatments) unless there was unacceptable toxicity or progression. Patients showing disease stabilization or response after 8 cycles could continue treatments.

Dose-limiting toxicity (DLT) was defined as grade  $\geq 3$  febrile neutropenia of any duration, grade 3 thrombocytopenia with significant bleeding or grade 4 thrombocytopenia  $\geq 5$  days, any grade 3 nausea, vomiting, or diarrhea that persisted for  $>48$  hours despite optimal medical management, or grade 4 (life threatening) nausea, vomiting, or diarrhea of any duration, or any other grade  $\geq 3$  nonhematologic toxicity at least possibly due to study drug, as well as the occurrence of any grade 3 infusion-related reactions.

On a scheduled treatment day, any patient with grade  $\geq 2$  treatment-related toxicity, with the exception of alopecia, had the treatment delayed in weekly increments of up to 2 weeks. Treatment was reinitiated once toxicity had resolved to grade  $\leq 1$ . The protocol also initially required all subsequent treatment doses to be reduced (25% if recovered within 1 week, 50% if within 2 weeks), but this was relaxed later in the trial when the protocol was amended to permit supportive care after the first cycle. However, if toxicity did not recover within 3 weeks or worsened, treatment was terminated. Importantly, a dose delay with reduction did not constitute a DLT, and therefore this allowed treatments to continue, but at a lower dose. Therefore, a patient requiring a dose delay/reduction who was able to continue treatment was not considered assessable for DLT, and was then replaced.

For determining the maximum tolerated dose (MTD; see Supplementary Information online) only DLTs occurring during the first treatment cycle were considered. However, as a DLT event resulted in the termination of all further treatments, a secondary objective was to assess a dose that could be tolerated over multiple cycles of treatment with minimal dose delays or reductions. This dose level was designated the maximum acceptable dose, and required patients to tolerate a given dose level in the first cycle

without having a delay or reduction during that cycle and leading up to the start of the second cycle.

### Pharmacokinetics and immunogenicity

Blood samples were taken within approximately 30 minutes from the end of the infusion (e.g., peak) and then before each subsequent injection (e.g., trough). Samples were separated and sera frozen for determination of total IgG and sacituzumab govitcan concentrations, as well as anti-hRS7 and anti-SN-38 antibodies, by ELISA. Serum samples from seven patients also were assayed for SN-38 content, both total (representing SN-38 bound to the IgG and free) and free SN-38 (i.e., unbound SN-38). Details of these assays are in the Supplementary Information online.

## Results

### Patient characteristics

Twenty-five patients (52–60 years old, 10 male, 15 female) were enrolled. Their demographics and cancer types are summarized in Table 1. Most patients had metastatic pancreatic cancer (PDC;  $n = 7$ ), followed by triple-negative breast cancer

(TNBC;  $n = 4$ ), colorectal cancer ( $n = 3$ ), small-cell lung cancer (SCLC;  $n = 2$ ), and gastric cancer ( $n = 2$ ), with single cases of esophageal adenocarcinoma, hormone-refractory prostate cancer (HRPC), non-small cell lung cancer (NSCLC), epithelial ovarian cancer (OVR or EOC), renal, tonsil, and urinary bladder cancers (UBC).

Immunohistology was performed on archival tissues from 17 patients, with 13 (76.4%) having 2+ to 3+ membrane and cytoplasmic staining on >10% of the tumor cells in the specimens; 1 specimen (5.9%) was 1+ and 3 specimens (17.6%) were negative. Several representative cases are provided in Supplementary Fig. S1. All patients had metastatic disease with a median of 4 (range 1–10) target lesions identified on baseline CT imaging and a median sum of largest tumor diameters of 9.7 cm (range 2.9–29.8 cm). The patients received at least one prior chemotherapy regimen (median, 3 prior therapies), and 11 had received prior radiotherapy. Only 7 patients responded to their last prior therapy and the median duration of their response was 3 months (range, 1–11 months). In addition, 9 patients received prior anti-topoisomerase-I therapy with either irinotecan ( $n = 7$ ) or topotecan ( $n = 2$ ), of whom 3 failed to respond to this prior therapy.

**Table 1.** Baseline demographics and disease characteristics ( $n = 25$  patients)

	8 mg/kg	10 mg/kg	12 mg/kg	18 mg/kg
Male/Female	2/5	3/3	3/6	2/1
Tumor type	N	N	N	N
Colorectal	2	1	0	0
Pancreas	3	1	3	0
TNBC	0	1	2	1
SCLC	0	0	1	1
Other <sup>a</sup>	2	3	3	1
	(EOC, gastric cancer)	(gastric cancer, RCC, Tonsil)	(UBC, NSCLC, HRPC)	(esophageal adenocarcinoma)
Age, y	60 (30–86)			
Median (range)	60 (30–86)			
ECOG performance status				
0	6			
1	19			
Prior therapy	N			
Radiotherapy	11			
Systemic therapy <sup>b</sup>				
1	7			
2	5			
3	4			
4	3			
≥5	6			
Prior topoisomerase-I inhibitor	9			
Tumor metastases (# patients)	N			
Target and nontarget sites				
Chest/head/neck	9			
Liver <sup>c</sup>	15 (9)			
Lungs <sup>c</sup>	13 (9)			
Lymph nodes	12			
Abdomen/pelvis	13			
Bone	6			
≥3 target lesions	14			
Patients treated	7	6	9	3
Delay/adjustment first cycle	1	0	5	2
Dose-limiting toxicity first cycle	0	0	0	2
# treatments at this dose, median (range)	3 (1–31)	10 (1–31)	3 (1–8)	1 (1–2)
Total # treatments, median (range)	6 (3–31)	10 (1–31)	12 (4–34)	4 (3–16)

