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Trodelvy® (sacituzumab govitecan-hziy) Use in Patients With Brain Metastases in mBC Studies

This document is in response to your request for information regarding the use of Trodelvy® (sacituzumab govitecan-hziy [SG]) in patients with brain metastases (BrM) in metastatic breast cancer (mBC) studies.

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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]

There is no information regarding use of SG for the treatment of brain metastases in the SG US FDA-approved prescribing information.

Use of SG in Patients With BrM: Clinical Studies in mBC

- In a systematic review and meta-analysis of pooled data from 11 studies that evaluated the efficacy of SG in patients with HER2- BCBMs (N=313), after a median follow-up of 6.7 to 17.5 mo across studies, mOS (95% CI) was 8.4 (6.7–10.5) mo. mPFS (95% CI) was 3.8 (2.8–5.3) mo, and median intracranial PFS (95% CI) was 2.9 (1.7–4.9) mo. ORR (95% CI) was 10.7% (0–37.9%), and intracranial ORR (95% CI) was 31.7% (15.5–54%). DCR (95% CI) was 45.4% (33.9–57.5%), and intracranial DCR (95% CI) was 55.6% (42.2–68.1%).[2]
- In **ASCENT**, a phase 3 study in 2L+ mTNBC, 12% of patients had previously treated and stable BrM at baseline (BMPos: SG, n=32; TPC, n=29).[3]
    - In a post hoc subgroup analysis in patients who were BMPos, mPFS (95% CI) was 2.8 (1.5–3.9) mo with SG vs 1.6 (1.3–2.9) mo with chemotherapy TPC; the safety profile in these patients was consistent with that observed in the overall safety population.[4]
- **ASCENT-03** is an ongoing, phase 3 study which is evaluating the efficacy and safety of 1L SG vs TPC in patients with locally advanced, unresectable or mTNBC who were not candidates for PD-(L)1 therapy. mPFS (95% CI) was 8.4 (4–9.7) mo vs 4.4 (1.5–8.1) mo, among patients with BrM treated with SG (n=15) vs TPC (n=14), respectively (HR, 0.38; 95% CI, 0.15–1.01).[5]

- **ASCENT-04** is an ongoing, phase 3 study (N=443) which is evaluating the efficacy and safety of SG + pembro (n=221) vs TPC (gemcitabine + carboplatin, paclitaxel, or nab-paclitaxel) + pembro (n=222), as 1L treatment in patients with PD-L1+ (combined positive score ≥10) inoperable, locally advanced or mTNBC. mPFS (95% CI) was 5.7 (0.5–NR) mo vs 3.7 (1.3–NR) mo, among patients with BrM treated with SG + pembro (n=8) vs TPC + pembro (n=6), respectively (HR, 0.64; 95% CI, 0.19–2.14).[6]
- In **TROPiCS-02**, a phase 3 study of SG vs TPC in pretreated HR+/HER2- mBC, patients with previously treated BrM were permitted to participate if their BrM are stable for ≥4 wk. Results for those with BrM have not been reported.[7]
- **ASCENT-07** is an ongoing, phase 3 study of 1L SG vs TPC in patients with HR+/HER2- locally advanced, inoperable, or mBC who have received prior ET. Overall, 18 patients (4%) treated with SG and 14 patients (6%) treated with TPC had BrM at baseline. At this time, the efficacy and safety of SG in patients with BrM have not been reported.[8]
- A phase 0/early phase 1 study evaluated the intratumoral concentrations and intracranial activity of SG in patients undergoing craniotomy for BCBM. In the BCBM cohort, most AEs were Grade 1 or 2. mPFS (range) was 8 (2–26.5) mo. SN-38 levels showed penetration into intracranial tumor tissue.[9]

