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CURRENT OPINION

Could a Long-Acting Prodrug of SN-38 be Efficacious in Sacituzumab Govitecan-Resistant Tumors?

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Abstract

We previously proposed that sacituzumab govitecan (SG, Trodelvy®) likely acts as a simple prodrug of systemic SN-38 as well as an antibody drug conjugate (ADC). In the present commentary, we assess whether a long-acting SN-38 prodrug, such as PLX038, might be efficacious in SG-resistant patients. We first describe possible mechanisms of action of SG, with new insights on pharmacokinetics and TROP2 receptor occupancy. We argue that SG is not an optimal conventional ADC and that the amount of systemic SN-38 spontaneously hydrolyzed from the ADC is so high it must have activity. Then, we describe the concept of time-over-target as related to the pharmacology of SG and PLX038 as SN-38 prodrugs. To be clear, we are not in any way suggesting that PLX038 or any SN-38 prodrug is superior to SG as an anticancer agent. Clearly, SG has the benefit over antigen-independent SN-38 prodrugs in that it targets cells with the TROP2 receptor. However, we surmise that PLX038 should be a more efficacious and less toxic prodrug of systemic SN-38 than SG. Finally, we suggest possible mechanisms of SG resistance and how PLX038 might perform in the context of each. Taken together, we argue that—contrary to many opinions—SG does not exclusively act as a conventional ADC, and propose that PLX038 may be efficacious in some settings of SG-resistance.

Key Points

Sacituzumab govitecan (SG) is a both a prodrug of SN-38 and an antibody drug conjugate (ADC).

SG was designed to target cancer cells that express the TROP2 receptor.

Long-acting SN-38 may be efficacious in some settings of SG-resistance.

1 Introduction

Sacituzumab govitecan (SG) is an antibody drug conjugate (ADC) of a humanized anti-TROP2 monoclonal antibody (mAb), hRS7, linked to ~ 8 molecules of SN-38—the active metabolite of irinotecan and a potent inhibitor of topoisomerase 1 (TOP1) [1]. The intended objective of the ADC was to deliver SN-38 to tumor cells abundant in TROP2 antigen. However, in contrast to conventional ADCs that have stable linkers and circulate for many days until internalization, SG contains a fast-cleaving linker that rapidly hydrolyzes in circulation to give SN-38 and free hRS7 with a half-life of only ~14 h in plasma [2]. The released SN-38 reaches very high systemic levels, so SG serves both as a short-lived ADC and as a systemic prodrug of SN-38 [3]; however, it is unknown how much each mechanism contributes to its anti-cancer activity. SG has been remarkably effective in many clinical trials and is US Food and Drug Administration (FDA)-approved for patients with metastatic triple-negative breast cancer (TNBC) and pre-treated HR^+/$HER2^-$ metastatic breast cancer [4, 5]. Unfortunately, the median progression-free survival is only ~ 6 months due to resistance [4, 6], and there are limited rescue therapies available. Prolynx and Curie are planning a clinical trial of

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PLX038—a long-acting releasable PEG~SN-38 prodrug of SN-38—with patients whose triple negative breast cancer disease has progressed under SG.

2 Commentary

2.1 Sacituzumab Govitecan (SG) Mechanisms, Pharmacokinetics, and Receptor Occupancy

An understanding of the mechanisms of action of a drug are essential to understanding mechanisms of resistance and developing approaches to circumvent them. SG was designed as a canonical ADC targeting the extra-cellular antigen TROP2 that is present on many tumors. The intent was that after binding target cells expressing the antigen, the ADC would internalize and release its toxic SN-38 payload. However, with SG the conventional ADC mechanism is complicated by its rapid hydrolysis to give SN-38 and free hRS7 in the systemic circulation [2]; indeed, the amount of SN-38 released systemically is high enough to have systemic effects akin to traditional chemotherapy [3].