<sup>a</sup>Other cancers include ovarian (EOC), gastric cancer, UBC, NSCLC, HRPC, esophageal adenocarcinoma, renal cell cancer (RCC), and a squamous cell carcinoma of the tonsil.

<sup>b</sup>Includes chemotherapy, biologic, and investigational agents.

<sup>c</sup>Number of patients with liver or lung involvement; in parenthesis number of these patients with both liver and lung involvement.

Multiple sacituzumab govitecan treatments (median, 10 doses) were given until there was definitive evidence of disease progression by CT. One patient withdrew after receiving 1 dose because of generalized deterioration, but all other patients received  $\geq 3$  treatments.

#### Dose assessment

At the starting dose level of 8.0 mg/kg, 3 patients were treated without DLT, dose delays, or reductions. At the next dose level of 12 mg/kg, 9 patients were enrolled because of protocol-required delays in administering the second dose were encountered. Five patients experienced a delay in cycle 1 (4 had a one-week delay, with 2 given myeloid growth factor support, and 1 patient having a 2-week delay before being given a second dose). All but 1 of these patients received 12 mg/kg as their second dose. Four of the 9 patients at the 12 mg/kg dose level had the third dose that started the second cycle decreased to 9 mg/kg, and the second cycle was delayed 1 additional week in 3 patients. Despite these protocol-required delays/reductions, none of the 9 patients had a dose-limiting event during the first cycle (e.g., one had disease-related grade 3 hemoglobin after first dose, 2 with grade 3 neutropenia after first dose were given myeloid growth factors, 1 had grade 3 neutropenia after first dose that recovered without support, 2 had grade 3 neutropenia after second dose, 2 patients had grade 2 neutropenia after the first or second dose, and 1 patient had no adverse events), and therefore accrual to the 18 mg/kg dose level was allowed. Here, all 3 patients had dose delays after their first treatment, with only 1 patient receiving the second treatment at 18 mg/kg. Two patients had dose-limiting grade 4 neutropenia, 1 after first dose, the other after the second 18 mg/kg dose, with this latter patient also experiencing grade 2 diarrhea. Therefore, with 0 of 9 patients having DLT in the first cycle at 12 mg/kg, this level was declared the MTD for a single-cycle regimen.

Additional dose-finding studies continued to refine the dose level that would allow multiple cycles to be given with minimal delay between treatments/cycles. Therefore, 4 more patients were

enrolled at the 8 mg/kg dose level, and a new intermediate level of 10 mg/kg was opened. Of the initial three patients enrolled at 8 mg/kg, two colorectal cancer patients continued treatment at 8 mg/kg for a total of 31 and 11 treatments, while a metastatic pancreatic cancer patient received three 8 mg/kg doses before dose reduction to 6 mg/kg because of a grade 2 neutropenia on the fourth dose, and then completed three more doses at this level before withdrawing due to disease progression. The additional 4 patients received 3 to 9 doses of 8 mg/kg before withdrawing with disease progression. Two of these patients received only 1 dose before a protocol-required reduction to 6 mg/kg, because of a grade 2 rash and neutropenia.

Five of the 6 patients enrolled at 10 mg/kg received 6 to 30 doses without reduction before withdrawing due to disease progression. One gastric cancer patient (#9) developed grade 3 febrile neutropenia as well as grade 4 hemoglobin after receiving 1 dose. While the febrile neutropenia was considered possibly related to treatment, because it occurred shortly after the first dose, a perforation in the stomach lining was found to likely contribute to the grade 4 hemoglobin, and was considered unrelated to drug. Ultimately, the patient had rapid deterioration and died 4 weeks from the first dose.

Thus, while the overall results supported 12 mg/kg as the MTD, as 8 to 10 mg/kg doses were better tolerated in the first cycle and permitted repeated cycles with minimal toxicity, phase II clinical studies are in progress to evaluate these two dose levels.