Use of SG in Patients With BrM: Real-World Studies in mBC

- A retrospective, observational cohort study assessed SG data from the Flatiron Health database to evaluate outcomes of patients with mTNBC who received SG in the 2L+ setting (N=381). Of 291 patients with ≥1 metastatic site recorded in the database, 68 (23%) had BrM; a subgroup analysis was conducted for OS in these patients. mOS (95 % CI) in the overall population was 11.3 (10–12.9) mo; mOS (95% CI) was 9 (6.6-11.3) mo in the group of patients with BrM. Safety data was not reported specifically for the group of patients with BrM.[10]
- A retrospective, observational, study evaluated the effectiveness and safety of SG in 159 patients with mTNBC. A subgroup analysis was conducted in 22 patients (13.8%) with CNS metastases; after a median follow-up of 6 mo, mPFS (95% CI) was 2.3 (1.3–3.2) mo. ORR was 13.6%, and DCR was 36.3%. Among patients with CNS metastases, 31.8% required at least one dose reduction, and no patients discontinued due to AEs.[11]
- A retrospective study assessed data in patients (N=132) with mTNBC. Of 24 patients (18%) with CNS metastases, 8 were diagnosed with BrM while on treatment with SG. mPFS (95% CI) and mOS (95% CI) in the overall population were 5.2 (4.5–6.6) mo and 8.7 (6.8–NA) mo, respectively. In patients with CNS disease, mPFS (95% CI) was 5.1 (1.6–6.6) mo and mOS was NR.[12]
- An ambispective, bicentric cohort study evaluated the use of SG in 103 patients with mTNBC with a focus on BrM and toxicity and included patients with active or stable BrM (n=32, 31.1%) and impaired performance status. mPFS (95% CI) was 3.7 (2.6–6.2) mo, and mOS (95% CI) was 6.7 (56.3–NR) mo in patients who were BMPos. ORR in the BMPos population was 19.8% (n=6).[13]
    - In the BMPos population, 26 patients (81.2%) discontinued SG mostly due to disease progression. AEs that led to SG dose reduction were reported in 4 patients (12.5%).[13]

- An observational study evaluated the effectiveness and safety of SG in patients aged ≥65 y with aTNBC (N=69), of which 11 (15.9%) had BrM. No significant differences in PFS were observed between patients with and without BrM (HR, 1.36; 95% CI: 0.47–3.95; *P*=0.6). OS was significantly shorter in patients with BrM vs those without BrM (HR, 5.58; 95% CI: 1.82–17.11; *P*=0.003). Safety data were not reported for patients with BrM.[14]
- A multicenter study evaluated the effectiveness and safety of SG in 58 patients with HER2- mBC, including 12 (20.69%) with BrM. In patients with BrM, ORR was 25% and DCR was 91.6. mPFS (95% CI) and mOS were 5.43 (2.73–NR) mo and 17.5 (17.5–NR) mo, respectively. CNS-ORR was 41.6%, and median (95% CI) CNS-PFS was 14.87 (10.16–NR) mo. Safety data were not reported for patients with BrM.[15]
- A retrospective study evaluated SG in 54 patients with mTNBC and CNS metastases, including subgroups with treated/stable BrM, active BrM, or LMD. mPFS (95% CI) in the overall population was 3.75 (3.06–7.89) mo. Median CNS-PFS was 9.26 (4.8–16.2) mo overall and was 12.1 (4–16.2), 4.8 (2–NA), and 4.1 (2.79–NA) mo in patients with treated/stable BrM, active BrM, and LMD, respectively. Safety data were not reported.[16]
- In a retrospective, observational study of SG in 33 patients with HER2- mBC and CNS metastases (treated/stable BrM, active BrM, and LMD), overall median (95% CI) CNS and extra-CNS PFS was 2.9 (2–4.3) mo and 2.6 (1.9–4) mo, respectively. Three patients (TNBC, n=2; HR+/HER2-, n=1) had bicompartmental PFS that was >10 mo; each had surgery and brain RT. Safety data were not reported.[17]
- A single-center, retrospective study evaluated the effectiveness of SG in 30 patients with mBC and CNS metastases. Overall, CNS-ORR was 20%, CNS-CBR at 6 mo was 26.7%, median (IQR) CNS-PFS was 4.5 (2.3–8.5) mo and mOS was 11.7 (6.2–24) mo. All CNS responses were PRs and occurred in patients who had received CNS-directed RT <1 mo prior to SG initiation. No CNS-ORRs were observed in patients with active BrM or LMD. Safety data were not reported.[18]
- In a retrospective, multicenter study of SG in 29 patients with mTNBC and BrM, mOS and mPFS (95% CI) were 8.9 (6.04–10.32) mo and 3.09 (2.4–4.11) mo, respectively. There was no statistically significant association between the number or size of CNS lesions and OS or PFS. No unexpected safety signals were reported. AEs resulted in dose delays in 15 patients (51.7%), dose reductions in 11 patients (37.9%), and discontinuations in 2 patients (7.7%).[19]
- A retrospective study evaluated the use of SG or T-DXd in 12 patients with mBC and active (n=5) or stable (n=7) BrM. Among patients treated with SG, median (95% CI) intracranial PFS was 2.7 (1.6–10.5) mo, and mOS (95% CI) was 6.4 (1.2–NR) mo. No statistically significant association between BrM status (active vs stable) and intracranial PFS or OS was observed (*P*=0.86 and *P*=0.63, respectively). In patients treated with SG, the most common AE was neutropenia (42%). Severe Grade ≥3 AEs included neutropenia (33%) and anemia (8%). Discontinuation of SG was most commonly due to intracranial progression (n=5 [42%]) or extracranial progression (n=3 [25%]) of disease, with 1 patient discontinuing due to treatment-associated neutropenia; overall, 7 patients (58%) had died by data cut-off. Dose reductions of SG occurred in 3 patients.[20]