Although ADC efficacy is usually related to antigen expression [7], clinical experience has enigmatically found little correlation of efficacy of SG with TROP2 expression levels [6]. Due to the rapid release of SN-38, the ADC has a short 14-h half-life in the systemic circulation while the concomitantly released hRS7 has a long 102-h half-life [2]. To our knowledge, the impact of the different lifetimes of these hydrolytic products of SG have largely gone unreported. The consequences we modeled from reported plasma pharmacokinetic data [2] are illustrated in Fig. 1, which shows the levels of the drug-bearing SG, free hRS7, as well as the total SG plus hRS7 over three dosing cycles. As shown, there are increases in free hRS7 with subsequent doses due to the half-life of hRS7 being long relative to the dosing interval. Importantly, the levels and duration of exposure of product hRS7 greatly exceed those of the parent ADC; here, over the 3-week cycle the $AUC_{0\text{-inf}}$ of hRS7 (70,800 h•μg/mL) is about sixfold higher than SG (11,700 h•μg/mL).

Typically, an ADC is not significantly cleaved in circulation and is intended to be the only component available for antigen binding. In contrast, the rapid rate of SG hydrolysis and production of the long-lived hRS7 [2] creates a situation where the ADC is greatly diluted and exceeded by hRS7 over time (Fig. 1). Both SG and free mAb bind target TROP2 cells, but only the ADC is active [8]. Hence, the effect of high levels of hRS7 is to compete with SG for TROP2 and greatly reduce the amount of ADC bound to TROP2 that internalizes and delivers its SN-38 cargo to the tumor. For example, after the first dose, SG represents only 12% of the total TROP2 binding Ab at day 2, and only 4% at day 3; after the second dose, the ADC is only 0.5% of the total TROP2 binding Ab 4 days later. Thus, although SG has the highest dosing regimen of any approved ADC, the levels and duration of exposure of the active ADC are remarkably low, and greatly exceeded by antigen-competitive hRS7.

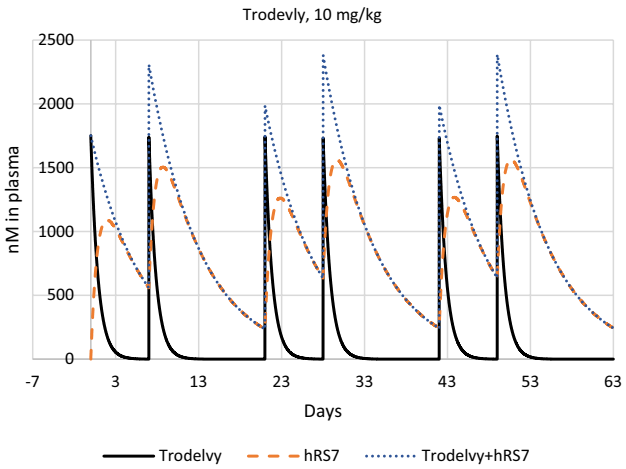

Fig. 1 Human pharmacokinetics of sacituzumab govitecan (SG) and product hRS7. SG (black line) at 10 mg/kg d1 and d8 over three 3-week cycles, hRS7 (red line) simulated from the parameters from Ref. [2] and SG + hRS7 (blue dotted line)

Assuming plasma pharmacokinetics qualitatively reflects tissue exposure, the important consequence of generating a high concentration of hRS7 is the reduction of TROP2 receptor occupancy by SG (Fig. 2). In the first dosing cycle the total ADC and equipotent hRS7 concentrations undergo a concentration transition from 1500 to 640 nM. At steady state the total mAb—SG plus hRS7—concentration greatly exceeds the TROP2 receptor and its nanomolar $K_{d,}$ and completely saturates the receptor. Figure 2 shows the calculated fraction of TROP2 receptor occupied by the labile SG in the setting of continuous hRS7 formation, as well as a typical ADC with a stable linker. As indicated, ≤ 10% of TROP2 is occupied by SG for 80% of the dosing cycle. Clearly, the duration of TROP2 occupancy by SG is short, which limits the amount of ADC that can be internalized as well as the duration of internalized SN-38 inhibition of TOP1. In short, if there is minimal occupancy of TROP2 by SG throughout its dosing cycle, SG cannot be considered an optimal ADC.

2.2 PLX038 is an Efficacious Prodrug of SN-38 and has a Long Time-Over-Target

The efficacy of a drug is often related to the time during which the target is effectively engaged by the drug—the "time-over-target" (TOT). For an enzyme target such as TOP1, the TOT translates into the length of time that the drug concentration is above the critical threshold necessary to maintain an effective level of enzyme inhibition.

