Comparable Pharmacokinetics and Immunogenicity of Sacituzumab Govitecan Between Patients With Metastatic Urothelial Cancer and Metastatic Triple-Negative Breast Cancer

Ya-Feng Wen[1], Anees M Dauki[1], Abhishek G Sathe[1], KahHiing John Ling[1], Ahmed A Othman[1]*

[1]Clinical Pharmacology Sciences, Gilead Sciences, Inc, Foster City, CA, USA
*Affiliation at the time of the study.

Poster 156
ASCENT
TROPHY U-01

Conclusions

- No clinically relevant PK differences were observed between patients with mUC and patients with mTNBC following administration of SG 10 mg/kg on days 1 and 8 of every 21-day cycle
- Population PK analyses across the mUC and mTNBC populations are underway to further characterize the PK of SG and its components and assess the impact of covariates on serum exposure
- In patients with mUC and mTNBC, the prevalence and incidence of anti-SG antibodies were low. With the limited available data, no clear impact of anti-SG antibodies on SG or total antibody concentrations was observed

Plain Language Summary

- There were no significant differences in how the drug was processed in the bodies of patients with metastatic urothelial cancer (mUC) and patients with metastatic triple-negative breast cancer (mTNBC) using the approved sacituzumab govitecan regimen
- Further studies are needed to understand if other factors affect how the drug is processed in patients with mUC and mTNBC
- Only a few patients developed antibodies against the study drug, and these antibodies did not affect the amount of the drug in blood

References: **1.** Trodelvy (sacituzumab govitecan-hziy) [prescribing information] Gilead Sciences, Inc., Foster City, CA; 2023. **2.** Tagawa ST, et al. *J Clin Oncol*. 2021;39:2474-85. **3.** Bardia A, et al. *N Engl J Med*. 2021;384:1529-41. **4.** Sathe AG, et al. *Clin Pharmacokinet*. 2024;63:669-81.

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Correspondence: Ya-Feng Wen, jay.wen3@gilead.com

Introduction

- Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) composed of an anti–Trop-2 antibody coupled to the potent SN-38 payload via a proprietary, hydrolyzable CL2A linker
- It is approved in multiple countries for patients with metastatic triple-negative breast cancer (mTNBC) who had received at least 2 prior chemotherapies (≥ 1 for metastatic disease), pretreated HR+/HER2– metastatic BC, and has accelerated approval in the US for patients with locally advanced or metastatic urothelial cancer (mUC) who had previously received a platinum-containing chemotherapy and immune checkpoint inhibitor[1]

Objectives

- Recognizing patient characteristics differ between mUC and mTNBC, we evaluated pharmacokinetics (PK) of SG (ADC), total antibody (hRS7 unconjugated or conjugated with SN-38), and free SN-38 (payload), as well as immunogenicity in the form of antidrug antibodies (ADA) following SG administration in these 2 patient populations

Methods

Study Design

- TROPHY U-01 (NCT03547973) was a multicenter, open-label phase 2 study conducted in patients with unresectable locally advanced/mUC[2]
- ASCENT (NCT02574455) was a multicenter, open-label, randomized phase 3 study conducted in patients with mTNBC who had received at least 2 prior chemotherapies[3]
- All patients in TROPHY U-01 and ASCENT received approved starting dose of 10 mg/kg SG on days 1 and 8 of every 21-day cycle

Pharmacokinetic Analyses

- Concentration-time data from patients who received ≥ 1 dose of SG and had intensive PK samples collected were analyzed using noncompartmental methods (Phoenix® WinNonlin version 8.2, Pharsight, Cary, NC)
- Serum samples for PK analyses were collected at pre-dose, 1 to 2 minutes prior to the end of the first infusion, and 0.5, 4, 24, 48, 72, and 168 hours after the first infusion in a subset of patients who received ≥ 1 dose of SG
- Separate validated liquid chromatography-tandem mass spectrometry methods were developed to measure concentrations of free SN-38 and total SN-38 to estimate the bound SN-38[4]
- A validated sandwich electrochemiluminescence (ECL) immunoassay was used to quantify total antibody concentrations. Four concentrations of SG were calculated from bound SN-38 concentrations assuming a drug-to-antibody ratio of 8[4]

