Antibody-drug conjugates targeting TROP-2 and incorporating SN-38: A case study of anti-TROP-2 sacituzumab govitecan

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ABSTRACT
Antibody-drug conjugates (ADCs) that exploit the active metabolite SN-38, which is derived from the popular anticancer drug, irinotecan (a camptothecin that inhibits the nuclear topoisomerase I enzyme, inducing double-stranded DNA breaks during the mitotic S-phase of affected cells), represent a substantial advance in the ADC field. SN-38 has been conjugated to a humanized antibody against trophoblast cell surface antigen 2 (TROP-2), which is involved in cancer signaling pathways and has increased expression by many cancer cell types, yielding the ADC sacituzumab govitecan. By conjugating a higher number of SN-38 molecules to the immunoglobulin (drug-to-antibody ratio = 7–8:1), and giving higher (10 mg/kg) and repeated therapy cycles (Days 1 and 8 of 21-day cycles), enhanced drug uptake by the targeted cancer cells is achieved. Based on a unique conjugation method, the lactone ring of the SN-38 molecule is stabilized and the molecule is protected from glucuronidation, a process that contributes to the untoward late diarrhea experienced with irinotecan. Finally, while the ADC is internalized, the use of a moderately stable linker permits release of SN-38 in an acidic environment of the tumor cell and its microenvironment, contributing to a bystander effect on neighboring cancer cells. Here, we discuss the development of sacituzumab govitecan and clinical results obtained using it for the management of patients with advanced, refractory breast, lung, and urinary bladder cancers. Sacituzumab govitecan, which is undergoing accelerated approval review by the US Food and Drug Administration while also being studied in Phase 3 clinical studies, was granted Breakthrough Therapy status from the FDA for advanced, refractory, metastatic triple-negative breast cancer patients.

Introduction
Although nearly a half-century in development, antibody-drug conjugates (ADCs) in the past decade have become an area of intensive research as a more selective cancer therapy, with four approved ADCs and over 80 in clinical trials (Janice Reichert, personal communication, April 8, 2019). Early conjugates were thought to have failed because they incorporated some of the more contemporary anticancer drugs of their era, such as doxorubicin and methotrexate, and began with immunogenic murine antibodies. Success was achieved ultimately with the introduction of human and humanized antibodies, as well as so-called ultratoxic agents, drugs that were several logs more potent than those used first, with activity in the picomolar range. The combination of drug, selective linker and tumor-targeting antibody was designed to reduce off-target toxicities. Issues of antibody-target specificity, antigen-antibody internalization, and conjugate pharmacokinetics and dosing also required attention in ADC development.

The ADCs currently approved, and most agents under development, use one of the three basic compounds: (1) calicheamicin (an enediyne antibiotic that causes double-stranded DNA breaks, e.g., gemtuzumab ozogamicin), (2) auristatin (most commonly monomethyl auristatin E (MMAE), but also the F derivative (MMAF), with anti-mitotic activity by inhibiting polymerization of tubulin, e.g., brentuximab vedotin), and (3) maytansine (maytansinoid analogues DM1 or DM4, which also are microtubule inhibitors, e.g., trastuzumab emtansine). These drugs are so potent that they cannot be used as stand-alone therapeutics, causing more toxicity than therapeutic gain. In order to use these ultratoxic drugs in ADCs, new chemistries were required, including specialized linkers, with the primary goal to sustain the bond between the antibody and the drug while the conjugate was in the circulation, but enabling release of the active drug when the conjugate was internalized by, or released on or adjacent to, the target cells (e.g., when trafficked to the lysosome). Thus, while bound to the antibody-linker, the drug should be inactive, but once released within or in the immediate environment of the tumor cell, it should effectively kill at relatively low concentrations due to its extreme potency. This resulted in ultratoxic ADCs that had relatively low ratios of drug to antibody (<4) and low dosing in order to control off-target toxicity.

