Editorial Commentary

Does sacituzumab-govitecan act as a conventional antibody drug conjugate (ADC), a prodrug of SN-38 or both?

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On April 22, 2020, the Food and Drug Administration granted accelerated approval to sacituzumab-govitecan (Trodelvy) for adult patients with metastatic triple-negative breast cancer (TNBC) who received at least two prior therapies for metastatic disease (1). Sacituzumab-govitecan is an antibody drug conjugate (ADC) of a humanized anti-Trop2 monoclonal antibody (mAb), RS7, linked to an average of 7.6 molecules of SN-38—the active metabolite of irinotecan and a potent inhibitor of Topoisomerase 1 (Topo1) (2). By chemically connecting the drug and mAb the goal was to deliver and release SN-38 to tumor cells abundant in Trop2. In the Phase III ASCENT study sacituzumab-govitecan demonstrated clinical benefit in patients with metastatic TNBC irrespective of Trop2 expression, albeit with greater efficacy in patients with a medium or high Trop2 score (3,4). In contrast, although sacituzumab-govitecan was efficacious in metastatic small cell lung cancer (mSCLC), progression-free and overall survival showed no clear relationship to Trop2 expression (5). Hence, there is an enigma as to how the anti-Trop2 ADC can be effective in cancers that either have or have not the Trop2 antigen. A knowledge of the mechanism of action of sacituzumab-govitecan in Trop2 low or absent tumors would facilitate further development of SN-38-based drugs or ADCs targeting Trop2, and we present hypotheses here that explains this effect.

It was anticipated that if sacituzumab-govitecan internalized in tumor cells, a protease site on the linker would be cleaved by lysosomal enzymes to release SN-38 intracellularly. However, the internalization of sacituzumab-govitecan may not be very efficient. In early efforts to establish Trop2 targeting, tumor uptake of the carrier mAb ^{131}I-RS7 was only ~7% to 16% of the initial dose/gm in a Trop2 TNBC xenograft—only ~2-fold higher than a control ^{131}I-mAb (6); by comparison, Trastuzumab shows an uptake of ~40% of the initial dose/gm in a HER2-positive tumor (7). However, in sacituzumab-govitecan, the linker attaching the monoclonal antibody to SN-38 also contains a hydrolysable carbonate moiety that has a cleavage half-life of only ~18 hours in neutral pH or sera—the "weakest link in the chain". It has been suggested that the hydrolytically labile linker allows time-dependent extracellular release of free drug in the tumor microenvironment so it can affect adjacent cells by a bystander effect (2).

The rapid spontaneous linker hydrolysis in sacituzumab-govitecan releases a very large amount of the SN-38 cargo systemically (8), much more than with other ADCs—which are generally designed to avert spontaneous drug release—or that can be accounted for by a targeted mechanism with limited target capacity. Thus, the question should be asked as to whether the antitumor effects of sacituzumab-govitecan are due to a conventional ADC mechanism, a bystander effect, systemically released SN-38, or a combination thereof.

The *Table 1* below shows the pharmacokinetic parameters of the SN-38 generated from sacituzumab-govitecan and from irinotecan—the prototypical SN-38 prodrug—in the human. Although the mechanisms of SN-38 generation are quite different, the exposure, or AUC, of the SN-38 released from sacituzumab-govitecan over a three-week cycle is over 15-fold higher than that from irinotecan at their maximally tolerated doses; also, the time over the target (TOT) concentration of ~10 nM SN-38 needed to inhibit Topo1 is significantly longer with sacituzumab-

Table 1 Pharmacokinetic parameters of SN-38 generated from sacituzumab-govitecan and irinotecan[A]

Drug	SN-38 C_{max}, nM	SN-38 $t_{1/2}$, h	$TOT_{3\ Wk}$[B] Days >10 nM	SN-38 $AUC_{3\ Wk}$, μM × h
Sacituzumab-govitecan 10 mg/kg, Q Wk, 2/3 Wks	320	18	7.5	20[C]
Irinotecan, 340 mg/m^2 Q3 Wk	140	21	4.4	1.2

[A], the C_{max}, $t_{1/2}$ and single-dose AUC values were obtained from the FDA label information for sacituzumab-govitecan and CPT-11 (Camptosar); [B], average time SN-38 is over 10 nM target concentration over 3 Wk; [C], the $AUC_{3\ Wk}$ of SN-38 released from sacituzumab-govitecan over 3 Wk was calculated as twice the reported $AUC_{168\ hr}$. Wk, week; AUC, area under the curve; TOT, time on target.

govitecan. Since the much lower levels of SN-38 generated from irinotecan have significant therapeutic and toxicity effects, it can be confidently concluded that much higher systemic levels of free SN-38 released from sacituzumab-govitecan must have equal or greater pharmacological effects. This could explain the efficacy of sacituzumab-govitecan observed in low Trop2 score mSCLC (5) and mTNBC (4).

Since sacituzumab-govitecan is so effective in TNBC, one can rightly ask the importance of understanding its mechanism. First, it would certainly be important to know whether Trop2 is indeed a suitable target to either encourage or dissuade work on Trop2-targeted ADCs with different payloads. As noted above, sacituzumab-govitecan is very active in small cell lung cancer but its efficacy is unrelated to Trop2 expression (5); also, PF-06664178, a potent Trop2-targeted ADC linked to a protease-cleavable auristatin has not fared well in early clinical trials (9). Second, whether sacituzumab-govitecan is or is not a target-directed ADC or prodrug would influence the stability of linkers chosen for similar therapeutics; DS-1062a and SKB264 are Trop2-targeting ADCs in early trials that also have Topo1 poison payloads—exatecan and belotecan, respectively—attached by protease-labile linkers that would not be released systemically and require intracellular delivery and payload release. Third, if maintenance of a high systemic concentration of free SN-38 is essential for efficacy of sacituzumab-govitecan it may limit the use of certain drug combinations. Currently, sacituzumab-govitecan is administered IV on days 1 and 8 of a 21-day cycle, so there is a near-continuous high systemic exposure of SN-38 with a minimal drug-free interval. PARP inhibitors are highly synergistic with Topo1 inhibitors such as SN-38, but the synergy exists for toxicities as well as efficacy. For example, the current sacituzumab-govitecan dosing schedule does not provide a sufficient SN-38-free interval in which a PARP inhibitor could be safely administered—as for example by using a gap schedule approach for combinations of Topo1 inhibitors and DNA damage response inhibitors (10)—hence, the use of a sacituzumab-govitecan-PARP inhibitor combination may not be feasible. Indeed, a recent small trial of sacituzumab-govitecan and rucaparib indicated efficacy of the combination, but at the expense of significant early grade 3/4 neutropenia (11). Finally, if the high AUC of free SN-38 is a major driver of sacituzumab-govitecan efficacy, a properly designed long-acting prodrug of SN-38 could achieve that AUC, as well as a lower C_{max} to lower systemic toxicity and a prolonged half-life to increase time over target; moreover, use of a prodrug would not be confined to tumors that have Trop2. Hence, comparing the efficacy of a long-acting non-targeted SN-38 prodrug to sacituzumab-govitecan at doses that provide equal exposure may resolve to what extent sacituzumab-govitecan acts as a SN-38 prodrug versus a targeted ADC.

Conclusions

Pharmacokinetic and biomarker data, together with considerations of its rapidly hydrolyzed linker, suggests that sacituzumab-govitecan might act as an SN-38-prodrug instead of or in addition to a conventional ADC.

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Footnote

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President of Prolynx, which developed PLX038. LC and FCB will act as investigators in a forthcoming clinical trial of PLX038. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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