Use of SG in Patients With BrM: Clinical Studies in mBC

Systematic Review and Meta-Analysis in Patients With HER2- BCBM[2]

A systematic review and meta-analysis of pooled data from 11 studies (two prospective trials and nine observational cohorts) evaluated the efficacy of SG in patients with HER2- BCBMs (N=313). Outcomes included OS, PFS, ORR, DCR, and intracranial efficacy measures, including intracranial PFS, ORR, and DCR. Random-effects models were used, with heterogeneity assessed by I^2 statistics. The median age ranged from 48 to 61.5 y, and 75% of evaluable patients had stable BrM at SG treatment initiation. Median follow-up was 6.7 to 17.5 mo across studies.

Efficacy outcomes are summarized below (Table 1).

Table 1. Efficacy Outcomes in Patients With HER2- BCBM[2]

Outcome	SG (N=313)
mOS (95% CI; I^2 %), mo	8.4 (6.7–10.5; 0)
mPFS (95% CI; I^2 %), mo	3.8 (2.8–5.3; 67.8)
Median intracranial PFS (95% CI; I^2 %), mo	2.9 (1.7–4.9; 0)
ORR (95% CI; I^2 %), %	10.7 (0–37.9; 86.8)
Intracranial ORR (95% CI; I^2 %), %	31.7 (15.5–54; 58.2)
DCR (95% CI; I^2 %), %	45.4 (33.9–57.5; 0)
Intracranial DCR (95% CI; I^2 %), %	55.6 (42.2–68.1; 0)

Safety was not reported.