#### Adverse events

There were 297 infusions of sacituzumab govitecan given over 2 to 3 hours, with no infusion-related events. While more than half of the patients experienced fatigue, nausea, alopecia, diarrhea, and neutropenia considered at least likely related to treatment, these were mostly grade 1 and 2 (Table 2). The most reported grade 3 or 4 toxicity was neutropenia ( $n = 9$ ), but seven of these patients were treated initially at 12 and 18 mg/kg. Febrile neutropenia occurred in 2 patients, one was the gastric cancer patient (#9) already mentioned who received only one 10 mg/kg dose, and a second metastatic pancreatic cancer patient (#19), who had

**Table 2.** Adverse events considered at least possibly treatment related<sup>a</sup>

Adverse event	Total (n = 25)	All grades (number of patients)				Grade 3 or 4 events (number of patients)			
		8 (n = 7)	10 (n = 6)	12 (n = 9)	18 (n = 3)	8 (n = 7)	10 (n = 6)	12 (n = 9)	18 (n = 3)
Fatigue	18 (72%)	5	4	7	2	2	1	0	0
Nausea	17 (68%)	6	4	4	3	0	0	0	0
Alopecia	13 (52%)	4	5	3	1	NA	NA	NA	NA
Diarrhea	13 (52%)	2	3	6	2	0	1	2	0
Neutrophil count decreased	14 (56%)	1	2	8	3	1	1	5	2 <sup>b</sup>
Vomiting	10 (40%)	3	1	4	2	0	0	0	0
Dysgeusia	5 (20%)	1	1	3	1	0	0	0	0
Abdominal pain	4 (16%)	1	1	1	1	0	0	0	0
Hypokalemia	4 (16%)	1	0	2	1	0	0	1	0
Skin hyperpigmentation	4 (16%)	0	1	3	0	0	0	0	0
Anemia	3 (12%)	1	0	1	1	1	0	1	0
Dehydration	3 (12%)	1	1	0	1	0	0	0	0
Hypomagnesaemia	3 (12%)	2	0	0	1	0	0	0	0
Pruritus	3 (12%)	2	0	1	0	0	0	0	0
Pyrexia	3 (12%)	2	0	1	0	0	0	0	0
WBC count decreased	3 (12%)	1	0	2	0	1	0	0	0
Febrile neutropenia	2 (8%)	0	1	1	0	0	1	1 <sup>b</sup>	0
Deep vein thrombosis	1 (4%)	0	0	1	0	0	0	1	0

<sup>a</sup>Included are drug-related events that occurred in at least 10% of patients or any drug-related grade 3 or 4 adverse events.

<sup>b</sup>Grade 4 events.



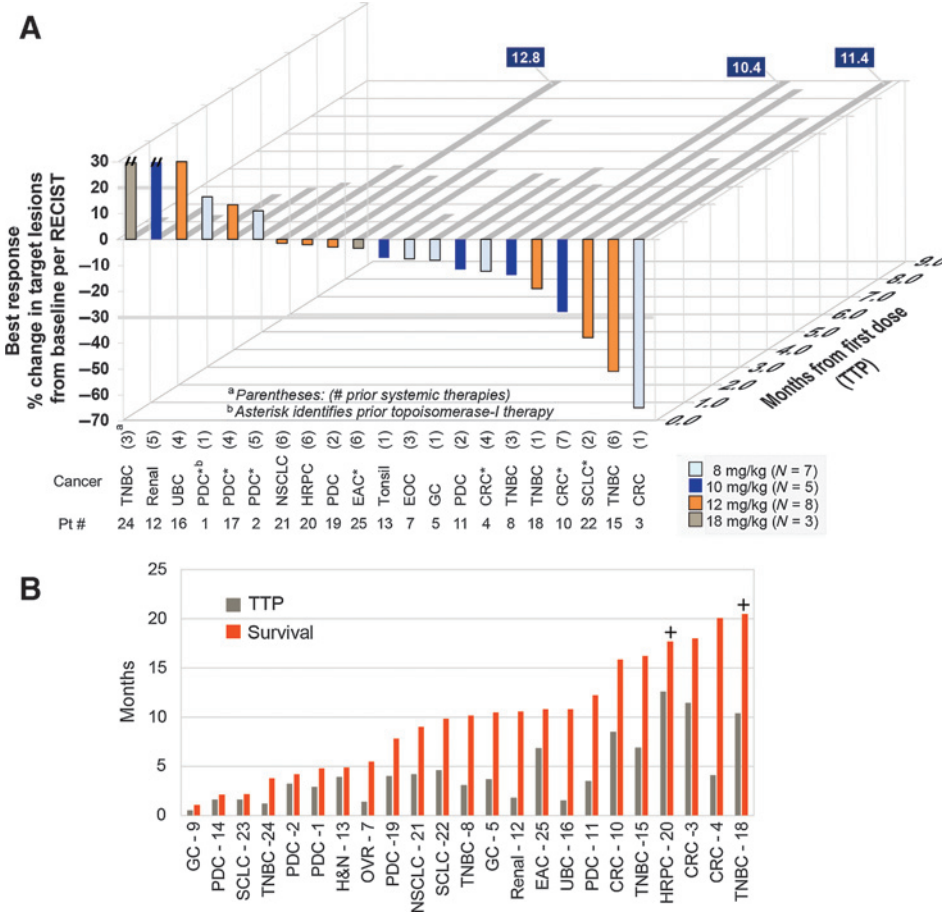
received 4 doses of 12 mg/kg. Diarrhea was mild in most patients, with only three (12%) experiencing grade 3. Two occurred at the 12 mg/kg dose level, 1 after receiving 4 doses, and the other after the first dose, but this patient received 6 more doses at 12 mg/kg with only grade 2 diarrhea reported. Subsequently, both patients were prescribed an over-the-counter antidiarrheal and treatment continued. There were no other significant toxicities associated with sacituzumab govitecan, but two patients reported a grade 2 rash and 3 patients had a grade 1 pruritus.

