GILEAD | Medical Information

Trodelvy® (sacituzumab govitecan-hziy) Use With Enfortumab Vedotin in Patients With mUC

This document is in response to your request for information regarding the use of Trodelvy® (sacituzumab govitecan-hziy [SG]) with enfortumab vedotin (EV) for metastatic urothelial carcinoma (mUC).

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.

For specific questions related to EV, please contact the relevant marketing authorization holder.

Trodelvy is not indicated for use in patients with mUC. 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

Clinical Studies on SG Use With EV in mUC

DAD is an ongoing, open-label, non-randomized, phase 1 study designed to assess the safety and MTDs of SG and EV in combination in patients with mUC.[1]

- The primary objective is an evaluation of SG and EV treatment through toxicity monitoring and estimation of MTDs. The MTD was estimated at SG 10 mg/kg + EV 1.25 mg/kg (maximum dose: 125 mg/dose) on Days 1 and 8 of a 21-day cycle.[1]
- Because of observed toxicities, the RP2D was selected at SG 8 mg/kg and EV 1.25 mg/kg (maximum dose: 125 mg/dose) on Days 1 and 8 of a 21-day cycle with G-CSF support.[1]
- At a preliminary analysis, with immature median follow-up of 14 months, the ORR was 70% (16/23; 95% CI: 47–87%) with 3 CRs, and the 12-month PFS and OS rates were 41% (95% CI: 18–62%) and 86% (95% CI: 61–95%), respectively.[1]
- After 22 months of follow up, no new safety signals were observed. The ORR remained at 70%, the median (range) DOR was 10 (3–33+) months, response was ongoing in 6 patients, and 1 patient was continuing treatment.[2]

Clinical Studies on SG Use With EV in mUC

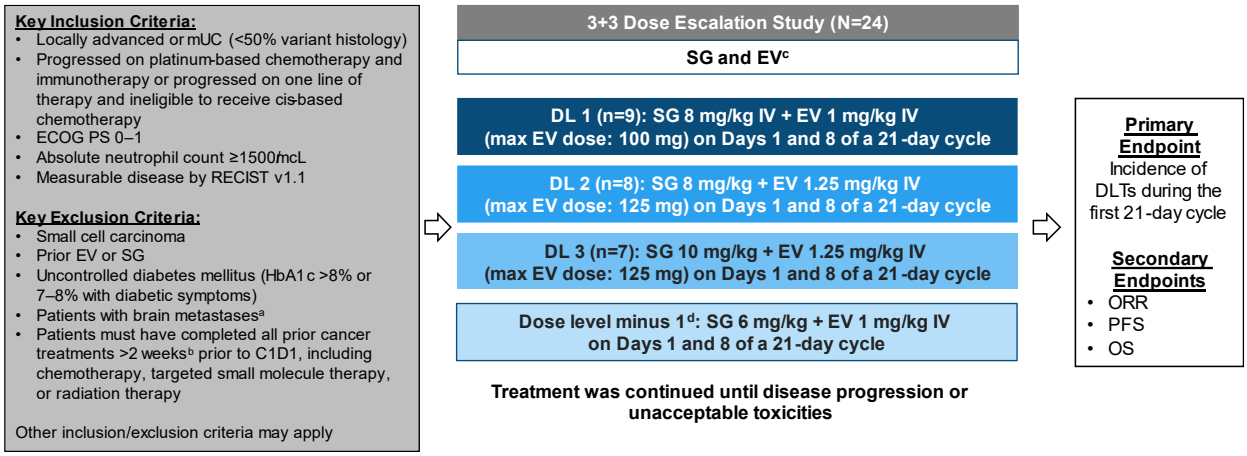
DAD Phase 1 Study in mUC

Study design and demographics[1]

DAD (NCT04724018) is an ongoing, open-label, non-randomized, phase 1 study assessing the safety and MTD of SG + EV in patients with mUC. The primary objective is an evaluation of the feasibility of SG + EV treatment through toxicity monitoring and estimation of MTDs. Secondary objectives include assessments of ORR, PFS, and OS.

In total, 24 eligible patients were enrolled across three DLs; patients received SG + EV on Days 1 and 8 of a 21-day treatment cycle alongside appropriate anti-emetic treatment (Figure 1). One patient was not treated on protocol and was excluded from analyses.

