GILEAD | Medical Information

Trodelvy® (sacituzumab govitecan-hziy) Impact of UGT1A1 Status on Safety Profile in Patients With mBC

This document is in response to your request for information regarding the impact of uridine diphosphate glucuronosyl transferase family 1 member A1 (UGT1A1) status on the safety profile of Trodelvy® (sacituzumab govitecan-hziy [SG]) in patients with metastatic breast cancer (mBC).

Gilead continually assesses safety data from all sources for unidentified drug reactions and updates the product label information accordingly to reflect the safety profile of SG. Because case reports of potential adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. For this reason, Gilead does not provide information from post-marketing spontaneous reports.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings for neutropenia and diarrhea are available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Summary

Relevant Product Labeling[1]

Do NOT substitute SG for or use with other drugs containing irinotecan or its active metabolite SN-38.

Warnings and Precautions: Neutropenia

Neutropenia occurred earlier in patients with reduced UGT1A1 activity.

Primary prophylaxis with G-CSF is recommended starting in the first cycle of treatment in all patients at increased risk of febrile neutropenia, including older patients, patients with previous neutropenia, poor performance status, organ dysfunction, or multiple comorbidities.

Warnings and Precautions: Increased Risk of Adverse Reactions in Patients with Reduced *UGT1A1* Activity

Patients homozygous for the *UGT1A1*28* allele are at increased risk for neutropenia, febrile neutropenia, and anemia; and may be at increased risk for other adverse reactions when treated with SG.

The incidence of neutropenia and anemia was analyzed in 948 patients who received SG and had *UGT1A1* genotype results. In patients homozygous for the *UGT1A1*28* allele (n=112), the incidence of Grade 3 to 4 neutropenia was 58%. In patients heterozygous for the *UGT1A1*28* allele (n=420), the incidence of Grade 3 to 4 neutropenia was 49%. In

patients homozygous for the wild-type allele (n=416), the incidence of Grade 3 to 4 neutropenia was 43%. In patients homozygous for the *UGT1A1*28* allele, the incidence of Grade 3 to 4 anemia was 21%. In patients heterozygous for the *UGT1A1*28* allele, the incidence of Grade 3 to 4 anemia was 10%. In patients homozygous for the wild-type allele, the incidence of Grade 3 to 4 anemia was 9%.

The median time to first neutropenia including febrile neutropenia was 9 days in patients homozygous for the *UGT1A1*28* allele, 15 days in patients heterozygous for the *UGT1A1*28* allele, and 20 days in patients homozygous for the wild-type allele. The median time to first anemia was 21 days in patients homozygous for the *UGT1A1*28* allele, 25 days in patients heterozygous for the *UGT1A1*28* allele, and 28 days in patients homozygous for the wild-type allele.

Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue SG based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity.

Drug interactions: Effect of Other Drugs on SG

UGT1A1 Inhibitors

Concomitant administration of SG with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with SG.

UGT1A1 Inducers

Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with SG.

Pharmacokinetics

Metabolism

No metabolism studies with SG have been conducted. SN-38 (the small molecule moiety of SG) is metabolized via UGT1A1. The glucuronide metabolite of SN-38 (SN-38G) was detectable in the serum of patients.

Drug Interaction Studies

No drug-drug interaction studies were conducted with SG or its components. Inhibitors or inducers of UGT1A1 may increase or decrease SN-38 exposure, respectively.

Pharmacogenomics

SN-38 is metabolized via UGT1A1. Genetic variants of the *UGT1A1* gene such as the *UGT1A1*28* allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous or heterozygous for the *UGT1A1*28* allele are at increased risk for neutropenia, febrile neutropenia, and anemia from SG compared to individuals who are wildtype (**1/*1*). Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the *UGT1A1*28* allele (**28/*28*). Approximately 40% of the Black or African American population, 50% of the White population, and 25% of the East Asian population are heterozygous for the *UGT1A1*28* allele (**1/*28*). Decreased function alleles other than *UGT1A1*28* may be present in certain populations.

