Pharmacokinetics of Sacituzumab Govitecan in Japanese Patients With Advanced Solid Tumors

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Poster 154

ASCENT-J02

ASCENT

Conclusions

- Serum SG and total antibody exposures in Japanese patients with advanced solid tumors from the ASCENT-J02 study were comparable to those in non-Japanese patients with mTNBC from the ASCENT study with administration of the clinical regimen of 10 mg/kg on days 1 and 8 of 21-day cycles
- Furthermore, the safety and efficacy profiles were consistent between the 2 populations.[3] Therefore, no dose adjustments are warranted based on ethnicity

Plain Language Summary

- The pharmacokinetics (the way a drug moves through the body) of sacituzumab govitecan (SG), and its related components in Japanese patients receiving SG intravenously was characterized
- The amount of SG and its components found in the blood of Japanese patients who received SG was found to increase, as expected, related to the dose that they received (6 or 10 mg/kg)
- The average clearance rate for SG in patients with metastatic triple-negative breast cancer was 0.108 liters per hour
- The amount of SG and its components in Japanese patients from the ASCENT-J02 study were similar to those in non-Japanese patients with metastatic triple-negative breast cancer from the ASCENT study

References: **1.** Trodelvy (sacituzumab govitecan-hziy) [prescribing information] Gilead Sciences, Inc., Foster City, CA; 2023. **2.** Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-41. doi: 10.1056/NEJMoa2028485. **3.** Kogawa T, et al. Presented at the 61st Annual Meeting of the Japan Society of Clinical Oncology. October 20, 2023. **4.** Sathe AG, et al. *Clin Pharmacokinet*. 2024;64:669-81. https://doi.org/10.1007/s40262-024-01366-3

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Introduction

- Sacituzumab govitecan (SG) is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to a potent SN-38 payload
- Free SN-38, the payload of SG, is mainly metabolized by *UGT1A1*
- SG was first approved in the United States for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) and hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer who have received 2 or more prior systemic therapies, including at least 1 of them for advanced disease[1]
- In the phase 3 ASCENT study (NCT02574455), SG showed significant clinical benefit vs physician's choice chemotherapy in patients with locally advanced unresectable or metastatic TNBC[2]
- ASCENT-J02 (NCT05101096) is an open-label, sequential dose-escalation, and dose-expansion study to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of SG in Japanese patients with advanced solid tumors[3]
  - The tolerability of SG 10 mg/kg in Japanese patients was consistent with the known safety profiles, with no new safety concerns

Objectives

- To evaluate the PK of SG in Japanese patients with advanced solid tumors
- To compare the PK of SG in Japanese and non-Japanese patients with advanced solid tumors based on noncompartmental analyses

Methods

Study Design

- The ASCENT-J02 phase 1 study was conducted using a 3 + 3 dose-escalation design, in which patients received SG doses starting at 6 mg/kg, with subsequent escalation to 10 mg/kg. Patients with *UGT1A1* wild type (*UGT1A1*-normal metabolizer) enrolled in cohort A first, followed by cohort B consisting of patients who were heterozygous or homozygous for *UGT1A1*28* or *UGT1A1*6* (*UGT1A1*-poor metabolizer)
- All patients received SG via intravenous infusion on days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity

Pharmacokinetics Analyses

- Serum samples for intensive PK analyses were collected during phase 1 at predose, end of infusion, 9, 24, 48, 72, and 168 hours relative to the start of the first infusion
- Serum concentration data for total SN-38 and free SN-38 were generated from serum samples using separate validated liquid chromatography–tandem mass spectrometry methods, whereas a validated sandwich electrochemiluminescence immunoassay was used to quantify total antibody (hRS7 unconjugated or conjugated with SN-38) concentrations. Serum concentrations of SG were calculated from bound SN-38 concentrations assuming a drug-to-antibody ratio of 8
- PK data from patients who received ≥ 1 dose of SG and had intensive PK assessments were analyzed using noncompartmental methods (Phoenix® WinNonlin version 8.2, Pharsight, Cary, NC)

Table 1. Baseline Characteristics of Patients With Advanced Solid Tumors in ASCENT-J02 (Japanese) and Patients With mTNBC in ASCENT (Non-Japanese) Who Received SG 10 mg/kg

