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Trodelvy® (sacituzumab govitecan-hziy) Use in Patients With mBC and Leptomeningeal Carcinomatosis

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) and its use in patients with metastatic breast cancer (mBC) and leptomeningeal carcinomatosis (LC).

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]

No information about the use of SG in patients with mBC and LC is available in the SG US FDA-approved prescribing information.

Clinical Data: Use of SG in Patients With LC

Several prospective Gilead studies evaluated SG in patients with BC: the phase 3 ASCENT study of SG vs TPC in patients with mTNBC[2]; the phase 3 TROPiCS-02 study of SG vs TPC in patients with HR+/HER2- mBC[3,4]; and the phase 1/2 IMMU-132-01 study of SG in patients with metastatic epithelial cancers, including mTNBC, HR+/HER2-, and HER2+ mBC[5,6]. Data specific to patients with LC were not reported in these studies.

Real-World Data

A real-world study retrospectively evaluated 33 patients with mBC (TNBC, n=23; HR+/HER2-, n=10) and CNS metastases, including 8 patients with LC. After a median follow-up of 6.7 months from SG initiation:[7]

- Median CNS-PFS was 2.9 months in the overall population and 2.1 months in patients with LC
- Median bi-compartmental PFS was 2.6 months in the overall population, and 2.4 months in patients with LC.
- Median OS was 6.9 months in the overall population and 3.8 months in patients with LC.
- CNS response (complete or partial) was 13.3% in the overall population and 28.6% in patients with LC.

An ambispective bicentric cohort study in France assessed the real-world effectiveness and safety of SG in 99 female (median age 55 years) patients with mTNBC. Two patients with LC were treated with SG and intrathecal chemotherapy (methotrexate). ORR was not reportable, however one patient had clinical progression leading to death after one cycle,

and the second patient achieved a complete cytological and biochemical response assessed on cerebrospinal fluid, which resulted in the control of LC for 4 months.[8]

Case Report[9]

A female patient with Stage IIIC TNBC who previously underwent chemotherapy, a radical mastectomy, and adjuvant radiation presented with clinical signs and laboratory findings consistent with LC, and SG was initiated. By Cycle 4 of SG, the patient was fully autonomous and experiencing no significant toxicities from treatment; she received a total of 8 cycles of SG. Treatment with SG was discontinued after tumor progression was noted on brain and spinal MRI, and the patient died 7 months after the first dose of SG for extensive and symptomatic LC.

Ongoing Clinical Study

A phase 1/2, open-label, uncontrolled clinical study (NCT06462092) will evaluate the safety, feasibility, and efficacy of SG with pemetrexed intrathecal chemotherapy in patients with HER2- BC with leptomeningeal metastases.

Prospective Clinical Studies in Patients With BC

Several prospective Gilead studies evaluated SG in patients with BC: the phase 3 ASCENT study of SG vs TPC in patients with mTNBC[2]; the phase 3 TROPiCS-02 study of SG vs TPC in patients with HR+/HER2- mBC[3,4]; and the phase 1/2 IMMU-132-01 study of SG in patients with metastatic epithelial cancers, including mTNBC, HR+/HER2-, and HER2+ mBC[5,6]. Data specific to patients with LC were not reported in these studies.

Real-World Studies

SG in Patients with mBC and LC[7]

Study design and demographics

A retrospective, observational real-world study evaluated 33 patients with mBC (TNBC, n=23; HR+/HER2-, n=10); 18 (54.5%) had treated/stable CNS metastases, 7 (21.2%) had active CNS metastases and 8 (24.3%) had LC.

The objective of this study was to evaluate the activity of SG in patients with CNS metastases, including LC, using a modified RANO response assessment criteria (excluding clinical status) for brain metastases and LC (RANO-LM), with confirmation through central radiologic review.

Survival endpoints and follow-up were described using the reverse Kaplan-Meier Method (reported with a 95% CI). PFS (CNS, extra-CNS, and bi-compartmental) was defined as the time from initiation of SG to disease progression (CNS, extra-CNS or either) or death from any cause. OS was defined as the time from initiation of SG to death from any cause. CNS-CBR was defined as response + stable disease ≥6 months.