**Efficacy**

Figure 1A shows the change in target lesions at best response for patients with at least one posttreatment CT assessment, as well as their time-to-progression (TTP). Four patients with disease progression by RECIST are not represented in the graph, because they did not have a follow-up CT assessment ( $n = 1$ ) or they had new lesions and therefore progressed irrespective of their target lesion status ( $n = 3$ ). Overall, 3 patients had more than a 30% reduction in their target lesions. The colorectal cancer and TNBC patients had confirmatory follow-up CTs, while the SCLC patient progressed at the next CT performed 12 weeks later, thus constituting two partial responses (PR) by RECIST1.1. Sixteen patients had stable disease (SD), and 7 progressed (PD) as the best response by RECIST 1.1. The median TTP from the start of treatment for 24 patients (excluding 1 patient who received only 1 treatment and

withdrew) was 3.6 months (range, 1–12.8 months); but 4.1 months (range, 2.6–12.8 months) for all patients with SD or PR ( $n = 18$ ). Of the 9 patients who received prior therapy containing a topoisomerase-I inhibitor, two had significant reductions of their target lesions (28% and 38%), 5 had stable disease, including 2 for sustained periods (4.1 and 6.9 months, respectively), whereas 2 progressed at their first assessment.

Table 3 summarizes prior therapies given these patients, including a topoisomerase-I inhibitor, comparing the response to the last prior therapy to the duration of response (TTP) due to IMM-132, ordered according to declining TTP from IMM-132. The duration of response (DR) to prior topoisomerase-I therapies ranged from 0 to 8 months in the 5 of 9 patients responding to this prior therapy. IMM-132 treatment gave a TTP ranging from 1.6 to 8.5 months in this group, with two responding to IMM-132 after failing a prior topoisomerase-I treatment-containing regimen, showing shrinkage of their target lesions of 28% and 12%, with TTP of 8.5 months and 4.1 months, respectively. Figure 1B compares TTP with survival of these patients, indicating that 6 patients survived from onset of therapy for 15 to 20+ months, including 2 with a PR, patients # 15 (TNBC) and #3 (colorectal cancer), and the other 4 with SD (2 colorectal cancer, 1 HRPC, 1 TNBC). Examples of radiologic responses in 2 patients with >30% reduction in the sum of diameters of their target lesions (PR) are provided in Fig. 2. In addition to the 3 patients with >30%



**Figure 1.** Response assessment following treatment with sacituzumab govitecan. A, composite schematic showing best response determined from target lesion measurements according to RECIST 1.1 (y-axis) and TTP measured from first dose until CT documentation of progression as per RECIST (z-axis; TTP expressed in months). Best response bars are color-coded to identify the 4 starting dose levels. Four of the 25 patients [numbers 6, 9, 14, and 23; 2 metastatic pancreatic cancer (PDC), 1 gastric cancer (GC), and 1 SCLC who were classified by RECIST with disease progression are not shown because either they did not have a follow-up CT with measurement of target lesions or they had new lesions despite having stable target lesions measurements. A bar break (//) shown for two PD patients denotes target lesions increased >30%, whereas TTP values in the boxes at top of the graph show the patients who exceeded 9 months. The number of prior therapies (in parentheses) and the patients who received prior topoisomerase-I therapy (asterisks) are indicated below the graph. B, graph showing the patients sorted according to survival, showing also their TTP. Survival data were unavailable for 2 metastatic pancreatic cancer patients (numbers 6 and 17 with TTP 1.0 and 2.9 months). CRC, colorectal cancer.

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**Table 3.** Prior therapies, including previous use of a topoisomerase-I inhibitor (alone or in a combination regimen), duration of response to the last prior therapy versus duration of response to IMMU-132