ASCENT Study in 2L+ mTNBC

ASCENT, a global, open-label, randomized, confirmatory, phase 3 study, investigated the efficacy and safety of SG vs TPC in patients with refractory or relapsed mTNBC who received ≥2 prior chemotherapies for unresectable, locally advanced, or metastatic disease. Patients received SG 10 mg/kg IV on Days 1 and 8 of a 21-d cycle (n=267) or single-agent TPC (n=262 [ie, eribulin, n=139; vinorelbine, n=52; gem, n=38; and cape, n=33]). The study protocol allowed a predefined maximum of 15% for patients with BrM for ≥4 wk. Patients with known BrM required baseline brain MRI/CT scans that were conducted every 6 wk for 36 wk and every 9 wk thereafter until disease progression led to study treatment discontinuation; confirmatory imaging was performed 4 to 6 wk after attaining responses.[3]

Post hoc subgroup analysis of patients with stable BrM[4]

A post hoc subgroup analysis evaluated the efficacy and safety of SG in patients who were BMPos, defined as having stable CNS disease for ≥4 wk by MRI, ≥2 wk from discontinuation of antiseizure medication, and corticosteroid dose (≤20 mg prednisone equivalent) that was stable or decreasing for ≥2 wk. Among the patients enrolled, 61 (12%) were BMPos (SG, n=32; TPC, n=29). From the SG and TPC groups, 2 (6%) and 6 (21%) patients, respectively, did not receive treatment. Baseline characteristics were generally balanced between the ITT and BMPos study populations (Table 2).

Table 2. ASCENT Subgroup Analysis in the ITT and BMPos Populations: Select Baseline Patient and Disease Characteristics[4]

Key Demographics and Characteristics	ITT (N=529)	BMPos (n=61)
Female, n (%)	527 (99)	61 (100)
Age, median (range), y	54 (27–82)	53 (27–81)
Race (self-reported), White, n (%)	418 (79)	49 (80)
ECOG PS, 0/1, n (%)	229 (43)/300 (57)	23 (38)/38 (62)
Number of prior chemotherapies, 2–3/>3, n (%)	365 (69)/164 (31)	35 (57)/26 (43)
Prior systemic regimens, median (range), n	4 (2–17)	5 (2–10)

Patient disease characteristics were generally similar between patients in the BMNeg and BMPos populations with a few exceptions. *BRCA* mutations were reported in 15% vs 7% of patients who were BMPos and BMNeg, respectively. In patients who were BMPos and BMNeg, 82% vs 69% of patients were diagnosed with TNBC initially, the median (range) number of prior anticancer regimens was 4 (2–9) vs 3 (1–16), 43% vs 30% had >3 prior chemotherapies, 79% vs 65% had prior cape therapy, and 43% vs 27% had previous checkpoint inhibitors prior to enrollment, respectively. Compared to 44% and 22% of patients who were BMNeg, 67% and 36% of patients who were BMPos had major tumor locations in the lung and bone, respectively.

Efficacy

For SG vs TPC, in the BMPos population, mPFS (95% CI) was 2.8 (1.5–3.9) mo vs 1.6 (1.3–2.9) mo, respectively (HR, 0.65; 95% CI: 0.35–1.22), and mOS (95% CI) was 7 (4.7–14.7) mo vs 7.5 (4.7–11.1) mo, respectively (HR, 0.96; 95% CI: 0.55–1.68). Response rates are presented in Table 3.

Table 3. ASCENT Subgroup Analysis in the BMPos Population: Response Rates[4]

Efficacy Measure		SG (n=32)	TPC (n=29)
ORR, n (%)		1 (3)	0
CBR,[a] n (%)		3 (9)	1 (3)
Best overall response, n (%)	CR	0	0
	PR	1 (3)	0
	SD	15 (47)	9 (31)
	SD for >6 mo	2 (6)	1 (3)
	PD	11 (34)	11 (38)
	NE	5 (16)	9 (31)
DOR, median (95% CI), mo		2.9 (NE–NE)	N/A[b]
TTR, median (range), mo		1.5 (1.5–1.5)	0

Abbreviations: DOR=duration of response; TTR=time to response.
[a]Proportion of patients with a confirmed best overall response of CR or PR and SD for ≥6 mo.
[b]No patients to report.