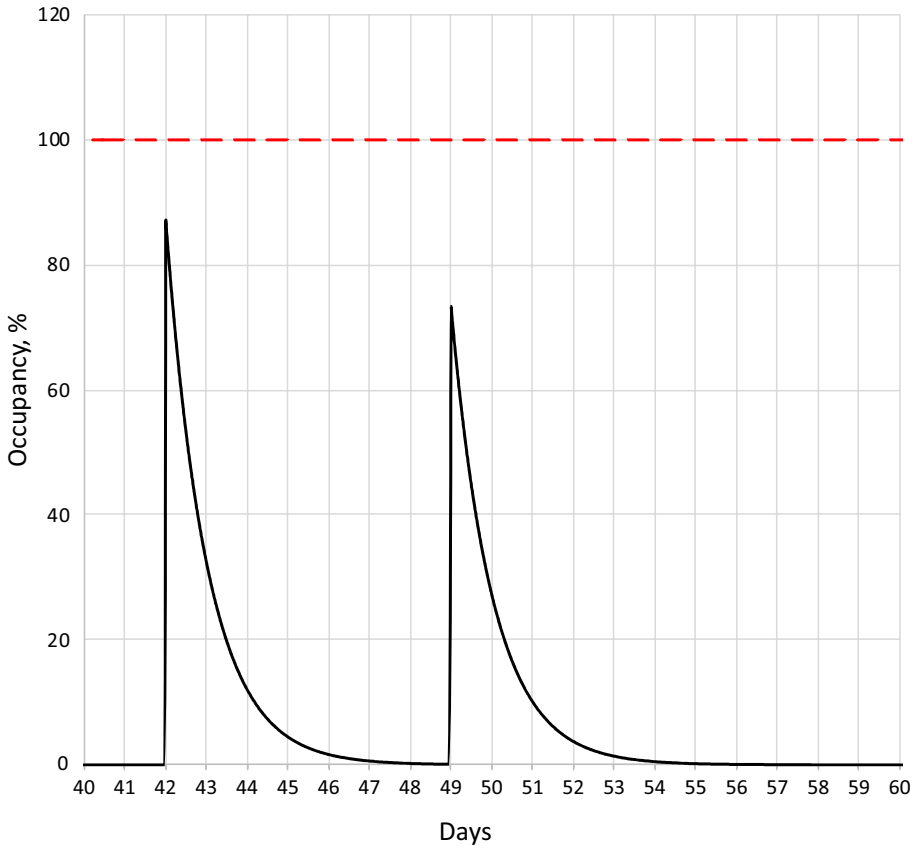

Fig. 2 TROP2 receptor occupancy by sacituzumab govitecan (SG) and a stable antibody drug conjugate (ADC). Percent of TROP2 occupied by SG versus time at steady state (doses five and six in standard regimen). The figure shows the %TROP2 occupied by SC (black line) or an exemplary stable TROP2 ADC as well as the total ADC + hRS7 (red line) assuming saturation of TROP2

The time-over-target hypothesis is summarized by the following statements:

- There is some "target concentration" of drug at which higher concentrations are not more beneficial.
- The longer a drug stays at or above the target concentration (i.e. time-over-target—TOT), the more efficacious it is.
- Drug concentrations above the target concentration do not provide additional benefit, but can result in toxicity, so AUC above the target concentration is considered "wasted AUC". High maximum concentration (C_{max}) values can also contribute to toxicities.

Thus, the most effective, least toxic administration is one where the drug is present at the target concentration, but not much above, for the longest period of time (i.e., longest TOT).

The documented need for continuous inhibition of TOP1 to effect continuous inhibition of DNA synthesis [9] emphatically suggests that TOP1 inhibition should follow the TOT hypothesis; that is, that low-dose, long TOT inhibition and prolonged exposure should be more efficacious than conventional high-intensity bolus treatments. Indeed, Houghton et al. [10, 11] showed that the efficacy of irinotecan—an SN-38 prodrug like PLX038—is schedule dependent and related to TOT: a given total dose of drug administered on a protracted schedule—two x 5-day courses every 21 days—was more efficacious than the same dose equivalents given as a single bolus. Higher dose intensity did not provide further benefit, but did increase toxicity—in accord with the TOT hypothesis. Moreover, in preclinical studies [12] and in a large phase III pancreatic cancer trial, the efficacy of the liposomal irinotecan prodrug was directly associated with the duration of free SN-38 above a threshold—that is, the TOT [13].