Clinical Data

In ASCENT,[2] in patients with metastatic triple-negative breast cancer (mTNBC), SG treated patients with the homozygous *UGT1A1* polymorphism *(*28/*28)* genotype (GT) vs those with heterozygous (*1/*28)* and wild-type (WT; **1/*1)* GTs had higher rates of Grade ≥3 treatment-related AEs (TRAEs), including neutropenia (59% vs 47% vs 53%), febrile neutropenia (18% vs 5% vs 3%), anemia (15% vs 6% vs 4%), and diarrhea (15% vs 9% vs 10%), respectively.[3]

In TROPiCS-02,[4] in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer (HR+/HER2- mBC), SG treated patients with the homozygous *UGT1A1* polymorphism *(*28/*28)* GT vs those with heterozygous (*1/*28)* and wild-type (WT; **1/*1)* GTs had higher rates of Grade ≥3 treatment-emergent AEs (TEAEs; 92% vs 75% vs 67%), Grade ≥3 neutropenia (64% vs 57% vs 45%), and Grade ≥3 diarrhea (24% vs 13% vs 6%), and higher rates of any-grade (but not Grade ≥3) anemia (48% vs 36% vs 33%), respectively.[5,6]

In IMMU-132-01, in patients with metastatic epithelial cancers (including patients with mTNBC and HR+/HER2- mBC), patients with the homozygous *UGT1A1*28* polymorphism (**28/*28*) had higher rates of neutropenia (61%) vs patients with the heterozygous *UGT1A1 (*1/*28;* 38%) or the WT (**1/*1;* 33%) alleles. Higher rates of diarrhea were also observed in the patients with the **28/*28* allele (61%) vs patients with the *1/*28 (*52%) or the WT (**1/*1;* 55%) alleles.[7]

A retrospective analysis of patients with metastatic and locally recurrent HER2-negative breast cancer (52 [76.5%] patients had TNBC) was conducted to evaluate the association between UGT1A1 status and safety in 68 patients who underwent GT testing for UGT1A1 alleles. An increased risk of discontinuation for toxicity was observed in patients homozygous for *UGT1A1*28* (Hazard ratio [HR] 5.52 [95% CI 1.15–26.49], *P*=0.03). No events of discontinuation for toxicity were observed in patients with a heterozygous GT (HR 0 [95% CI 0], *P*≤0.0001). However, 76% of patients with a *UGT1A1*28* homozygous GT either started on a lower dose, had a dose reduction, or were intolerant. Treatment alterations and discontinuations for intolerance were observed in 71% and 56% of patients in the heterozygous and WT groups, respectively.[8]

Clinical Data

ASCENT Study in mTNBC

ASCENT, a global, open-label, randomized, phase 3 study (N=529) investigated the efficacy and safety of SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle (n=267) vs treatment of physician's choice (TPC [n=262; eribulin, vinorelbine, gemcitabine, or capecitabine]) in patients with refractory or relapsed mTNBC who had received ≥2 prior chemotherapies for unresectable, locally advanced, or metastatic disease.[2] Patients in the SG arm received a median of 7 treatment cycles (range: 1–33), with a median treatment duration of 4.4 months (range: 0.03–22.9).[9]

An exploratory safety subgroup analysis of 243 SG treated patients with known UGT1A1 allele status at baseline (**1/*1*, n=113; **1/*28*, n=96; **28/*28*, n=34) was performed. The median SG relative dose intensity was 99.8%, 99.5%, and 99.8%, and mean time to first dose reduction was 2.7, 2.4, and 1.8 months in the**1/*1*, **1/*28*, and **28/*28* groups, respectively. Patients with the **28/*28* allele had a higher incidence of Grade ≥3 TRAEs, including neutropenia, febrile neutropenia, anemia, and diarrhea, vs patients with the **1/*1*

or **1/*28* alleles. The rate of treatment discontinuation due to TRAEs was greater among those with the**28/*28* (6%) GT vs those with the **1/*1* (2%) or **1/*28* (1%) alleles. TEAEs leading to dose reductions were greater among those with the **28/*28* (35%) GT vs those with the **1/*1* (18%) or **1/*28* (19%) GT. Further detail can be found in Table 1.[3]

Table 1. ASCENT: Key TRAEs by UGT1A1 GT[3]