ADCs that incorporate ultratoxic drugs require a high level of stability between the antibody-drug bond when in the blood, with activity only possible if the conjugate is internalized by the tumor cell. This places a specific requirement on the target, i.e., the antigen must be on the surface of the tumor cells, in high concentration, and accessible, and a high level of tumor specificity is needed in order to preclude off-target toxicities. The antigen-antibody must be internalized, and in some cases, the conjugate needs to be trafficked selectively to
sites within the cells that will enable the cleavage of the linker-drug bond. While the advent of stably linked ultratoxic agents conjugated to relatively cancer-specific human or humanized monoclonal antibodies led to the approval of several ADCs,\textsuperscript{12} the testing of new ADCs has shown that success is not guaranteed based solely on the use of any one conjugate platform or drug. Other factors, such as the selection and level of tumor expression of the target, target antigen biosynthesis and heterogeneity during the course of therapy, tumor progression (all influencing therapeutic resistance), and specific properties of the cancer type and stage also play important roles.

This perspective presents our experience in the development of an alternative ADC platform utilizing a drug of lower potency than the ultratoxic agents (i.e., with nanomolar toxicity) that is coupled to antibodies with a moderately stable linker, but one that essentially releases most of the drug while the conjugate is in the circulation over a period of about 3 days. The linker is particularly susceptible to pH changes, thereby accelerating drug release when the conjugate is internalized and delivered to the acidic lysosomes, or even if the conjugate is bound to the antigen within the tumor microenvironment, where a lower pH would facilitate drug release. We focus on sacituzumab govitecan (IMMU-132), a conjugate targeting the tumor-associated antigen, TROP-2 (trophoblast cell surface antigen 2, or TROP-2), conjugated with a topoisomerase-I inhibitor (or TOPO-I),\textsuperscript{13,14} developed by Immunomedics, Inc.

**TROP-2**

TROP-2 was first described about 40 years ago as a surface marker of trophoblast cells\textsuperscript{15} and was rediscovered years later as tumor-associated calcium signal transducer 2 (TACSTD2), membrane component chromosome 1 surface marker 1 (M1S1), gastrointestinal antigen 733–1 (GA733–1), and epithelial glycoprotein-1 (EGP-1).\textsuperscript{16,17} We first identified the RS7 murine monoclonal antibody, developed against human non-small-cell lung cancer (NSCLC), finding it also bound to human breast, colon, renal, and prostate cancers, with staining also in many normal tissues.\textsuperscript{18} Subsequently, we determined the molecular properties of the antigen bound by RS7 as a 46-kDa glycoprotein (35 kDa when deglycosylated), showing it was phosphorylated by protein kinase C on serine-303 in the cytoplasmic domain, suggesting a role in signal transduction across the cell membrane.\textsuperscript{19,20} RS7 was subsequently classified as binding to an antigen that at the time was given the name epithelial glycoprotein-1.\textsuperscript{20,21} The RS7 antibody also showed rapid cell internalization.\textsuperscript{18,22} TROP-2 and its biological functions have been reviewed recently.\textsuperscript{14}

**Development and properties of sacituzumab govitecan (IMMU-132)**

Early ADCs used payloads composed of common chemotherapeutic agents, but these had potencies in the micromolar range, whereas the successful ultratoxic agents were all active at picomolar levels (Figure 1). A potential concern for the stably linked ultratoxic conjugates was that there was limited information on the free drug’s pharmacological activity. Therefore, we examined more conventional drugs whose pharmacological activity was known, hypothesizing that agents with cytotoxic activity in the low nanomolar range would be preferred.

SN-38, a semi-synthetic camptothecin that is the active component of irinotecan, was chosen because irinotecan’s clinical properties were well known. Camptothecins kill cells by interacting with TOPO-I, which in turn introduces double-stranded DNA breaks while cells are in the S-phase. In our experience, SN-38 had an IC\textsubscript{50} of approximately 1.0–6.0 nM against several human cancer cell lines of different origins.\textsuperscript{13,23} While SN-38 had the desired potency, the preparation of an active conjugate was challenging, since SN-38 is highly hydrophobic, with a limited number of coupling sites that could be used without jeopardizing its activity. In addition, while SN-38’s pharmacology was known, it is complex, with modifications to its structure that naturally occur in the body significantly reducing SN-38’s potency, such as glucuronidation and the opening of the lactone ring.\textsuperscript{24,25} In the case of SN-38, a dipiperidino side chain was added at the hydroxyl on the C10 position to improve water solubility, yielding the well-known chemotherapeutic agent, irinotecan.\textsuperscript{24} The carbamate bond of this side chain was cleavable by carboxylesterases found primarily in the liver, releasing SN-38, which is as much as 1000-fold more potent than irinotecan.\textsuperscript{24} However, once cleaved, this site also could be quickly glucuronidated, primarily by UGT-1A, a uridine diphospho-glucuronosyltransferase enzyme.\textsuperscript{24}