Immunogenicity Analyses

- Patients from both studies who received at least 1 dose of SG and had at least 1 nonmissing reportable ADA test result were included in the immunogenicity analysis. An ECL-based immunoassay was utilized to test for anti-SG antibodies using a 3-tier approach: screen, confirm, and titer. Neutralizing activity of the ADA (NAb) against SG were evaluated using a separate ligand-binding ECL assay method

Results

- Baseline characteristics of patients who received SG and those with intensive PK samples collected in TROPHY U-01 and ASCENT study are summarized in **Table 1**

Table 1. Baseline Characteristics of Patients Who Received SG From TROPHY U-01 (mUC) and ASCENT (mTNBC) Studies

	mUC		mTNBC	
	Intensive PK (n = 11)	All (N = 148)	Intensive PK (n = 29)	All (N = 258)
Female, n (%)	1 (9.1)	40 (27.0)	28 (96.6)	256 (99.2)
Race, n (%)				
White	9 (81.8)	112 (75.7)	20 (69.0)	211 (81.8)
Black or African American	1 (9.1)	4 (2.7)	4 (13.8)	25 (9.7)
Asian	0	3 (2.0)	2 (6.9)	11 (4.3)
Other	1 (9.1)	29 (19.6)	3 (10.3)	11 (4.3)
Age (years), mean (SD)	59.4 (11.8)	71.3 (10.6)	53.8 (11.5)	54.1 (54.1)
Weight (kg), mean (SD)	82.0 (16.9)	76.3 (15.5)	74.0 (20.9)	71.6 (17.8)

mTNBC, metastatic triple-negative breast cancer; mUC, metastatic urothelial cancer; PK, pharmacokinetics.

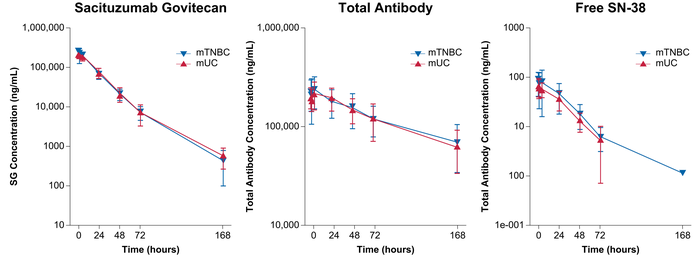
- Data from 11 (of 148) and 29 (of 258) patients with intensive PK collection were included in the PK analyses for TROPHY U-01 and ASCENT, respectively, but the number of patients with enough data points to calculate the different parameters varied
- The estimated PK parameters for SG, total antibody, and free SN-38 in patients with mUC and mTNBC are shown in **Table 2**. Serum concentration-time profiles for SG, total antibody, and free SN-38 are shown in **Figure 1**
- The estimated mean clearance (CL) and volume of distribution (V_{ss}) for SG were 0.147 L/hr and 2.84 L, respectively, in patients with mUC, and closely aligned with 0.134 L/hr and 2.65 L, respectively, in patients with mTNBC
- In the mUC and mTNBC studies, 4 (3.0%) of 133 and 4 (1.6%) of 258 patients, respectively, developed antibodies to SG (**Table 3**) with no discernible impact on SG serum exposures (data not shown)
- Patients with mUC appeared to have lower maximum observed serum concentration (C_{max}) and area under the serum concentration-time curve from time 0 to 168 hours ($AUC_{0\text{-}168hr}$) of free SN-38 compared with patients with mTNBC (**Table 4**), but values were generally within the PK variability

Table 2. PK Parameters and Summary Statistics for SG Stratified by Analyte for the 10 mg/kg Dose in Patients With mUC and mTNBC