TRAEs, n (%)		SG (n=243)[a]					
		**1/*1* (n=113)		**1/*28* (n=96)		**28/*28* (n=34)	
		All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic	Neutropenia[b]	76 (67)	60 (53)	55 (57)	45 (47)	24 (71)	20 (59)
	Anemia[c]	37 (33)	5 (4)	29 (30)	6 (6)	16 (47)	5 (15)
	Leukopenia[d]	18 (16)	10 (9)	13 (14)	9 (9)	8 (24)	5 (15)
	Lymphopenia[e]	10 (9)	1 (1)	5 (5)	1 (1)	4 (12)	2 (6)
	Febrile neutropenia	3 (3)	3 (3)	5 (5)	5 (5)	6 (18)	6 (18)
	Thrombocytopenia[f]	3 (3)	0	6 (6)	0	4 (12)	4 (12)
GI	Diarrhea	65 (58)	11 (10)	57 (59)	9 (9)	21 (62)	5 (15)

Note: Patients could have reported ≥1 TRAE per preferred term. Abbreviation: GI=gastrointestinal
[a]Patients with UGT1A1 GT in the safety population of the SG arm. UGT1A1 GTs were not listed for 7 patients.
[b]Neutropenia and decreased neutrophil count were combined.
[c]Anemia, and decreased hemoglobin were combined.
[d]Leukopenia and decreased WBC count were combined.
[e]Lymphopenia and decreased lymphocyte count were combined.
[f]Thrombocytopenia and decreased platelet count were combined.

TROPiCS-02 Study in HR+/HER2- mBC

A phase 3, open-label, randomized, multicenter study compared the safety and efficacy of SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle with TPC (eribulin, vinorelbine, capecitabine, or gemcitabine) in 543 patients with HR+/HER2- mBC who received ≥2 and ≤4 prior chemotherapy regimens for metastatic disease, including ≥1 endocrine therapy, taxane and cyclin-dependent kinase 4/6 inhibitor therapy in any setting. In the overall safety population (OSP; n=517), patients received a mean of 8.2 SG cycles (range: 1–35) over a median (range) duration of 4.1 months (0.03–24.2).[4]

An exploratory safety analysis by UGT1A1 GT status was conducted in patients treated with SG; 38% had WT (**1/*1*; n=103), 44% had heterozygous (**1/*28*; n=119) and 9% had homozygous (**28/*28*; n=25) *UGT1A1* GT. Three patients (1%) treated with SG had other GTs, one each of **1/*36*, **1/*37*, and **28/*36*.[5,6] Median relative dose intensity (cumulative dosage received divided by total assigned dosage) was 99%, 98%, and 94% for patients with WT (**1/*1*), heterozygous (**1/*28*), and homozygous (**28/*28)* UGT1A1 GTs, respectively and the median duration of exposure was 3.9, 4.8, and 2.8 months, respectively.[10] Patients with homozygous (**28/*28* allele) GT had higher rates of Grade ≥3 TEAEs and TEAEs leading to discontinuation vs patients with WT (**1/*1*) or heterozygous (**1/*28*) GT. Patients with heterozygous (**1/*28*) or homozygous (**28/*28* allele) GT had higher rates of TEAEs leading to dose reduction vs those with WT (**1/*1*) GT. Further detail can be found in Table 2.[5,6]

Table 2. TROPiCS-02: TEAEs by UGT1A1 GT[5,6]

TEAEs, n (%)	SG (n=268)					
	**1/*1* (n=103)		**1/*28* (n=119)		**28/*28* (n=25)	
	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
All TEAEs	103 (100)	69 (67)	119 (100)	89 (75)	25 (100)	23 (92)
That led to dose reduction	26 (25)	NR	49 (41)	NR	10 (40)	NR
That led to treatment interruption	70 (68)	NR	76 (64)	NR	19 (76)	NR

TEAEs, n (%)		SG (n=268)					
		*1/*1 (n=103)		*1/*28 (n=119)		*28/*28 (n=25)	
		All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
That led to dose discontinuation		5 (5)	NR	7 (6)	NR	3 (12)	NR
Special interest TEAEs	Neutropenia[a]	73 (71)	46 (45)	86 (72)	68 (57)	19 (76)	16 (64)
	Diarrhea	60 (58)	6 (6)	77 (65)	15 (13)	17 (68)	6 (24)
	Anemia[b]	34 (33)	6 (6)	43 (36)	10 (8)	12 (48)	2 (8)
	Febrile neutropenia	6 (6)	6 (6)	8 (7)	8 (7)	1 (4)	1 (4)

NR=not reported
[a]Combined preferred terms of neutropenia and neutrophil count decreased.
[b]Combined preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased.