Our group investigated several types of linkers coupled to C10, as well as the C20 position, which is off the lactone ring (Figure 2).\textsuperscript{13,26–28} Short polyethylene glycol (PEG) groups that

\begin{figure}[h]
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\caption{Relative range of potency for some of the more commonly used ADC payloads against human cancer cell line in vitro (adapted from Nakada et al.\textsuperscript{15}).}
\end{figure}
Sacituzumab govitecan (IMMU-132) composition. Sacituzumab govitecan is composed of the humanized monoclonal IgG (designated hRS7) that binds to TROP-2. The IgG is mildly reduced to expose 8 sulfhydryl-binding sites that are subsequently coupled to the CL2A-SN-38 linker-drug through the maleimide moiety of the CL2 linker. As indicated, the CL2A linker has a short PEG (polyethylene glycol) residue to aid in solubility and is coupled to SN-38 at the 20th position of the lactone ring, which stabilizes the ring from opening to the less active carboxylate form. The bond between CL2A and SN-38 is pH sensitive, being more susceptible to release in a low pH environment (e.g., found in lysosome or even in the microenvironment of tumors). The 10th position of SN-38 is protected from glucuronidation while SN-38 is bound to the IgG. Thus, SN-38, while bound to the antibody, remains in its most potent form until released.

Enhanced solubility and minimized aggregation were a key component. A maleimide group was added so that the linker-drug complex reacts with the sulfhydryl groups generated on the immunoglobulin (IgG), thereby forming a stable thioether bond between the linker and the IgG. Several derivatives contained a cathepsin B cleavage site (CL2 derivative), since this did not affect the rate of SN-38 release and improved product quality and yields. This initial linker was modified further to remove phenylalanine at the cathepsin B cleavage site (CL2A derivative), since this did not affect the rate of SN-38 release and improved product quality and yields. The resulting conjugate of CL2A-SN-38 coupled to the IgG, thereby forming a stable thioether bond between the linker and the IgG, designated CL2, was neither the most nor least stably linked (e.g., SN-38 release half-life >7 days to only 0.5 days, respectively), but rather was one with an intermediate stability of 1–2 days. Critical assessments included determination of conjugate yield, aggregate formation, and retention of immunoreactivity. Conjugates with reasonable production properties were subjected to additional testing. Interestingly, studies examining in vitro stability in serum revealed the conjugate of choice, with a linker designated CL2, was neither the most nor least stably linked (e.g., SN-38 release half-life >7 days to only 0.5 days, respectively), but rather was one with an intermediate stability of 1–2 days.

This suggested that its rapid clearance would preclude off-target toxicity.

Specificity was revealed using an assay to detect double-stranded DNA breaks. Studies examining the conjugate’s mechanism of action identified upregulation of an early pro-apoptotic signaling effect with subsequent poly ADP ribose polymerase (PARP) cleavage, expected events occurring in cells with significant DNA damage. While the native hRS7 IgG showed antibody-dependent cell-mediated cytotoxicity (ADCC), the conjugate’s ADCC activity was decreased by as much as 60%. This loss was due to the reduction of the IgG and not the insertion of the linker-SN-38, since the reduced and blocked IgG had levels of ADCC that were similar to the conjugate. No complement-dependent cytotoxicity (CDC) was detectable using the native IgG or conjugate by in vitro assays. Others have reported the direct anti-tumor activity with a phage-display derived anti-Trop-2 Fab. This anti-Trop-2 Fab was also conjugated with doxorubicin, which was shown to have anti-tumor activity in vitro against human pancreatic cancer cell lines.