Characteristics	ASCENT-J02 (N = 15)	ASCENT (N = 29)
Female	11 (73.3%)	28 (96.6%)
Race		
White	0 (0.0%)	20 (69.0%)
African American	0 (0.0%)	4 (13.8%)
Asian	15 (100.0%)	2 (6.9%)
Other	0 (0.0%)	3 (10.3%)
Age (years)	51 (11.3)	53.8 (11.5)
Weight (kg)	57.6 (13.56)	74.0 (20.9)

Data are presented as mean (SD) for continuous variables and count (percentage) for categorical variables.
mTNBC, metastatic triple-negative breast cancer; SG, sacituzumab govitecan.

Data and Results

- Baseline characteristics of patients receiving SG 10 mg/kg in the ASCENT-J02 and ASCENT studies are presented in **Table 1**
- All patients in phase 1 of ASCENT-J02 who received SG 6 mg/kg (n = 6) or 10 mg/kg (n = 9) were included in the noncompartmental analyses for SG, total antibody, and free SN-38. A total of 29 (of 258) patients with intensive PK collection in the ASCENT study were included in PK analyses. Results from the noncompartmental analyses for ASCENT-J02 are presented in **Table 2**
- At the SG 10 mg/kg dose level, total antibody, SG, and free SN-38 had a median serum elimination half life of approximately 112, 23, and 19 hours, respectively. The estimated mean clearance and the volume of distribution at steady state of SG were 0.108 L/h and 2.26 L, respectively. The increase in SG, total antibody, and free SN-38 exposures was dose proportional across the evaluated dose range in Japanese patients with advanced solid tumors **(Table 2)**

Table 2. PK Parameters for SG, Total Antibody, and Free SN-38 After First SG 6 mg/kg or 10 mg/kg Dose in Japanese Patients (ASCENT-J02)

PK Parameter	Sacituzumab Govitecan		Total Antibody		Free SN-38	
SG Dose	**6 mg/kg (n = 6)**	**10 mg/kg (n = 9)**	**6 mg/kg (n = 6)**	**10 mg/kg (n = 9)**	**6 mg/kg (n = 6)**	**10 mg/kg (n = 9)**
T_{max} (hours)	3.19 [2.95-3.40]	3.30 [3.05-3.45]	3.28 [3.03-8.67]	8.50 [3.20- 9.07]	3.32 [3.03-8.77]	3.43 [3.05-8.93]
C_{max} (ng/mL)	136,000 (10%)	228,000 (14%)	119,000 (14%)	233,000 (26%)	29.2 (19%)	44.4 (28%)
$AUC_{0\text{-}168hr}$ (ng•h/mL)	3,460,000 (13%)	5,360,000 (12%)	12,000,000 (15%)	19,600,000 (23%)	1050 (22%)	1660 (25%)
$t_{1/2}$ (hours)	23.8 [22.8-25.4]	22.6 [13.4-24.4]	120 [84.4-131]	112 [54.4-130]	21.0 [16.5-24.1]	19.4 [14.8-25.5]

Data are presented as mean (CV%) for C_{max} and $AUC_{0\text{-}168h}$ and median [range] for T_{max} and $t_{1/2}$.
Not all PK parameters of a given analyte could be robustly estimated for enrolled patients with intensive PK samples.
$AUC_{0\text{-}168hr}$, area under the serum concentration-time curve from time 0 to 168 hours; C_{max}, maximum observed serum concentration; CV, coefficient of variation; PK, pharmacokinetics; SG, sacituzumab govitecan; $T_{1/2}$, elimination half life; T_{max}, time to reach the maximum observed serum concentration.