The SN-38 released from SG reaches concentrations exceeding that of any SN-38 prodrug, and we previously proposed that SG must be acting as a prodrug of SN-38 in addition to or instead of as an ADC [3]. The structurally related labetuzumab govitecan, which contains the same unstable linker as SG, should also release SN-38, but the tumor targets likely have different sensitivities to SN-38. The rationale for this hypothesis with SG is as follows. In humans the C_{max} and AUC values of SG are > twofold and tenfold higher, respectively, than the SN-38 provided by irinotecan (Fig. 1; Table 1). Since the SN-38 from irinotecan has significant anti-tumor activity, the much higher amount of free SN-38 released from SG must also have activity. It may be relevant that in six of six TROP2-containing human solid tumor lines the in vitro cytotoxicity of SN-38 exceeded that of SG [8], suggesting in vitro equivalence of the small molecule and ADC. Hence, the ability of SG as a prodrug for SN-38 should be considered a contributing source of its efficacy as well as toxicities.

Table 1 Pharmacokinetic parameters of SN-38 prodrugs

	Schedule	Dose/3-week cycle mg/m^2	SN-38 equivalents/3-week cycle, mg/m^2	SN-38 $t_{1/2}$, h	SN-38 C_{max}, nM	TOT[a] % cycle	SN-38 AUC, μM•h	Wasted AUC, %
PLX-038	q3w	1730	60[b]	125	51	~ 70	9	72
SG	qw x2, q3w	776[c]	14	18	320	~ 48	20	92
Irinotecan	q3w	340	21[d]	~ 12	140	~ 12	2	88

AUC area under the concentration time curve; C_{max} maximum concentration; *q3w* every 3 weeks; *SG* sacituzumab govitecan; $t_{1/2}$ half-life; *TOT* time-over-target

[a]Time over target assumed 5 nM target for SN-38 inhibition of TOP1

[b]With losses due to renal elimination of the prodrug, the efficiency of delivery is 35% and actual SN-38 delivered is 21 mg/m^2/cycle. Efficiency of SG is 100% and irinotecan is 10%

[c]From 10 mg/kg or 388 mg/m^2 per administered dose

[d]Estimated 10% conversion of irinotecan

PLX038 and PLX038A are long-acting prodrugs of SN-38 composed of a four-arm 40 kDa PEG attached to four SN-38 moieties by linkers that slowly cleave to release the drug [14–16]. PLX038 is being developed as a long-duration DNA-damaging agent for use in DNA damage-response deficiencies and inhibitors. The released SN-38 has a low C_{max} and long half-life of about 5 days in humans, about tenfold longer than the SN-38 released from irinotecan or SG (Fig. 3; Table 1). Although PLX038 does not actively target tumors, the small 15 nm PLX038 nanomolecule penetrates large pores of tumor vasculature, and accumulates and is retained in the tumor for long periods—half-life ~ 2 weeks [17]. Remarkably, *single doses* of PLX038A are sufficient to suppress tumor growth and induce regressions for prolonged periods in most xenografts tested [18].

Based on the TOT hypothesis, PLX038 contends to be a very effective prodrug of SN-38. As shown in Fig. 3 and Table 1, the SN-38 released from SG exceeds the target concentration for only 50% its 3-week cycle. Although this is ~ fourfold longer than the SN-38 TOT from irinotecan, the TOT of the SN-38 from SG is significantly less that that from PLX038. And, DNA damage parallels TOP1 inhibition for periods exceeding 3 weeks [19]. The TOT hypothesis also posits that the amount of drug over the target concentration ("wasted AUC")—~ 90% for SG and irinotecan—would not contribute to efficacy, but might to toxicity. The SN-38 released from PLX038 remains above the target concentration 70% of its 3-week dosing cycle, with only ~ 70% wasted AUC, so it should be effective and less toxic. Also, the C_{max} of SN-38 has been directly associated with toxicities [13] and the C_{max} of the systemically released SN-38 from SG is > sixfold higher than that from PLX038.

Taken together, increasing the TOT of TOP1 inhibition through the use of long-acting SN-38 prodrugs such as PLX038 is expected to significantly increase the duration of DNA damage, and increase the probability of the released SN-38 being present during the sensitive S phase of the cell cycle. They should also be good candidates for use in combinations with drugs targeting DNA damage-response proteins such as PARP1 and ATR inhibitors. Finally, they should minimize on-target/off-tumor engagement and toxicity through reduction of SN-38 wasted AUC and C_{max}. Hence, according to the TOT hypothesis, PLX038 should prove be a highly effective prodrug of SN-38.