Human tumor xenograft models in mice were used to assess activity in a variety of solid tumor cell lines, including breast.
gastrointestinal, and lung.\textsuperscript{13,23,29,37} Again, enhanced activity was found in most cases when compared to irinotecan or free SN-38, as well as when compared to a non-targeting SN-38 ADC, but activity did not necessarily correlate with antigen expression measured in the cell line. This outcome most likely is based on differences in their sensitivity to a given drug (in this case, SN-38). In order to evaluate the role of TROP-2 expression on efficacy, the MDA-MB-231 breast cell line, which we found to be resistant to sacituzumab govitecan treatment, in part due to its increased expression of Rad51, was transfected with the TROP-2 gene.\textsuperscript{37} Two transfectants with 4- and 25-fold higher expression of TROP-2 than the parental cell line were isolated. Both had similar Rad51 levels as the parental cell line, but they were more susceptible to sacituzumab govitecan treatment, presumably because higher TROP-2 levels increased SN-38 exposure. While these studies suggest TROP-2 expression can influence the therapeutic response, immunohistology studies found examples of heterogeneous antigen expression that also could have contributed to the effect.\textsuperscript{23} This is consistent with our clinical observations that determination of TROP-2 expression levels in clinical tumor specimens may not be predictive of therapeutic outcome, but this needs further study.\textsuperscript{38–41}

While the anti-TROP-2 antibody used in sacituzumab govitecan internalizes,\textsuperscript{18,22} given the tendency for the conjugate to release SN-38 with a half-life measured in serum of ~1 day, we speculate that some portion of the therapeutic activity of sacituzumab govitecan could result from bystander effects, manifested by the local release of SN-38 from the conjugate bound to antigen in the tumor microenvironment, being released before the intact conjugate is internalized. However, because sacituzumab govitecan had improved therapeutic responses over an irrelevant conjugate, specific targeting and internalization are likely the major contributing factors. This is an important distinction between this SN-38 ADC and the ultratoxic ADC platforms, where the stable linkage prevents drug release unless internalized, presumably by antigen-expressing cells, albeit IgG can be absorbed non-specifically by cells. Therefore, while bystander effects might be possible with stably linked conjugates (e.g., when active drug is released after targeted cell death),\textsuperscript{42} the slow, local release of SN-38 represents a distinctly different mechanism than with most ultratoxic ADCs. Indeed, since SN-38 is active in the cell-cycle S-phase, maintaining low concentrations of SN-38 in tumors over time could improve potency, which is consistent with the clinical protocol of administering repeated high doses of sacituzumab govitecan, as discussed below.

Studies quantifying SN-38 concentrations in tumor xenografts indicated that the drug was detected over 3 days with sacituzumab govitecan compared to no more than 8 h for irinotecan-treated animals. Thus, despite administering 28-fold less mole-equivalents of SN-38 with sacituzumab govitecan compared to irinotecan, analysis of area-under-the-curve (AUC) indicated sacituzumab govitecan enhanced SN-38 concentrations in tumor xenografts by 20-fold to as much as 136-fold, compared to the AUC for SN-38 delivered by irinotecan.\textsuperscript{30} This finding is perhaps even more significant because mice are able to process irinotecan to SN-38 much more efficiently than in humans,\textsuperscript{43} and therefore SN-38 levels released from irinotecan in mice would be inflated. Thus, these findings support the view that the ADC’s selective targeting enhances the delivery of SN-38.