Safety

The safety profile in patients who were BMPos was consistent with that observed in the overall safety population. Any-grade TEAEs, with an incidence >20%, in the BMPos subgroup are summarized in Table 4.

Table 4. Any-Grade TEAEs (with an incidence >20%) in the BMPos Subgroup[4]

TEAEs, %	SG (n=32)	TPC (n=29)
Fatigue	63	52
Neutropenia	63	52
Diarrhea	50	13
Nausea	43	26
Decreased appetite	30	17
Anemia	23	35
Alopecia	23	13
Constipation	23	22

TEAEs leading to treatment discontinuation in the BMPos subgroup occurred in 2 (7%) and 2 (9%) patients in the SG and TPC groups, respectively. In this subgroup, there were no reports of treatment-emergent death with SG and 1 report of treatment-emergent death in a patient treated with TPC.

ASCENT-03 Study in 1L PD-(L)1 Inhibitor–Ineligible mTNBC

ASCENT-03 is an ongoing, phase 3 study of 1L SG (n=279) vs TPC (taxane [56%] or gem + carboplatin [44%]; n=279) in patients with locally advanced, unresectable or mTNBC who were not candidates for PD-(L)1 inhibitor therapy.[5] Patients with BrM who were treated and radiographically stable for ≥4 wk and were clinically stable for ≥2 wk on a prednisone-equivalent dose of ≤10 mg/d were eligible for inclusion.[21] Overall, 15 patients (5%) treated with SG and 14 patients (5%) treated with TPC had a history of BrM at baseline.[5] mPFS outcomes in patients with and without BrM treated with SG versus TPC are summarized below (Table 5).[5]

Table 5. Efficacy of SG vs TPC in Patients With and Without BrM[5]

	Patients With BrM		Patients Without BrM	
	SG (n=15)	TPC (n=14)	SG (n=264)	TPC (n=265)
mPFS (95% CI), mo	8.4 (4–9.7)	4.4 (1.5–8.1)	9.7 (8–11.4)	7 (5.6–8.3)
HR (95% CI)	0.38 (0.15–1.01).		0.66 (0.53–0.82).	

Safety data were not reported for patients with BrM.

ASCENT-04 Study in 1L PD-L1+ mTNBC

ASCENT-04 is an ongoing, phase 3 study (N=443) which is evaluating the efficacy and safety of SG + pembrolizumab (n=221) vs TPC (gemcitabine + carboplatin, paclitaxel, or nab-paclitaxel) + pembrolizumab (n=222), as 1L treatment in patients with PD-L1+ (combined positive score ≥10) inoperable, locally advanced or mTNBC.[6]

Patients with BrM who were treated and radiographically stable for ≥4 wk and were clinically stable for ≥2 wk on a prednisone-equivalent dose of ≤10 mg/d were eligible for inclusion.[22]

mPFS outcomes in patients with and without BrM treated with SG + pembro versus TPC + pembro are summarized below (Table 6).

Table 6. Efficacy of SG + Pembro vs TPC + pembro in Patients With and Without BrM[6]

	Patients With BrM		Patients Without BrM	
	SG + Pembro (n=8)	TPC + Pembro (n=6)	SG + Pembro (n=213)	TPC + Pembro (n=216)
mPFS (95% CI), mo	5.7 (0.5–NR)	3.7 (1.3–NR)	11.7 (9.3–16.8)	8.4 (7.4–9.3)
HR (95% CI)	0.64 (0.19–2.14)		0.65 (0.5–0.84)	

Safety data were not reported for patients with BrM.