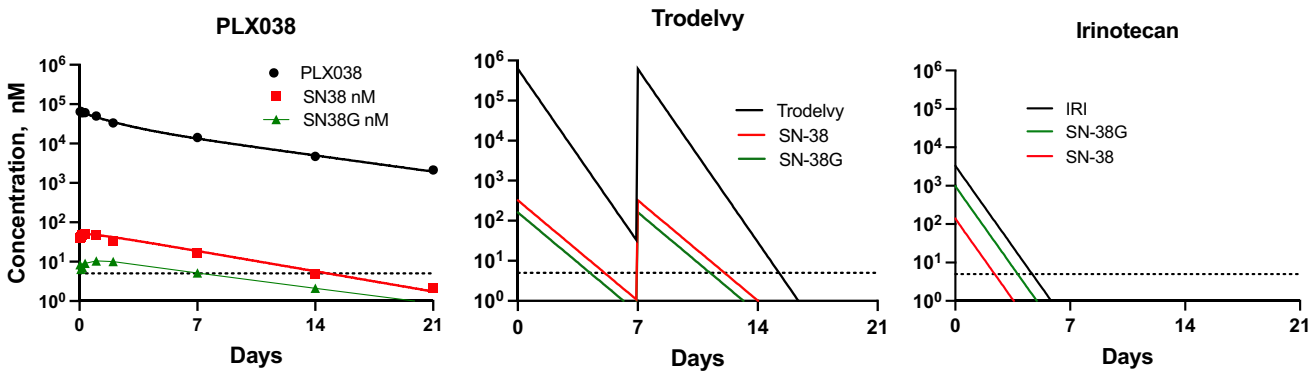

Fig. 3 Concentration versus time plots of PLX038, sacituzumab govitecan (SG), and irinotecan. SG and irinotecan pharmacokinetics simulated using recommended doses in humans

2.3 PLX038 may Overcome SG Resistance

Resistance to SG may be related to development of mechanisms associated with ADC internalization or countering the cytotoxicity of SN-38. The most likely mechanisms of SG resistance include (1) mutations of TROP2 that reduce ADC internalization needed for cell-killing, (2) qualitative (mutations) and quantitative (low levels) alterations of TOP1 that reduce sensitivity to SN-38, and (3) over-expression of the transporter ABCG2 that causes SN-38 efflux from tumor cells.

(1) Mutations of *TROP2* that reduce SG internalization could confer resistance because of the reduced intracellular SN-38 available for TOP1 inhibition or bystander effects. Indeed, Coates et al. recently reported that two of three tumors analyzed from a patient with acquired SG resistance emanated from either lowered expression or mutated *TROP2* that reduced binding to hRS7 [20]. When the isolated *TROP2*^{T256R} mutant was reconstituted in TNBC or 3T3 cells it retained SG resistance but had no change in free SN-38 sensitivity.

How does one reconcile the fact that cell uptake of SG requires TROP2 with the finding that the level of TROP2 expression on tumor did not impact efficacy in the TROPiCS-02 trial [6]. Clearly, some level of TROP2 is necessary for SG efficacy since TROP2 absence or very low levels causes resistance [20]. One possibility is that the levels of TROP2 required for efficacy were already present in tumors assessed by H-score as "low" TROP2, so no stratification of clinical efficacy with TROP2 was observed. Another possibility is that retained efficacy of SG in low TROP2 tumors is due to released free SN-38 rather than the intact ADC. If the latter is correct, the potential superior prodrug properties of PLX038 versus SG might successfully treat patients with resistant tumors that have low or mutated TROP2.

(2) Mutations of the TOP1 target of SN-38 could also confer resistance to SG. SN-38 resistant mutations of TOP1 are well known [21, 22], and a *TOP1*^{E418K} somatic mutation of the TOP1 gene has been demonstrated in acquired SG -resistance [20]. A SN-38 resistant TOP1 would not be expected to respond to a conventional prodrug of SN-38 such as PLX038.