Another important finding was that levels of SN-38G, the inactivated, glucuronidated form of SN-38, were significantly lower in the serum of sacituzumab govitecan-treated mice.\textsuperscript{40} SN-38G (glucuronidated SN-38)/SN-38 AUC ratios in humans given irinotecan are most often >4:1,\textsuperscript{44} while in mice, this ratio for irinotecan was about 1:1.\textsuperscript{30} With the estimated irinotecan-to-SN-38 conversion rate in mice was about 25%, whereas it is ~5% in humans.\textsuperscript{24} However, in sacituzumab govitecan-treated animals, the AUC for SN-38G was about 5- to 10-times lower than the AUC for SN-38,\textsuperscript{30} subsequently, human data showed an SN-38G/SN-38 AUC ratio of 1:5.\textsuperscript{45} In patients given irinotecan therapy, the formation of SN-38G is a well-known process for the elimination of SN-38 and has been implicated in the development of so-called “late” diarrhea in patients, a significant complication with irinotecan. With irinotecan, a large portion of the injected dose of irinotecan and SN-38 is eliminated very quickly by the liver into the intestinal tract, inducing “early” diarrhea, whereas SN-38G recirculates by the hepatointestinal pathway, delaying its elimination; but when it enters the intestine, bacteria convert SN-38G to SN-38.\textsuperscript{46}

In sacituzumab govitecan, the C10 position is available for enzymatic glucuronidation after the conjugate is injected; however, \textit{in-vitro} studies confirmed that the C10 is protected from glucuronidation while SN-38 remains bound on the IgG.\textsuperscript{30} Another important detoxification process for SN-38 involves the opening of the lactone ring, leading to the carboxylate form.\textsuperscript{24} This is a dynamic process that occurs naturally for both irinotecan and SN-38, with levels of the carboxylate form averaging ~35% of the total product.\textsuperscript{24} Coupling the linker to the C20 position of SN-38 stabilizes the lactone ring,\textsuperscript{47} which we confirmed with another TOPO-I-based ADC targeting carcinoembryonic antigen cell-adhesion molecule-5 (CEACAM5).\textsuperscript{48}

Thus, the SN-38 that remains bound to the IgG/linker is protected until released, which means that SN-38 released locally at the tumor will be in its fully active form, while SN-38 released from the conjugate in the serum or other tissues will be detoxified in a similar manner as found with irinotecan.

**Clinical experience**

Clinical studies with sacituzumab govitecan began in 2012, first as a dose-finding basket trial (NCT01631552) with patients having diverse epithelial cancers who failed conventional treatments, initially including colorectal, gastric, hepatocellular, NSCLC, small-cell lung cancer (SCLC), ovarian, pancreatic, prostate, triple-negative breast (TNBC), and urothelial cancers (UC).\textsuperscript{41} Since over 80% of the tumor tissue specimens evaluated by immunohistochemistry showed positive staining for TROP-2, its expression was not a criterion for inclusion.

This trial was designed for patients to receive multiple cycles of sacituzumab govitecan, at a starting dose of 8 mg/kg given on Days 1 and 8 of a 21-day cycle. Treatment
continued until disease progression or drug intolerance. Responses were determined every 8 weeks, requiring confirmation every 4–6 weeks, in accordance with RECIST 1.1 criteria for objective responses.\textsuperscript{41} Although the maximum-tolerated dose from the Phase 1 study was 12 mg/kg, for repeated therapy with multiple cycles, starting doses of 8 and 10 mg/kg were preferred.\textsuperscript{41} However, the final starting dose of 10 mg/kg, given twice (days 1 and 8) in each 21-day cycle of a multiple-cycle therapy was determined after further studies at these two dose levels.\textsuperscript{45} Safety and pharmacokinetics (PK) were reported in 81 patients first given a starting dose of 8 mg/kg, followed by 97 patients enrolled with a starting dose of 10 mg/kg.\textsuperscript{45} There was no difference in PK for these two dose levels, but assays monitoring the clearance of the intact IgG and the ADC showed the ADC cleared more quickly (e.g., half-life of 12 to 14 h), confirming that SN-38 was released from the conjugate, while the IgG remained in the circulation (e.g., half-life of 103 to 114 h). Further, as discussed above, levels of glucuronidated SN-38 were much less than reported for therapy with irinotecan,\textsuperscript{44,49} which may explain the lower rate of diarrhea (grade ≥3 in only 10% of patients given 10 mg/kg), compared with irinotecan therapy.\textsuperscript{46,49} Dose delays or reduction were due almost exclusively to neutropenia, which was similar to that experienced with irinotecan therapy. There was no evidence at this time for a higher risk of diarrhea or neutropenia based on uridine diphosphate glucuronosyltransferase haplotype status,\textsuperscript{45} but additional data are necessary. Given the relative similarity between the dosing tolerability and toxicity, but with a suggestion of improved therapeutic response in one indication (triple-negative breast cancer), the 10 mg/kg dose level given weekly for the first 2 weeks of a 3-week treatment cycle was selected for future clinical trials.