IMMU-132-01 Study in Metastatic Epithelial Cancer

IMMU-132-01, a phase 1/2, single-arm, open-label basket study investigated the efficacy and safety of SG IV on Days 1 and 8 of a 21-day cycle in patients with metastatic epithelial cancers (including patients with mTNBC and HR+/HER2- mBC) who had relapsed after or were refractory to ≥1 prior therapy for metastatic disease. UGT1A1 testing was performed in all patients.[7]

Impact of UGT1A1 status on safety

The OSP (N=495) included all patients who received ≥1 dose of SG. Descriptive analysis was performed to analyze the incidence of AEs in 81.4% of patients in the OSP who had UGT1A1 GT data available (n=403).[7]

The pattern and incidence of AEs were broadly similar between patients who were heterozygous (**1/*28*) and those who had the WT allele. Safety outcomes according to UGT1A1 status can be found in Table 3.[11]

Table 3. IMMU-132-01: Safety Outcomes According to UGT1A1 Status[11]

Safety Outcomes, n (%)		UGT1A1 Status		
		*1/*1 (n=177)	*1/*28 (n=180)	*28/*28 (n=46)
Any grade TEAE		177 (100)	179 (99.4)	46 (100)
Grade ≥3 TEAE		121 (68.4)	141 (78.3)	41 (89.1)
Any grade TRAE		175 (98.9)	173 (96.1)	44 (95.7)
Grade ≥3 TRAE		95 (53.7)	110 (61.1)	38 (82.6)
SAE		64 (36.2)	66 (36.7)	27 (58.7)
Treatment-related SAE		25 (14.1)	18 (10)	19 (41.3)
TEAE that led to discontinuation of SG		12 (6.8)	12 (6.7)	2 (4.3)
TEAE that led to dose interruption		82 (46.3)	87 (48.3)	33 (71.7)
TEAE that led to on-treatment death[a]		5 (2.8)	8 (4.4)	1 (2.2)
Most common TRAEs (≥30% of patients in any UGT1A1 status group)	Nausea	112 (63.3)	103 (57.2)	31 (67.4)
	Diarrhea	97 (54.8)	93 (51.7)	28 (60.9)
	Fatigue	80 (45.2)	80 (44.4)	21 (45.7)
	Alopecia	74 (41.8)	73 (40.6)	15 (32.6)
	Vomiting	72 (40.7)	56 (31.1)	23 (50)
	Anemia	66 (37.3)	57 (31.7)	23 (50)
	Neutropenia	59 (33.3)	69 (38.3)	28 (60.9)
	Decreased appetite	39 (22)	50 (27.8)	18 (39.1)

Abbreviations: SAE=serious adverse event
[a]Defined as death that occurred between the start of SG treatment and 30 days after the last dose.

Retrospective Analysis of Patients with the *UGT1A1*28* polymorphism[8]

A retrospective analysis of patients with metastatic and locally recurrent HER2-negative breast cancer (52 [76.5%] patients had TNBC) was conducted to evaluate the association between UGT1A1 status and safety in 68 patients who underwent GT testing for UGT1A1 alleles. The most common polymorphism was *UGT1A1*28*, which was homozygous in 17 (25%) patients and heterozygous in 24 patients (35.3%; including one patient with **1/*37 UGT1A1* polymorphism). The remaining 27 (39.7%) patients had the WT GT. Patients received a median (range) of 8.5 (1–54) doses of SG and were observed for a median (range) of 3.9 (0.9–23.7) months. Fifty-eight patients started treatment with SG 10 mg/kg and 10 patients started at reduced doses of SG 7–8 mg/kg.

Results

An increased risk of discontinuation for toxicity was observed in patients homozygous for *UGT1A1*28* (HR 5.52 [95% CI 1.15–26.49], *P*=0.03). No events of discontinuation for toxicity were observed in patients with a heterozygous GT (HR 0 [95% CI 0], *P*≤0.0001). However, 76% of patients with a *UGT1A1*28* homozygous GT either started on a lower dose, had a dose reduction, or were intolerant. Treatment alterations and discontinuations for intolerance were observed in 71% and 56% of patients in the heterozygous and WT groups, respectively.

References

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Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Trodelvy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Follow-Up

For any additional questions, please contact Trodelvy Medical Information at:

☎1-888-983-4668 or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or 🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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