Pt no.	Cancer	# Prior treatment	Prior Topo-I (DR, mo)	Last prior treatment		BR% Δ TL <sup>a</sup>	IMMU-132		
				Agent/regimen	DR (mo)		TTP (mo)	Start dose (mg/kg)	Total doses <sup>b</sup>
20	HRPC	6	No	Docetaxel/prednisone	0	-2	12.6	12	34 [Y;3]
3	Colorectal cancer	1	No	FOLFOX	3	-65	11.4	8	31 [N]
18	TNBC	1	No	Paclitaxel/carboplatin	0	-19	10.4	12	26 [Y;7]
10	Colorectal cancer	7	Yes (6)	Regorafenib	0	-28	8.5	10	29 [N]
15	TNBC	6	No	Capecitabine	0	-51	6.9	12	18 [5]
25	Esophageal adenocarcinoma	6	Yes (5)	Docetaxel	0.5	-3	6.9	18	16 [Y;2]
22	SCLC	2	Yes (0)	Topotecan	0	-36	4.6	12	12 [Y;3]
21	NSCLC	6	No	Gemcitabine	1	-2	4.2	12	12 [Y;8]
4	Colorectal cancer	4	Yes (0)	Regorafenib	0	-12	4.1	8	11 [N]
19	Metastatic pancreatic cancer	2	No	Capecitabine	0	-3	4.0	12	9 [Y;6]
13	Tonsil	1	No	Cisplatin	11	-7	3.9	10	10 [N]
5	Gastric cancer	1	No	Carboplatin/paclitaxel	6	-8	3.7	8	11 [N]
11	Metastatic pancreatic cancer	2	No	5-fluorouracil	0	-15	3.5	10	17 [N]
2	Metastatic pancreatic cancer	5	Yes (0)	Investigational radioimmunotherapy	3	11	3.2	8	6 [Y;4]
8	TNBC	3	No	Cisplatin	0	-14	3.1	10	10 [N]
17	Metastatic pancreatic cancer	4	Yes (6)	Gemcitabine + abraxane	0	12	2.9	12	8 [N]
1	Metastatic pancreatic cancer	1	Yes (8)	FOLFIRINOX	8	16	2.6	8	6 [Y;2]
12	Renal	3	No	Everolimus + BNC105	0	38	2.1	10	6 [N]
14	Metastatic pancreatic cancer	2	Yes (3)	Gemcitabine + abraxane	0	NL	1.6	12	3 [N]
23	SCLC	2	Yes (0)	Topotecan	0	NL	1.6	18	4 [Y;3]
16	UBC	4	No	Docetaxel	0	30	1.5	12	4 [Y;3]
7	OVR	3	No	Docetaxel/Carboplatin	36	-8	1.4	8	4 [Y;2]
24	TNBC	3	No	Carboplatin/Gemcitabine	0	57	1.2	18	3 [Y;2]
6	Metastatic pancreatic cancer	1	No	Gemcitabine (adjuvant)	0	NL	1.0	8	3 [N]
9	Gastric cancer	1	No	mFOLFOX + onartuzumab or placebo	3	IER	0.5	10	1 [N]

NOTE: Data are in descending order for IMMU-132 TTP.

Abbreviations: DR, duration of response to last prior therapy; IER, inevaluable for response; NL, new lesion; Topo-1, topoisomerase I inhibitor.

<sup>a</sup>BR%Δ TL, Best response, percent change in the sum of the diameters for the target lesions.

<sup>b</sup>Total number of treatments given followed in brackets by whether the starting dose was reduced (Y or N, yes or no), and if Y, the dose number when the reduction first occurred. Additional reductions occurred in several patients (not indicated).

shrinkage in their target lesions, there were several notable cases of extended stable disease that are discussed in the Supplementary Information.

### Trop-2 tissue expression

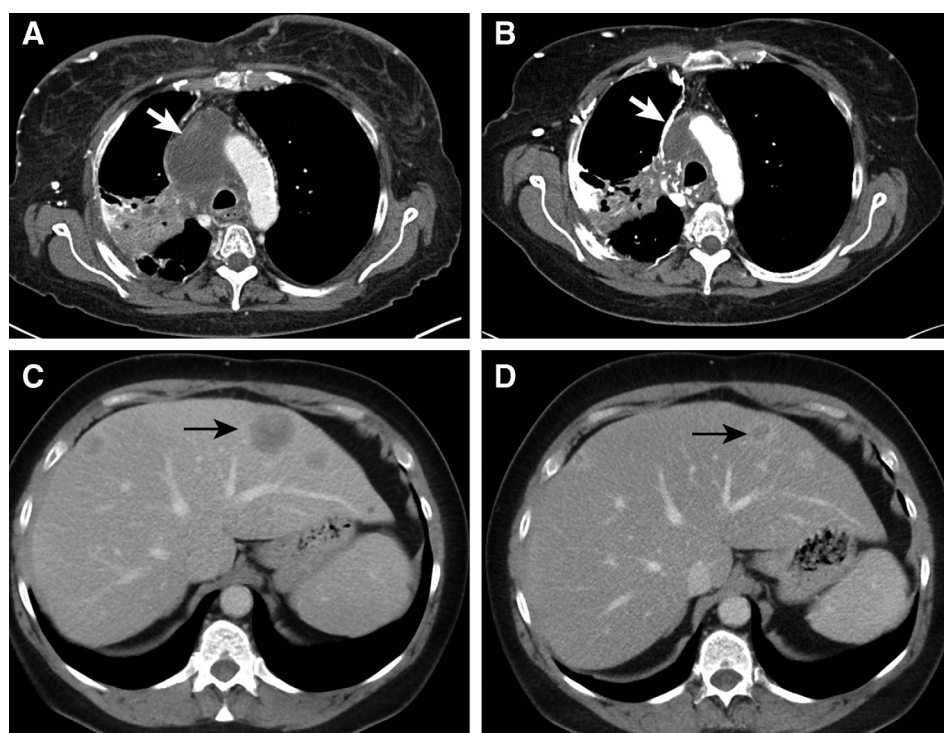
The potential utility of testing Trop-2 expression in archived samples from this small sampling of 17 patients with diverse cancers is insufficient for definitive assessment, primarily because most showed elevated expression. An overview of the IHC staining score versus best response and time to progression is provided in Supplementary Fig. S2.