(3) Tumors frequently acquire resistance to TOP1 inhibitors by overexpression of the efflux transporter ABCG2, and inhibitors of this protein increase the efficacy of SG in resistant tumors [23]. The PEG~SN-38 prodrug ENZ-2208 overcomes ABCG2 resistance by accumulation in tumors by the EPR effect [24], after which the high local release and influx of SN-38 counteracts the efflux pump. The accumulation of ENZ-2203 is due to the 15 nm PEG nanomolecule carrier, which is the same in PLX038, so PLX038 should likewise overcome SN-38 resistance due to overexpression of ABCG2.

Taken together, we posit that PLX038 would not be effective in tumors resistant to SG because of SN-38-resistant *TOP1* mutations, but may be in tumors with TROP2 defects or that overexpress drug efflux transporters. Hence, pre-treatment biopsies could identify mechanisms of resistance that might project efficacy or resistance to PLX038; if so, the information might ultimately lead to biomarker-defined patient selection.

3 Summary

It is confounding how a TROP2-mediated mechanism for SG can account for efficacy when there is no close correlation between TROP2 levels and efficacy; however, for a drug as important as SG, efficacy trumps understanding. We take a contrary view that an ADC mechanism may not be the only driver of SG efficacy and that systemic release of SN-38 plays an important role in efficacy and toxicity. The very high and long TROP2 occupancy by the released hRS7 that competes with the SN-38-conjugated SG also advocates a weakened conventional ADC mechanism. We believe PLX038 might provide rescue therapy for SG failures in two ways. First, assuming free systemic SN-38 is a major contributor to anti-tumor effects, we posit that PLX038 should be more efficacious as a SN-38 prodrug. Second, we suggest that PLX038 might overcome SG resistance in subsets of patients where resistance is due to a quantitative or qualitative defect in TROP2. Finally, as with a related PEG~SN-38 nanomolecule, tumor accumulation of the prodrug and high SN-38 influx may counteract resistance by efflux pumps. Hence, we posit that PLX038 could be effective in some SG-resistant tumors.

To be clear, we are not in any way suggesting that PLX038 is superior to SG as an anticancer agent. We do opine that SG acts as both an antigen-specific ADC and as an antigen-independent prodrug of high levels of systemic SN-38. And, that the amount of systemic SN-38 spontaneously hydrolyzed from the ADC is so high it must have activity. We also assert that PLX038 is superior as a prodrug of SN-38 and, to the extent that systemic SN-38 contributes to efficacy, PLX038 could provide significant benefit. Finally, we posit that PLX038 might overcome some, but not all, mechanisms of SG resistance.

Declarations

Funding No external funding was used in the preparation of this work.

Conflicts of interests DVS and GWA are co-founders of Prolynx, which is developing PLX038. LC and FCB will act as investigators in a clinical trial of PLX038, but have no financial interests in Prolynx. The authors have no other conflicts of interest to declare.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors' contributions DVS, GWA, LC, and F-CB all contributed to the concepts and conclusions described here. DVS did the initial writing of the commentary.