Figure 1. DAD Study: Study Design[1,3]



Abbreviations: C1D1=Cycle 1, Day 1; RECIST=Response Evaluate Criteria in Solid Tumors.
[a]Had stable central nervous system disease for ≥4 weeks and were receiving ≤20 mg/day of prednisone or equivalent.
[b]Had a prior anti-cancer biologic agent within 4 weeks of C1D1 or had prior chemotherapy, targeted small molecule therapy, or radiotherapy within 2 weeks of C1D1.
[c]Either drug could be held on Day 8 in response to toxicity, but patients were required to receive SG + EV on Day 1 of each cycle. After a protocol amendment was approved in March 2023, patients could continue SG or EV after C1D1. The maximum weight for EV dose calculations in each DL was 100 kg.
[d]Dose de-escalation of EV to 6 mg/kg with the starting dose of EV 1 mg/kg was permitted if unacceptable DLTs occurred at DL 1.

Dose reductions of EV and SG were permitted independently of each other and were based on investigator-led assessments of toxicities. Reductions in EV dose were permitted in the following sequence: 1 mg/kg, 0.75 mg/kg, and 0.5 mg/kg. SG dose reductions were based on the initial dose: 10 mg/kg could be reduced to 7.5 mg/kg, then 5 mg/kg; 8 mg/kg could be reduced to 6 mg/kg, then 5 mg/kg; and 6 mg/kg could be reduced to 5 mg/kg. Prophylactic G-CSF was allowed at the investigator's discretion starting at Cycle 1.

The median (range) age of enrolled patients was 70 (41–88) years. The majority of patients (22/23) had received ≥2 prior lines of therapy, and 26% of patients had liver metastases.

Table 1. DAD Study: Baseline Demographic and Disease Characteristics[1]

Key Demographics and Characteristics	Overall (N=23)
Age, median (IQR); [range], years	70 (63–76); [41–88]
Sex, male/female, n (%)	18 (78)/5 (22)
Race/ethnicity, White/Asian/Hispanic or Latinx, n (%)	19 (83)/2 (9)/2 (9)
ECOG PS, 0/1, n (%)	14 (61)/9 (39)
Primary site, bladder/upper tract/urethra, n (%)	16 (70)/6 (26)/1 (4)
Histology, pure urothelial/mixed urothelial, n (%)	16 (70)/7 (30)
Cis eligible, n (%)	19 (83)
Lines of prior therapy, 1/2/3–5, n (%)	1 (4)/11 (48)/11 (48)
Prior therapy, immunotherapy[a]/cis-based/carboplatin-based, n (%)	22 (96)/18 (78)/6 (26)
Metastatic sites, lymph nodes/bone/liver/lung/kidney, n (%)	17 (74)/6 (26)/6 (26)/5 (22)/3 (13)

[a]Immunotherapy included avelumab, pembrolizumab, and nivolumab.

July 2023 data cutoff[1]

Starting doses, dose reductions, and patient disposition

Starting doses and dose reductions are provided in Table 2. Overall, 18 patients received prophylactic G-CSF during their treatment (n/N: DL 1, 5/9; DL 2, 7/8; DL 3, 6/6) with 14 patients who received G-CSF during Cycle 1 (DL 1, n/N=3/9; DL 2, n/N=6/8; DL 3, n/N=6/6)

The median follow-up was 14 months, and 4 patients remained on therapy at the data cutoff. Eleven patients discontinued due to disease progression, and there was 1 death prior to the first imaging assessment in DL 3. Four patients halted treatment in the absence of disease progression, at the investigator's discretion due to concern for cumulative neuropathic toxicity in the setting of durable response (after 11–18 cycles). Two patients discontinued due to intolerable Grade 2 neuropathy after 13 and 18 cycles, respectively.