The expanded Phase 2 clinical trial results at the 10 mg/kg starting dose have been reported for patients with TNBC, hormone-positive, HER2-negative breast cancer (HR+/HER2\textsuperscript{−} BC), NSCLC, SCLC, and UC reported in Table 1. Given that these patients failed or relapsed after multiple prior therapies, the confirmed objective response rates, as well as median duration of responses, median progression-free survival, and the median overall survival rates are very encouraging, especially in the context of a very acceptable safety profile consisting of neutropenia, fatigue, diarrhea, and anemia.

An example of the efficacy of sacituzumab govitecan in patients with TNBC, an indication that was awarded Breakthrough Therapy Designation by the US Food and Drug Administration and is the potential first therapeutic target being sought for commercial approval, is presented in Figure 3. Sacituzumab govitecan is being evaluated in a Phase 3 study of patients with refractory/relapsed TNBC (NCT02574455) while it is undergoing FDA review for accelerated approval, in addition to being studied in patients with HR+/HER2\textsuperscript{−} BC who have failed at least two prior chemotherapeutic regimens (NCT03901339), in metastatic uterine cancers after failure of platinum-based regimen or anti-PD-1/PD-L1 immunotherapy (NCT03547973), and in metastatic NSCLC, SCLC, head, and neck squamous carcinomas, endometrial, and hepatocellular carcinoma (NCT03964727).

In summary, based on the study results currently available, the TROP-2-targeted ADC sacituzumab govitecan appears to show good efficacy and manageable toxicity (mostly neutropenia and diarrhea) as a monotherapy in several cancer indications. We believe it represents a paradigm change in ADCs through its: (1) use of a drug with moderate (nM) toxicity, SN-38; (2) use of a moderately stable linker; (3) high ratio (−8:1) of drug to antibody; and (4) short conjugate half-life. The administration of repeated high doses of the ADC over prolonged periods is another differentiating factor. All of these attributes contribute, we believe, to enhanced drug targeting and concentration in the tumor, resulting in less off-target toxicity and possible bystander effects to cancer cells with reduced target antigen expression.

### Other TROP-2 ADCs

It should be noted that TROP-2 as a target for ADCs has attracted the interest of additional companies, and several other anti-TROP-2 ADCs have been evaluated in clinical studies, although none has progressed further than Phase 1.

#### RNR927C (PF-06664178, pfizer)

This ADC is composed of a different anti-TROP-2 antibody conjugated with a potent auristatin microtubule inhibitor, with a substitution ratio of 2.0.\textsuperscript{55} The Phase 1 trial of 31 patients with diverse metastatic cancers, where the ADC was given every 21 days with doses escalating from 0.15 mg/kg to 4.8 mg/kg, showed unacceptable toxicities of fatigue, constipation, nausea, chills, infusion reactions, neutropenia, rash, weight loss, arthralgia, decreased appetite, diarrhea, dyspnea, mucosal inflammation, and pruritis, with neutropenia and rash being the most common grade ≥3 adverse events.\textsuperscript{56} At tolerable doses, stable disease was the best response. There was also an anti-drug antibody response in almost all patients. Apparently, this ADC has been abandoned.

| Cancer type\(^a\) (Ref) | Number of patients | Confirmed ORR\(^b\) | Median DoR (months)\(^c\) | Median PFS (months)\(^d\) | Median OS (months)\(^e\) |
|------------------------|-------------------|-------------------|---------------------------|--------------------------|--------------------------|
| TNBC\(^{-52}\) | 108 | 33 | 7.7 | 5.5 | 13.0 |
| mBC\(^{-51}\) | 54 | 31 | 7.4 | 6.8 | NR |
| UC\(^{-54}\) | 45 | 31 | 12.9 | 7.3 | 16.3 |
| SCLC\(^{-39}\) | 50\(^f\) | 14 | 5.7 | 3.7 | 7.5 |
| NSCLC\(^{-50}\) | 47\(^f\) | 19\(^f\) | 6.0\(^f\) | 5.2\(^f\) | 9.5\(^f\) |

\(^a\) TNBC, triple-negative breast cancer; UC, urothelial cancers; SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer.