PK Parameter	Sacituzumab Govitecan		Total Antibody		Free SN-38	
Tumor Type	mUC (n = 11)	mTNBC (n = 29)	mUC (n = 11)	mTNBC (n = 29)	mUC (n = 11)	mTNBC (n = 29)
T_{max} (hr)	3.58 [1.58, 20.5]	3.10 [1.23, 5.40]	5.55 [2.98, 27.6]	3.95 [1.23, 51.6]	4.53 [2.98, 20.5]	3.25 [1.23, 6.30]
C_{max} (ng/mL)	213,000 (26.9%)	242,000 (21.8%)	229,000 (23.6%)	261,000 (30.4%)	69.0 (39.7%)	94.9 (69.8%)
$AUC_{0\text{-}168hr}$ (ng•hr/mL)	5,500,000 (27.3%)[a]	5,560,000 (23.5%)[b]	21,100,000 (32.3%)[a]	21,300,000 (29.3%)	1970 (36.6%)[a]	2740 (41.3%)

Not all PK parameters of a given analyte could be robustly estimated for enrolled participants with intensive PK samples. Data are presented as mean (CV%) for C_{max} and $AUC_{0\text{-}168hr}$ and median [range] for T_{max}.
[a]10, 9, and 8 evaluable patients with mUC for $AUC_{0\text{-}168hr}$ of sacituzumab govitecan, total antibody, and free SN-38, respectively.
[b]28 patients with mTNBC for $AUC_{0\text{-}168}$ of sacituzumab govitecan.
$AUC_{0\text{-}168hr}$, area under the serum concentration-time curve from time 0 to 168 hours; C_{max}, maximum observed serum concentration; CV, coefficient of variation; mTNBC, metastatic triple-negative breast cancer; mUC, metastatic urothelial cancer; PK, pharmacokinetics; T_{max}, time to reach the maximum observed serum concentration.

Figure 1. Mean (±SD) Serum Concentration-Time Profiles in Patients With mUC and mTNBC



Values BLQ were treated as 0 for predose and postdose time points for summary purpose. Postdose concentration values ≤ LLOQ are not presented on the figure.
LLOQ was defined as 374 ng/mL for total antibody, 1 ng/mL for free SN-38.
BLQ, below the lower limits of quantification; LLOQ, lower limit of quantification; mTNBC, metastatic triple-negative breast cancer; mUC, metastatic urothelial cancer; SG, sacituzumab govitecan.

Table 3. Anti-SG Antibodies Prevalence and Incidence in Patients With mUC and mTNBC

	mUC	mTNBC	Total
ADA prevalence	4/133 (**3.0%**)	4/258 (**1.6%**)	8/391 (**2.0%**)
ADA incidence (treatment emergent)	4/109 (**3.7%**)	4/242 (**1.7%**)	8/351 (**2.3%**)
NAb incidence (treatment emergent)	2/109 (**1.8%**)	3/242 (**1.2%**)	5/351 (**1.4%**)

Evaluable for ADA prevalence population includes participants who have at least 1 nonmissing reportable ADA result.
Evaluable for ADA incidence population includes participants who have at least 1 nonmissing postbaseline ADA result.
ADA, anti-drug (SG) antibody; mTNBC, metastatic triple-negative breast cancer; mUC, metastatic urothelial cancer; NAb, neutralizing antibody.

Table 4. Differences in PK Parameters Between Patients With mUC and mTNBC

PK Parameter	Sacituzumab Govitecan	Total Antibody	Free SN-38
C_{max} (ng/mL)	-12.0%	-12.3%	-27.3%
$AUC_{0\text{-}168hr}$ (ng•hr/mL)	-1.1%	-0.9%	-28.1%

Differences compared the percentage changes in PK parameters between patients with mUC and patients with mTNBC using the mTNBC PK parameters as reference.
$AUC_{0\text{-}168hr}$, area under the serum concentration-time curve from time 0 to 168 hours; C_{max}, maximum observed serum concentration; mTNBC, metastatic triple-negative breast cancer; mUC, metastatic urothelial cancer; PK, pharmacokinetic.

Discussion

- The PK of SG and total antibody are similar between patients with mUC and patients with mTNBC, supported by the similar PK parameters, including CL (SG only), V_{ss} (SG only), T_{max}, C_{max}, and $AUC_{0\text{-}168hr}$
- The lower free-SN38 exposure in patients with mUC compared with patients with mTNBC in the 2 studies could be attributed in part to the different sample processing because the release of free SN-38 from SG is sensitive to the duration of clot formation at ambient temperature. Improved sample handling in TROPHY U-01 resulted in lower free SN-38 seen in the patients with mUC