Patients with CNS metastases who had received at least one dose of SG between 2018 and 2022 as part of their routine clinical care were included in this study. Patients with LC were defined as having metastases in the leptomeningeal space with or without BM.

Median age at SG initiation in the overall population was 56.7 years, and 50.9 years in patients with LC. Data for the 33 patients in the overall population, and the subset of 8 patients with LC are presented below.

Of the 8 patients with LC (HR+/HER2-, n=2; TNBC, n=6), 7 had associated BM, and all 8 patients had extra-CNS metastases (lung, n=1; liver, n=3; bone, n=5; other, n=6). Median follow-up for the entire cohort was 6.7 months (95% CI; 3.1–10.0). Select additional patient characteristics can be found in Table 1.

Table 1. Real-World Study in Patients With mBC and CNS Metastases: Select Characteristics in the Overall mBC Population and in Patients with LC[7]

Patient Characteristic	Overall (N=33)	Patients With LC (n=8)
Time from mBC diagnosis to initiation of SG, median (range), months	21.5. (1.1–138.1)	17.3 (7.4–24.4)
Time from CNS metastases diagnosis to SG, median (range), months	7.5 (0.6–94.8)	9.3 (2.7–21.5)
Prior lines of treatment before SG for mBC, median, n (range)	3 (0–10)	3.5 (2–6)
Prior trastuzumab deruxtecan, yes/no, n (%)	3 (9.1)/ 30 (90.9)	0/ 8 (100)
Prior surgery for CNS metastases, yes/no, n (%)	16 (48.5)/ 17 (51.5)	2 (25)/ 6 (75)
Prior radiation for CNS metastases, yes/no, n (%)	28 (84.8)/ 5 (15.2)	5 (62.5)/ 3 (37.5)
Time from prior radiation for CNS metastases to SG, median (range), months	2.0 (0.2–44.0)	8.8 (1.2–15.2)

Efficacy Results

Efficacy outcomes are shown in Table 2

Table 2. Real-World Study in Patients With mBC and CNS Metastases: Efficacy Results in the Overall Population and in patients with LC[7]

RW Response to SG	Overall (N=33)	Patients With LC (n=8)
CNS response, n (%)	**N=30**	**N=7**
Response (complete or partial)	4 (13.3)	2 (28.6)
Stable disease	16 (53.3)	3 (42.9)
Progressive disease	10 (33.3)	2 (28.6)
DCR	20 (66.7)	5 (71.4)
CBR at 6 months	8 (26.7)	1 (14.3)
Median CNS-PFS, median (95% CI), months	2.9 (2–4.3)	2.1 (0.4–7.7)
Extra-CNS response	**N=29**	**N=7**
Response	1 (3.4)	1 (14.3)
Stable disease	12 (41.4)	2 (28.6)
Progressive disease	16 (55.2)	4 (57.1)
DCR	13 (44.8)	3 (42.9)
CBR at 6 months	4 (13.8)	1 (14.3)
CNS-ORR, %	13.3	28.6
OS, median (95% CI), months	6.9 (3.1–10.2)	3.8 (1.7–11.9)
Bi-compartmental PFS, median (95% CI), months	2.6 (1.9–4)	2.4 (0.4–5.1)

Thirty-two patients discontinued SG due to progression. Most patients (53.1%) experienced both CNS and extra-CNS disease progression. Further detail on site of disease progression on SG can be found in Table 3.

Table 3. Real-World Study in Patients With mBC and CNS Metastases: Site of Disease progression in the Overall Population and in Patients with LC[7]

n (%)	Overall (N=32)	Patients With LMD (n=8)
CNS only	1 (3.1)	1 (12.5)
Extra-CNS only	9 (28.1)	1 (12.5)
CNS and extra-CNS	17 (53.1)	6 (75)
Death	5 (15.6)	0

Safety Results

One patient discontinued SG due to toxicity. Of the five patients who died while receiving SG, two suffered from neurological death. Comprehensive safety data or symptoms, particularly neurological, were not reported due to incomplete data on retrospective chart abstraction.