### Pharmacokinetics and immunogenicity

Concentrations of sacituzumab govitecan and IgG in the 30-minute serum sample are provided in Supplementary Table S1, which show a general trend for the values to increase as the dose increased. Figure 3 presents a representative case of a patient with TNBC (#15) who received multiple doses, starting at 12 mg/kg, with subsequent reductions over the course of her treatment. Concentrations of the IgG and sacituzumab govitecan in the 30-minute serum over multiple doses by ELISA (panel A) were similar over time, adjusting lower when the dose was reduced. While residual IgG could be found in the serum drawn immediately before the next dose (trough samples), no sacituzumab govitecan could be detected.

Total SN-38 concentration in the 30-minute serum sample of patient 15 was 3,930 ng/mL after the first dose in cycle 1 (C1D1), but when sacituzumab govitecan treatment was reduced to

9.0 mg/kg for the second dose of the first cycle (C1D2), the level decreased to 2,947 ng/mL (Fig. 3B). A further reduction to 2,381 ng/mL was observed in the sixth cycle, when the dose was further reduced to 6.0 mg/kg. The amount of free SN-38 in these samples ranged from 88 to 102 ng/mL (2.4% to 3.6% of total SN-38), illustrating that >96% of the SN-38 in the serum in these peak samples was bound to IgG. Twenty-eight 30-minute serum samples from 7 patients were analyzed by high-performance liquid chromatography (HPLC), with free SN-38 averaging 2.91% ± 0.91% of the total SN-38 in these samples. Free SN-38G concentrations measured in 4 patients never exceeded SN-38 levels, and were usually several fold lower. For example, patient #25 had determinations assessed in the 30-minute sample for 12 injections over 8 cycles of treatment. At a starting dose of 18 mg/kg, he had 5,089 ng/mL of SN-38 in the acid-hydrolyzed sample (total SN-38) and just 155.2 ng/mL in the non-hydrolyzed sample (free SN-38; 3.0%). Free SN-38G (glucuronidated form) in this sample was 26.2 ng/mL, or just 14.4% of the total unbound SN-38 + SN-38G in the sample. The patient continued treatment at 13.5 mg/kg, with SN-38 averaging 3,309.8 ± 601.8 ng/mL in the 11 remaining peak, acid-hydrolyzed samples, while free SN-38 averaged 105.4 ± 47.7 ng/mL (i.e., 96.8% bound to the IgG), and free SN-38G averaging 13.9 ± 4.1 ng/mL (11.6% of the total SN-38 + SN-38G). Importantly, in nearly all of the patients, concentrations of SN-38G in the acid-hydrolyzed and nonhydrolyzed samples were similar, indicating that none of the SN-38 bound to the conjugate was glucuronidated.



**Figure 2.**

CT studies in 2 patients showing treatment response. A and B (patient #22), 65-year-old woman with poorly differentiated SCLC (Trop-2 expression by immunohistochemistry, 3+) who received 2 months of carboplatin/etoposide (topoisomerase-II inhibitor) and 1 month of topotecan (topoisomerase-I inhibitor) with no response, followed by local radiation for 6 weeks (3,000 cGy), but continued to progress. Four weeks later, the patient started sacituzumab govitecan at 12 mg/kg (2 doses), which was reduced to 9.0 mg/kg (1 dose), and finally to 6.75 mg/kg for 9 doses. The sum of the longest diameters (SLD) of the target lesions at study entry was 19.3 cm. The largest lesion is shown at baseline (A). After 4 doses, the SLD had reduced by 38%, including a substantial reduction in the main lung lesion (5.8 to 2.7 cm; B). C and D (patient #3), 62-year-old woman, who 5 months after her initial diagnosis and surgery for colon cancer had a hepatic resection for liver metastases and then received 7 months of treatment with FOLFOX and 1 month of only 5-fluorouracil. She entered the study with multiple lesions, primarily in the liver (C). Immunohistochemistry showed a 2+ staining of her primary cancer; her plasma CEA was 781 ng/mL. Therapy was initiated at 8 mg/kg and 6 treatments later (12 weeks), the 3 target lesions had reduced from a sum of 7.9 to 5.0 cm (–37%; PR). The response was confirmed 6.6 weeks later (after 10 doses), with additional shrinkage to 3.8 cm (–52%). D, the target lesion 32 weeks from the start of treatment and after receiving 18 doses when there was a 59% reduction in the sum of the diameters of all target lesions. The patient continued therapy, achieving a maximum tumor reduction of 65% 44 weeks after treatment was initiated (28 doses). Plasma CEA decreased to 26.5 ng/mL after 18 doses, but thereafter began to increase despite continued radiologic evidence (target and nontarget lesions) of additional disease reduction or stabilization. Approximately 1 year from the start of treatment (31 doses given), one of the 3 target lesions progressed.

None of these patients had a positive baseline level (i.e., >50 ng/mL) or a positive antibody response to either the IgG or SN-38 over their course of treatment.