\(^b\) ORR, objective response rate = (complete response + partial response)/number of patients.

\(^c\) DoR, duration of response.

\(^d\) PFS, progression-free survival; OS, overall survival.

\(^e\) OS data based on 54 patients.

\(^f\) N = 47 patients who were response-assessable out of the 54 treated. PFS and OS data based on 54 patients.
Preclinical studies were reported recently with another microtubule inhibitor (maytansine) conjugated using a novel uncleavable linker to an anti-TROP-2 antibody that is glycoengineered to have enhanced ADCC activity. It is currently listed as starting Phase 1 clinical testing in patients with epithelial cancers that are positive for TROP-2 expression (NCT03884517).

**Figure 3.** (a) Waterfall plot illustrating the best response data in 108 triple-negative breast cancer patients treated with sacituzumab govitacan (adapted from Bardia et al., with permission). (b–d) Tumor shrinkage by CT in triple-negative breast cancer patient given sacituzumab govitacan (from Bardia et al., with permission). Case study: A 48-year-old woman with an initial diagnosis of triple-negative breast cancer in received four prior lines of treatment (including an anti-PD-L1 immune checkpoint inhibitor) and presented with lung and lymph node metastases at enrollment. She achieved a partial response that started 1.7 months after initiation of treatment with sacituzumab govitacan, with the best response of 54% reduction at 9.0 months and progression occurring at 14.4 months (partial response duration, 12.7 months). (b) Baseline image of two of the three target lesions: a 24 x 19-mm left-upper-lung mass (arrow) and a mediastinal lymph node (17 x 29-mm; circle). (c) After 16 doses, these two target lesions decreased to 13 x 7 and 9 x 19 mm, respectively. (d) TROP-2 expression in an archived tumor specimen by immunohistochemistry that shows 1+ to 2+ staining (overall, 2+).
profiles and safety in Cynomolgus monkeys. Preliminary data from a Phase 1 clinical trial in patients with relapsed NSCLC (NCT03401385) indicate that the agent has been safely tolerated at doses of up to 2 mg/kg, with 1 partial response in 18 tumor evaluable patients. An update of the data presented at the 2019 ASCO meeting included 39 patients given doses as high as 8.0 mg/kg. At this time, 10 partial responses were reported, with 41% of the patients having at least one treatment-emergent grade ≥3 adverse event; 1 dose-limiting maculopapular rash at 6 mg/kg. Unlike its companion ADC, [fam-] trastuzumab deruxtecan (DS-8201a), which targets HER2 and uses a substitution ratio of 8 DXd/antibody, DS-1062a has a substitution ratio of 4 DXd/antibody. Thus, DS-1062a represents a second ADC platform utilizing a TOPO 1 inhibitor, but unlike sacituzumab govitecan, it employs a drug considered to have “ultratoxic” potency (i.e., 10-times higher than SN-38), requiring a linker with high stability in serum and a reduced substitution ratio.

Conclusion

In addition to the observation that TROP-2 is a prognosticator for a number of cancers and has a role in controlling cancer growth and spread by various signaling pathways, its enhanced expression in a large number of cancers, with minimal expression in normal tissues, suggests that it is a unique target for precision cancer medicine approaches, including ADCs. It is anticipated that sacituzumab govitecan will achieve its first clinical use in the treatment of advanced TNBC, followed by advanced HR+ , ER+ breast and urothelial cancers. This ADC also can be incorporated into combination therapy with poly(ADP-ribose)polymerase and immune checkpoint inhibitors, which may improve clinical outcomes.

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Competing Interests

The authors own Immunomedics stock or stock options. Dr. Goldenberg has royalty-bearing patented inventions. Dr. Goldenberg is the founder and retired Chief Scientific Officer of Immunomedics, Inc. Dr. Sharkey is a consultant to Immunomedics.

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