Ambispective bicentric cohort study[8]

An ambispective bicentric cohort study in France assessed the real-world effectiveness and safety of SG in 99 female (median age 55 years) patients with mTNBC. Of the 31 (31%) patients with brain metastases, median (95% CI) PFS and OS were 3.7 (2.6–6.2) and 6.7 (6.3–NR) months, respectively. Two patients with LC were treated with SG and intrathecal chemotherapy (methotrexate). ORR was not reportable, however one patient had clinical progression leading to death after one cycle, and the second patient achieved a complete cytological and biochemical response assessed on cerebrospinal fluid, which resulted in the control of LC for 4 months.

Of the 99 patients, 75 (76%) discontinued SG; progressive disease (n=70 [93%]), toxicity (n=1 [1%]; Grade 4 neutropenia), physical deterioration (n=3 [4%]), and patient's request (n=1 [1%]). Seventeen patients (17%) required dose reductions, within a median of 3 cycles.

Nine patients had hematological AEs (neutropenia; n=6, febrile neutropenia; n=2; anemia; n=1) and 6 patients had gastrointestinal AEs (diarrhea: Grade 2; n=1, Grade 3; n=5).

Case Report

There are limitations in the interpretation of case reports. Case reports cannot be generalized. Unlike controlled clinical trials, causality cannot be inferred based on uncontrolled observational data. In addition, incidence or prevalence cannot be estimated due to the lack of a representative population sample. Other limitations of case reports include the retrospective design and publication bias.[10]

Use of SG in a Patient with TNBC and LC[9]

A female patient aged 62 years presented with Stage IIIC TNBC; she received chemotherapy (as part of a clinical study; carboplatin and paclitaxel, followed by epirubicin, cyclophosphamide, and atezolizumab) and underwent a radical mastectomy with axillary

dissection. The patient achieved a pathological complete response and continued treatment with adjuvant radiation followed by atezolizumab/placebo. Fourteen months after initial diagnosis, she presented with gait instability and recent dysphagia. A cranial MRI identified a single brainstem lesion, which was treated with stereotactic radiotherapy, dexamethasone, and additional chemotherapy plus bevacizumab after radiation. Another brain MRI revealed that partial response was maintained for 6 months.

Approximately 2 years after the initial diagnosis, the patient was admitted after presenting to the emergency room with worsened neuropathic pain and partial ascending paresis of the lower limbs. Findings on a lumbar puncture led to a likely diagnosis of leptomeningeal involvement, and treatment with SG was initiated. Spinal MRI showed diffuse and extensive signs of LC, with perimedullary enhancement at the cervical and dorsal spine, as well as conus medullaris and cauda equina. A clinical response was observed after the first cycle of SG, with a PFS of 6 months. By Cycle 4 of SG, the patient was fully autonomous and reported no significant toxicities from the treatment; she received a total of 8 cycles of SG.

Another brain and spinal MRI showed a decrease in diffuse root involvement, and a new nodular lesion in the spinal cord at the D3 level suggested tumor progression. Treatment with SG was discontinued and 1 cycle of carboplatin and gemcitabine was administered; however, the patient's functional status declined rapidly, and palliative care was initiated. The patient subsequently died 7 months after the first dose of SG for extensive and symptomatic LC.

Ongoing Clinical Study

A phase 1/2, open-label, uncontrolled clinical study (NCT06462092) will evaluate the safety, feasibility, and efficacy of SG with pemetrexed intrathecal chemotherapy in patients with HER2- BC with leptomeningeal metastases.

References

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Abbreviations

BC=breast cancer
BCBM=breast cancer brain metastases
BM=brain metastases
CNS=central nervous system
CNS-CBR=CNS clinical benefit rate
HER2-/+=human epidermal growth factor receptor 2-negative/positive
HR+=hormone receptor-positive
LC=leptomeningeal carcinomatosis
mBC=metastatic breast cancer
mTNBC=metastatic triple-negative breast cancer
OS=overall survival
PFS=progression-free survival
RANO=Response Assessment in Neuro-Oncology
SG=sacituzumab govitecan
TNBC=triple-negative breast cancer
TPC=treatment of physician's choice

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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