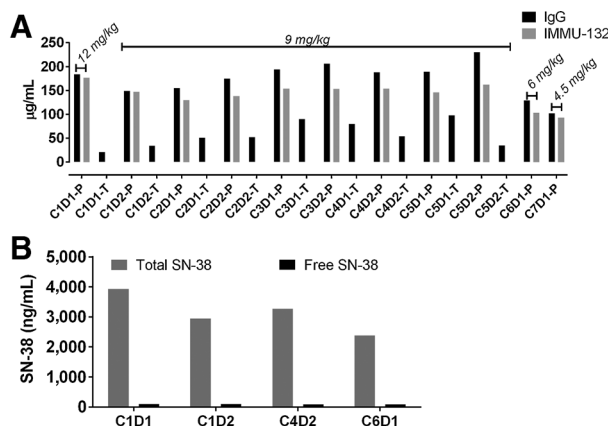
## Discussion

Trop-2 is expressed abundantly in many epithelial tumors, making it an antigen of interest for targeted therapies (10, 11), especially as it is considered a prognostic marker and oncogene in several cancer types (7, 9–12). Although its expression in normal tissues and relationship to another well-studied tumor-associated antigen, EpCAM, drew some initial words of caution regarding the safety of developing immunotherapeutics to Trop-2 (13), our studies in *Cynomolgus* monkeys that express Trop-2 in tissues similar to humans indicated sacituzumab govitecan was very well tolerated at a human equivalent dose totaling approximately 40 mg/kg (7). At higher doses, animals experienced neutropenia and diarrhea, known side-effects associated with SN-38 derived from irinotecan therapy, yet evidence for significant histopathologic changes in Trop-2-expressing normal tissues was lacking (7). Thus, with other preclinical studies finding sacituzumab govite-

can was potent at the low nanomolar level and effective in a variety of human epithelial tumor xenografts at nontoxic doses (7), a phase I trial was undertaken in patients who had failed one or more standard therapies for their diverse metastatic epithelial tumors.

A major finding of this study was that despite using a more conventional drug that is not considered as ultratoxic (drugs active in picomolar range, whereas SN-38 has potency in the low nanomolar range), the sacituzumab govitecan anti-Trop-2–SN-38 conjugate proved clinically to be therapeutically active in a wide range of solid cancers at doses with moderate and manageable toxicity, thus exhibiting an encouraging therapeutic index. A total of 297 doses of sacituzumab govitecan were given to 25 patients without incident; 4 patients received >25 injections. Importantly, no antibody response to the hRS7 IgG or SN-38 was detected, even in patients with multiple cycles of treatment for up to 12 months. Although Trop-2 is expressed in low quantities in a variety of normal tissues (7), neutropenia was the only dose-limiting toxicity, with myeloid growth factor support used in 2 patients given  $\geq 12$  mg/kg of sacituzumab govitecan to expedite recovery and allow continuation of treatment in patients who had exhausted





**Figure 3.**

Concentrations of IgG and sacituzumab govitecan (IMMU-132) by ELISA and SN-38 (total and free) in serum samples (patient 15). The top panel shows the concentrations of hRS7 IgG and sacituzumab govitecan as determined by ELISA in the peak (P) and trough (T) samples of a TNBC patient. CID1 and CID2 represent the first and second dose in cycle 1; data for 7 cycles are shown. The protein dose of sacituzumab govitecan for each treatment is provided above the bars. The bottom panel shows the concentrations of SN-38, either unbound (free) or total (acid-hydrolyzed sample) for 4 samples over the course of treatment.

their therapy options. While the MTD was declared to be 12 mg/kg, 8.0 and 10.0 mg/kg dose levels were selected for further expansion, as patients were more likely to tolerate additional cycles at these levels with minimal supportive care, and responses were observed at these levels. Only 2 of 14 patients (14.3%) experienced grade 3 neutropenia at these dose levels. The grade 3 and 4 neutropenia incidence for irinotecan monotherapy given weekly or once every 3 weeks in a front- or second-line setting is reported as 14% to 26% (14). With sacituzumab govitecan, only 1 patient at the 10 mg/kg dose level had grade 3 diarrhea. This incidence is lower than the 31% of patients given 4 weekly doses of irinotecan who experienced grades 3 and 4 late diarrhea (14). Other common toxicities attributed to sacituzumab govitecan included fatigue, nausea, and vomiting, most being grade 1 and 2, as well as alopecia. Two incidents of febrile neutropenia and one of grade 3 deep vein thrombosis also occurred at the 10 and 12 mg/kg dose levels. UGT1A1 monitoring was not initiated until after dose exploration was completed, so its contribution to toxicity cannot be reported now.

Patients enrolled in this trial were not preselected for Trop-2 expression, primarily because immunohistologic assessments of tissue microarrays of diverse cancers (such as prostate, breast, pancreas, colorectal, and lung cancers) had indicated the antigen was present in >75% of the specimens (Immunomedics, data on file). In addition, Trop-2 was not found in the sera of 12 patients with diverse metastatic cancers, further suggesting that a serum assay would not be useful for patient selection. Although we are attempting to collect archival specimens of the tumors from patients enrolled in the phase II trial, there is insufficient evidence at this time to suggest patient selection based on immunohistologic staining will correlate with antitumor activity, so no patient enrichment based on Trop-2 expression has been undertaken.