Table 2. DAD Study: Treatment Summary According to DL (Data Cutoff: July 2023)[1]

DLs	Cycles Initiated,[a] Median (Range)	Cycles at Planned Dose, Median (Range)		Starting Dose, mg/kg		Patients With One Dose Reduction (SG and EV Doses), n		Patients With Two Dose Reductions (SG and EV Doses), n	
		SG	EV	SG	EV	SG	EV	SG	EV
DL 1 (n=9)	12 (2–19)	9 (2–19)	4 (1–19)	8	1	4 (6 m/kg)	1 (0.75 mg/kg)	1 (5 mg/kg)	3 (0.5 mg/kg)
DL 2 (n=8)	10 (2–15)	7 (1–15)	7 (1–15)	8	1.25	2 (6 mg/kg)	2 (1 mg/kg)	0 (5 mg/kg)	1 (0.75 mg/kg)
DL 3 (n=6)[b]	9 (1–16)	1 (1–14)	1 (1–14)	10	1.25	3 (7.5 mg/kg)	3 (1 mg/kg)	1 (5 mg/kg)	1 (0.75 mg/kg)

[a]Through March 2023, a cycle was counted as initiated when both SG and EV were administered. From March 2023 onward, a cycle was counted as initiated after the administration Cycle 1 for either SG or EV.
[b]One patient did not receive Cycle 1, Day 8 of therapy due to an unrelated UTI and was not evaluable for DLT assessments.

Safety

Of the 9 patients treated at DL 1, the following 2 DLTs were reported: Grade 3 febrile neutropenia and Grade 4 sepsis in the setting of no prophylactic G-CSF. Of the 8 patients who were treated at DL 2, 1 DLT was reported: a delay of Cycle 2, Day 1 by >3 weeks due to delayed autoimmune colitis, which was attributed to prior pembrolizumab therapy. Three of 5 patients who were evaluable at DL 3 experienced a DLT (Grade 3 febrile

neutropenia, delay of treatment by >3 weeks, and Grade 3 mucositis). One patient in DL 3 did not receive Day 8 of therapy due to an unrelated UTI; this patient was not evaluated as part of DLT assessments.

The MTD (primary endpoint) was estimated at DL 3 (SG 10 mg/kg + EV 1.25 mg/kg [maximum dose: 125 mg/dose] on Days 1 and 8 of a 21-day cycle) using the combination of number of patients and DLTs at each DL. As a result of the observed cumulative toxicities at DL 3, the RP2D was selected at DL 2 (SG 8 mg/kg + EV 1.25 mg/kg [maximum dose: 125 mg/dose] on Days 1 and 8 of a 21-day cycle) with G-CSF support.

Seventy-eight percent of patients (18/23) experienced Grade ≥3 adverse events regardless of attribution at any DL. The most common any-grade TRAEs included diarrhea, anemia, neutropenia, fatigue, alopecia, neuropathy, and nausea. The most commonly reported Grade ≥3 TRAEs across all DLs included anemia, neutropenia, UTI, fatigue, and diarrhea (Table 3).

Table 3. DAD Study: Summary of TRAEs[a] (Data Cutoff: July 2023)[1]

TRAE, n (%)	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	12 (52.2)	6 (26.1)	2 (8.7)	-
AST increased	9 (39.1)	1 (4.3)	-	-
Fatigue	8 (34.8)	5 (21.7)	2 (8.7)	-
ALT increased	8 (34.8)	2 (8.7)	-	-
Nausea	7 (30.4)	2 (8.7)	1 (4.3)	-
Alkaline phosphatase increased	6 (26.1)	1 (4.3)	-	-
Maculopapular rash	6 (26.1)	1 (4.3)	-	-
Peripheral sensory neuropathy	5 (21.7)	8 (34.8)	-	-
Constipation	5 (21.7)	1 (4.3)	-	-
Dysgeusia	5 (21.7)	1 (4.3)	-	-
Watering eyes	5 (21.7)	1 (4.3)	-	-
Anemia	4 (17.4)	5 (21.7)	8 (34.8)	-
Dry eye	4 (17.4)	2 (8.7)	-	-
Hypomagnesemia	4 (17.4)	1 (4.3)	-	-
Alopecia	3 (13)	11 (47.8)	-	-
Neutrophil count decreased	3 (13)	5 (21.7)	4 (17.4)	4 (17.4)
Weight loss	3 (13)	4 (17.4)	-	-
Mucositis	2 (8.7)	6 (26.1)	1 (4.3)	-
Anorexia	2 (8.7)	1 (4.3)	1 (4.3)	-
Pruritus	1 (4.3)	4 (17.4)	-	-
Hypophosphatemia	1 (4.3)	3 (13)	-	-
UTI	-	1 (4.3)	3 (13)	-

[a]Observed in >10% of 23 patients treated at any DL (July 2023 data cutoff). There was 1 case of Grade 5 pneumonitis, possibly related to EV, that was not included in the table.