- Overall, based on the noncompartmental analyses presented in **Table 3** for the ASCENT-J02 and ASCENT studies, SG and total antibody serum exposures in Japanese patients from the ASCENT-J02 study (SG 10 mg/kg) are comparable to those in non-Japanese patients from the ASCENT study (SG 10 mg/kg). While observed free SN-38 serum exposures in Japanese patients were lower on average, free SN-38 exposures were mostly within the range of observed free SN-38 exposures in non-Japanese patients from the ASCENT study[4]

Table 3. PK Parameters for SG, Total Antibody, and Free SN-38 After First SG 10 mg/kg Dose in Japanese Patients (ASCENT-J02) Relative to Non-Japanese Patients (ASCENT)

PK Parameter	Sacituzumab Govitecan		Total Antibody		Free SN-38	
Study	**ASCENT (n = 29)**	**ASCENT-J02 (n = 15)**	**ASCENT (n = 29)**	**ASCENT-J02 (n = 15)**	**ASCENT (n = 29)**	**ASCENT-J02 (n = 15)**
T_{max} (hours)	3.10 [1.23-5.40]	3.30 [3.05-3.45]	3.95 [1.23-51.6]	8.50 [3.20-9.07]	3.25 [1.23-6.30]	3.43 [3.05-8.93]
C_{max} (ng/mL)	242,000 (22%) [151,000-346,000]	228,000 (14%) [194,000-302,000]	261,000 (30%) [156,000-510,000]	233,000 (26%) [141,000-359,000]	94.9 (70%) [35.8-368]	44.4 (28%) [25.8-68.0]
$AUC_{0\text{-}168hr}$ (ng•h/mL)	5,560,000 (23%) [3,330,000-8,660,000]	5,360,000 (12%) [4,540,000-6,280,000]	21,300,000 (29%) [9,950,000-32,800,000]	19,600,000 (23%) [15,200,000-27,800,000]	2740 (41%) [1280-6700]	1660 (25%) [1000-2320]

Data are presented as mean (CV%) for C_{max} and $AUC_{0\text{-}168h}$ and median [range] for T_{max}.
Not all PK parameters of a given analyte could be robustly estimated for enrolled patients with intensive PK samples.
$AUC_{0\text{-}168hr}$, area under the serum concentration-time curve from time 0 to 168 hours; C_{max}, maximum observed serum concentration; CV, coefficient of variation; PK, pharmacokinetics; SG, sacituzumab govitecan; T_{max}, time to reach the maximum observed serum concentration.

- Serum PK parameters following administration of SG are summarized by *UGT1A1* phenotype in **Table 4.** SG, total antibody, and free SN-38 serum exposures were comparable between Japanese patients who are *UGT1A1*-poor metabolizer and Japanese patients who are *UGT1A1*-normal metabolizer

Table 4. PK Parameters for SG, Total Antibody, and Free SN-38 After First SG 10 mg/kg Dose in Japanese Patients (ASCENT-J02) by *UGT1A1* Phenotype

PK Parameter	Sacituzumab Govitecan		Total Antibody		Free SN-38	
***UGT1A1* phenotype**	**Normal metabolizer (n = 6)**	**Poor metabolizer (n = 3)**	**Normal metabolizer (n = 6)**	**Poor metabolizer (n = 3)**	**Normal metabolizer (n = 6)**	**Poor metabolizer (n = 3)**
T_{max} (hours)	3.30 [3.05-3.45]	3.40 [3.2-3.43]	8.70 [3.3-9.07]	3.43 [3.20-8.67]	3.38 [3.05-8.93]	3.43 [3.20-8.67]
C_{max} (ng/mL)	218,000 (9%)	249,000 (20%)	220,000 (22%)	259,000 (34%)	39.4 (25%)	54.5 (22%)
$AUC_{0\text{-}168hr}$ (ng•h/mL)	5,350,000 (11%)	5,390,000 (16%)	20,000,000 (23%)	18,800,000 (26%)	1450 (21%)	2070 (12%)
$t^{1/2}$ (hours)	23.6 [13.4-24.4]	14.6 [13.4-22.6]	112 [54.4-130]	80.3 [77.0-114]	19.6 [14.8-22.4]	18.5 [16.5-25.5]

Data are presented as mean (CV%) for C_{max} and $AUC_{0\text{-}168h}$ and median [range] for T_{max}.
Not all PK parameters of a given analyte could be robustly estimated for enrolled patients with intensive PK samples.
$AUC_{0\text{-}168hr}$, area under the serum concentration-time curve from time 0 to 168 hours; C_{max}, maximum observed serum concentration; CV, coefficient of variation; PK, pharmacokinetics; SG, sacituzumab govitecan; T_{max}, time to reach the maximum observed serum concentration.