As a monotherapy, sacituzumab govitecan had good antitumor activity in patients with diverse metastatic, relapsed/refractory, epithelial tumors, showing appreciable reductions in target lesions by CT, using RECIST1.1 criteria, including sustained

disease stabilization. Three of the 25 patients [1 each of SCLC (after progressing with topotecan), TNBC, and colon cancer] had >30% reductions of their target lesions before progressing 2.9, 4.3, and 7.1 months, respectively, from the onset of therapy, but only two are considered to have a PR according to RECIST 1.1, which requires a confirmatory scan. Thus, 16 patients had SD, with 9 of these progressing after >4 months from the start of treatment. Responses or disease stabilization occurred in 7 of 9 patients who had prior therapy with a topoisomerase-I inhibitor-containing drug or regimen. Four of these failed to respond to their prior topoisomerase-I inhibitor therapy (irinotecan or topotecan), yet sacituzumab govitecan induced tumor shrinkage in 2 of them: 12% in a patient with colon cancer (#4) and 36% in the other with SCLC (#22). Thus, sacituzumab govitecan may be therapeutically active in those who failed or relapsed to a prior topoisomerase-I-containing regimen, which is being examined further in the phase II study.

Although the largest number of patients enrolled in this trial had advanced pancreatic ductal cancer ( $n = 7$ ; median time to progression 2.9 months; range, 1.0–4.0 months), there were encouraging reductions in target lesions and CA19-9 serum concentrations to suggest activity because of the advanced disease in these patients (15). However, responses in patients with TNBC and SCLC are of particular interest, given the need for targeted therapies in these indications. Indeed, additional partial responses in patients with TNBC and SCLC observed in the ongoing expansion phase of this trial (16, 17) have suggested further emphasis on these cancers, but encouraging responses in NSCLC, esophageal adenocarcinoma, UBC, and colorectal cancer are also being followed. Indeed, in a recent update of the ongoing phase II trial of sacituzumab govitecan, an overall response rate (PR) of 30%, with 40% clinical benefit rate (PR + SD  $\geq 6$  months) has been observed in 23 patients with metastatic TNBC (16). Long-term survival (15–20+ months) was observed for almost 25% (6/25) of the patients studied, and included 2 with PRs and 4 with SD, including patients with TNBC ( $n = 2$ ), colorectal cancer ( $n = 3$ ), and HRPC ( $n = 1$ ).

Analysis of the serum samples 30 minutes after the end of infusion showed >96% of the SN-38 was bound to the IgG. More detailed pharmacokinetics will be available when the phase II portion of the trial is completed. HPLC analysis also detected only trace amounts of free SN-38G in the serum, whereas with irinotecan therapy the AUC for the less active SN-38G is >4.5-fold higher than SN-38 (18). Comparison of SN-38 delivery in tumor-bearing animals given sacituzumab govitecan and irinotecan has indicated the SN-38 bound to the IgG is not glucuronidated, whereas in animals given irinotecan, >50% of the total SN-38 in the serum is glucuronidated (17). More importantly, SN-38 concentrations were as much as 135-fold higher in Capan-1 human pancreatic cancer xenografts given sacituzumab govitecan than irinotecan (17). Thus, sacituzumab govitecan has distinct advantages over nontargeted forms of topoisomerase-I inhibitors: (i) a mechanism that selectively retains the conjugate in the tumor (anti-Trop-2 binding), and (ii) the targeted SN-38 also appears to be fully protected (i.e., nonglucuronidated and in the lactone form), such that any SN-38 accreted by the tumor cells either by the direct internalization of the conjugate or through its release into the tumor microenvironment from the conjugate bound to the tumor will be in its most potent form. These results suggest that a moderately toxic, but well understood, cytotoxic agent, SN-38, can be effective as part of a tumor-targeting ADC, such as



sacituzumab govitecan. By administering an ADC with a moderately toxic drug conjugated at a high drug:antibody ratio (7.6:1), higher concentrations of SN-38 can be delivered to the cancers targeted, as suggested in the improved concentration of SN-38 achieved with sacituzumab govitecan compared with that released from irinotecan (17).

In conclusion, this phase I experience has indicated that sacituzumab govitecan is tolerated with moderate and manageable toxicity, all related to the activity of SN-38, with no evidence of damage to normal tissues known to contain Trop-2. Importantly, sacituzumab govitecan is active in patients with diverse metastatic solid tumors, possibly even after failing prior therapy with topoisomerase-I inhibitors, which needs to be studied further. This clinical trial is continuing, focusing on starting doses of 8 and 10 mg/kg in patients with TNBC, SCLC, NSCLC, and other cancers, even when these are not known to be responsive to topoisomerase-I inhibitors.

### Disclosure of Potential Conflicts of Interest

M.J. Guarino reports receiving speakers bureau honoraria from Immunomedics. S.S. Thomas reports receiving speakers bureau honoraria from Bristol-Myers Squibb, Ipsen, and Novartis and is a consultant/advisory board member for Bristol-Myers Squibb. S.V. Govindan and D.M. Goldenberg have ownership interest (including patents) in Immunomedics, Inc. No potential conflicts of interest were disclosed by the other authors.

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