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References

1. Goldenberg DM, Sharkey RM. Sacituzumab govitecan, a novel, third-generation, antibody-drug conjugate (ADC) for cancer therapy. Expert Opin Biol Ther. 2020;208:871–85.
2. Ocean AJ, Starodub AN, Bardia A, Vahdat LT, et al. Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: Safety and pharmacokinetics. Cancer. 2017;12319:3843–54.
3. Santi D, Cabel L, Bidard F-C. Does sacituzumab-govitecan act as a conventional antibody drug. Ann Transl Med. 2021:2–3.
4. Bardia A, Hurvitz SA, Tolaney SM, Loirat D, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med. 2021;38416:1529–41.
5. Rugo HS, Bardia A, Marme F, Cortes J, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023. https://doi.org/10.1016/S0140-6736(23)01245-X.
6. Rugo H, Bardia A, Marmé F, Cortés J, et al. Sacituzumab govitecan (SG) vs treatment of physician's choice (TPC): efficacy by trop-2 expression in the TROPiCS-02 study of patients (Pts) with HR+/HER2– metastatic breast cancer (mBC) San Antonio breast cancer symposium; San Antonio, TX2022.
7. Bussing D, Sharma S, Li Z, Meyer LF, Shah DK. Quantitative evaluation of the effect of antigen expression level on antibody-drug conjugate exposure in solid tumor. AAPS J. 2021;233:56.
8. Cardillo TM, Govindan SV, Sharkey RM, Trisal P, Goldenberg DM. Humanized anti-Trop-2 IgG-SN-38 conjugate for effective treatment of diverse epithelial cancers: preclinical studies in human cancer xenograft models and monkeys. Clin Cancer Res. 2011;1710:3157–69.
9. Pommier Y, Marchand C. Interfacial inhibitors: targeting macromolecular complexes. Nat Rev Drug Discov. 2011;111:25–36.
10. Ma MK, Zamboni WC, Radomski KM, Furman WL, et al. Pharmacokinetics of irinotecan and its metabolites SN-38 and APC in children with recurrent solid tumors after protracted low-dose irinotecan. Clin Cancer Res. 2000;63:813–9.
11. Thompson PA, Gupta M, Rosner GL, Yu A, et al. Pharmacokinetics of irinotecan and its metabolites in pediatric cancer patients: a report from the children's oncology group. Cancer Chemother Pharmacol. 2008;626:1027–37.
12. Kalra AV, Kim J, Klinz SG, Paz N, et al. Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor prodrug conversion. Cancer Res. 2014;7423:7003–13.
13. Adiwijaya BS, Kim J, Lang I, Csoszi T, et al. Population pharmacokinetics of liposomal irinotecan in patients with cancer. Clin Pharmacol Ther. 2017;1026:997–1005.
14. Santi DV, Schneider EL, Ashley GW. Macromolecular prodrug that provides the irinotecan (CPT-11) active-metabolite SN-38 with ultralong half-life, low C(max), and low glucuronide formation. J Med Chem. 2014;576:2303–14.
15. Thomas A, Fontaine SD, Diolaiti ME, Desai P, et al. PLX038: a long-acting topoisomerase i inhibitor with robust antitumor activity in ATM-deficient tumors and potent synergy with PARP inhibitors. Mol Cancer Ther. 2022;2111:1722–8.
16. Fontaine SD, Hann B, Reid R, Ashley GW, Santi DV. Species-specific optimization of PEG~SN-38 prodrug pharmacokinetics and antitumor effects in a triple-negative BRCA1-deficient xenograft. Cancer Chemother Pharmacol. 2019;844:729–38.
17. Beckford Vera DR, Fontaine SD, VanBrocklin HF, Hearn BR, et al. PET imaging of the EPR effect in tumor xenografts using small 15 nm diameter polyethylene glycols labeled with zirconium-89. Mol Cancer Ther. 2020;192:673–9.
18. Ghilu S, Li Q, Fontaine SD, Santi DV, et al. Prospective use of the single-mouse experimental design for the evaluation of PLX038A. Cancer Chemother Pharmacol. 2020;852:251–63.
19. Barbier S, Beaufils B, de Miguel R, Reyre M, et al. Liposomal irinotecan shows a larger therapeutic index than non-liposomal irinotecan in patient-derived xenograft models of pancreatic cancer. Oncol Ther. 2023;111:111–28.
20. Coates JT, Sun S, Leshchiner I, Thimmiah N, et al. Parallel genomic alterations of antigen and payload targets mediate polyclonal acquired clinical resistance to sacituzumab govitecan in triple-negative breast cancer. Cancer Discov. 2021;1110:2436–45.
21. Gongora C, Vezzio-Vie N, Tuduri S, Denis V, et al. New topoisomerase I mutations are associated with resistance to camptothecin. Mol Cancer. 2011;10:64.
22. Jensen NF, Agama K, Roy A, Smith DH, et al. Characterization of DNA topoisomerase I in three SN-38 resistant human colon cancer cell lines reveals a new pair of resistance-associated mutations. J Exp Clin Cancer Res. 2016;35:56.
23. Chang CH, Wang Y, Zalath M, Liu D, Cardillo TM, Goldenberg DM. Combining ABCG2 inhibitors with IMMU-132, an anti-trop-2 antibody conjugate of SN-38, overcomes resistance to SN-38 in breast and gastric cancers. Mol Cancer Ther. 2016;158:1910–9.
24. Zander SA, Sol W, Greenberger L, Zhang Y, et al. EZN-2208 (PEG-SN38) overcomes ABCG2-mediated topotecan resistance in BRCA1-deficient mouse mammary tumors. PLoS ONE. 2012;79: e45248.