Forty-eight percent of patients (11/23) required dose reductions of EV and SG due to TRAEs. Two patients were discontinued from protocol therapy due to toxicity (neuropathy and pneumonitis, n=1 each). Diarrhea (87%) and neuropathy (57%) of any grade were the most common TRAEs that required dose reductions of SG and EV, respectively. Of the 6 patients treated at DL 3, 1 patient died within 32 days of Cycle 1, Day 8 due to pneumonitis that was possibly related to EV, 3 patients required SG dose reduction on Cycle 2, Day 1 for toxicity, and 1 patient required a dose reduction on Cycle 3, Day 1.

Efficacy

Overall, the reported ORR was 70% (16/23; 95% CI: 47–87%). Three patients (13%) had PD as the best response (Table 4). Immature median follow-up was 14 months with 12-month PFS and OS rates of 41% (95% CI: 18–62%) and 86% (95% CI: 61–95%), respectively. Most patients (87%; 20/23) had any degree of tumor reduction in target lesions. At the time of data cutoff, 9 patients had no disease progression; including 6 of 8 patients who halted treatment for reasons other than disease progression but had no further progression after 15 months.

Table 4. DAD Study: Objective Response in Overall Cohort and Across DLs (Data Cutoff: July 2023)[1]

Parameter		Overall (N=23)	DL 1 (n=9)	DL 2 (n=8)	DL 3 (n=6)
ORR, % (95% CI)		70 (47–87)	78 (40–97)	75 (35–97)	50 (12–88)
Best overall response, n	CR	3[a]	1	1	1
	PR	13	6	5	2
	Stable disease	3	1	1	1
	PD	3	1[b]	1	1
	Not evaluated	1	0	0	1

[a]Two patients had lymph node lesions.
[b]Although this patient had a decrease in the target lesion size, PD was noted due to de novo development of a non-target lesion.

April 2024 data cutoff[2]

After a median follow-up of 22 months, which was composed of a median (range) of 11 (1–22+) SG + EV cycles, no new safety signals or unexpected delayed safety events were reported. Fifteen of the 23 patients required G-CSF support with Cycle 1.

ORRs, overall (70%) and by DL (DL 1, 78%; DL 2, 75%; DL 3, 50%), aligned with those recorded at the earlier data cutoff. The median (range) DOR was 10 (3–33+) months. Six patients had ongoing responses, including the 4 patients who initially achieved PR and eventually achieved CR: DL 1, n=3 (PR, n=2; PR→CR, n=1); DL 2, n=2 (both PR→CR; 1 is continuing treatment); DL 3, n=1 (PR→CR).

References

1. McGregor BA, Sonpavde GP, Kwak L, et al. The Double Antibody Drug conjugate (DAD) Phase I trial: Sacituzumab govitecan plus enfortumab vedotin for metastatic urothelial carcinoma. *Annals of Oncology.* 2024;35(1):91-97.
2. McGregor BA, Sonpavde G, Kwak L, et al. Updated efficacy profile of the Double Antibody Drug conjugate (DAD) Phase I trial: Sacituzumab govitecan plus enfortumab vedotin in ≥ second line in metastatic urothelial carcinoma [Poster 1944]. Paper presented at: European Society for Medical Oncology (ESMO) Congress; 13-17 September, 2024; Barcelona, Spain.
3. ClinicalTrials.gov. Sacituzumab Govitecan Plus EV in Metastatic UC. Available at: https://www.clinicaltrials.gov/study/NCT04724018.

Abbreviations

cis=cisplatin
CR=complete response
DL=dose level
DLT=dose-limiting toxicity
DOR=duration of response
ECOG PS=Eastern Cooperative Oncology Group Performance Status
EV=enfortumab vedotin
G-CSF=granulocyte-colony stimulating factor

MTD=maximum tolerated dose
mUC=metastatic urothelial carcinoma
ORR=objective response rate
OS=overall survival
PD=progressive disease
PFS=progression-free survival
PR=partial response
RP2D=recommended phase 2 dose
SG=sacituzumab govitecan-hziy
TRAE=treatment-related adverse event
UTI=urinary tract infection

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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