TROPiCS-02 Study in Pretreated HR+/HER2- mBC

In TROPiCS-02, an open-label, randomized, multicenter, phase 3 study comparing the safety and efficacy of SG with TPC (eribulin, cape, gem, or vinorelbine) in patients with HR+/HER2- mBC who have received ≥2 and ≤4 prior chemotherapy regimens for metastatic disease, as well as ≥1 ET, taxane, and cyclin-dependent kinase 4/6 inhibitor.[23] Patients with stable BrM for ≥4 wk were eligible for inclusion.[7]

Efficacy and safety of SG in the patient subgroup with stable BrM have not been reported.[23]

ASCENT-07 Study in 1L Post-ET in HR+/HER2- mBC[8]

ASCENT-07 is an ongoing, phase 3 study comparing the efficacy and safety of 1L SG (n=456) vs TPC (cape, paclitaxel, or nab paclitaxel; n=234) in patients with HR+/HER2- (IHC 0, IHC 1+, IHC 2+/ISH-) locally advanced, inoperable, or mBC who have received prior ET. Overall, 18 patients (4%) treated with SG and 14 patients (6%) treated with TPC had BrM at baseline.

At this time, the efficacy and safety of SG in patients with BrM have not been reported.

Prospective, Single-Center Study: SG in BCBM

Study design and demographics[9]

A prospective, single-center, window-of-opportunity, phase 0/early phase 1 study evaluated intratumoral concentrations and intracranial activity of SG in patients undergoing craniotomy for BCBM or recurrent glioblastoma. Patients received a single IV dose of SG 10 mg/kg 1 d before surgical resection. Patients resumed treatment with SG 10 mg/kg on Days 1 and 8 of 21-d treatment cycles following recovery from surgery. Tumor and serum levels of SG, SN-38, and SN-38G were collected during surgery.

In the BCBM cohort, 13 female patients were screened for inclusion and 1 patient failed screening; patients had a mean age (range) of 48.5 (33–70) y, 12 (93%) were White, 1 (7%) was Black/African American, 7 (54%) were HR+, 7 (54%) were HER2+, and 3 (23%) had TNBC.

Preliminary safety and efficacy results

In the BCBM cohort, most AEs were Grade 1 or 2, which included diarrhea, neutropenia, nausea, hypokalemia, and fatigue.[9]

Efficacy outcomes in the BCBM cohort are shown in Table 7.

Table 7. Preliminary Efficacy Results for the BCBM Cohort[9]

	mOS (Range), Mo	mPFS (Range), Mo	iORR, %	iPR, %	iCR, %
BCBM	35.2 (2.7–37)[a]	8 (2–26.5)	50	25	25

Abbreviations: iORR=intracranial objective response rate, iPR=intracranial partial response, iCR=intracranial complete response.
[a]mOS for HER2+ BCBM for patients with CNS metastasis at or after diagnosis was 30 to 38 mo, respectively, and was 12.5 mo for patients with HR+ BCBM.

Primary outcome: SN-38 levels and biomarker data

In the BCBM cohort, SN-38 levels showed penetration into intracranial tumor tissue (n=13, matching tissue and serum samples; n=3, CSF samples). SN-38 levels, molarity, and minimum IC_{50} values are shown in Table 88. Within the BCBM cohort, SN-38G was only detected in small amounts or not at all in the CSF.[9,24]

Table 8. Total SN-38 Levels, Molarity, and Minimum IC_{50} in Tumor Tissue, Serum, and CSF From Patients in the BCBM Cohort[9a]

Total SN-38 Tumor Tissue			Total SN-38 Serum			Total SN-38 CSF			Observed SN-38 Level, mcM	Minimum IC_{50}, mcM[b]
n	Level, Median (Range), ng/g	Molarity, mcM	n	Level, Median (Range), ng/mL	Molarity, mcM	n	Level, ng/mL	Molarity, mcM		
13	197.3 (86.5–652)	0.0523	13	2462.4 (1266.8–5659.6)	6.27	3	9.4[c]	0.035	0.662	0.000551

[a]Used brain tissue density of 1.04 g/mL. [b]Molecular weight=392.4 g/mol. [c]Median value; range: 5–26.5 ng/mL.

Additionally, several assays were evaluated to investigate potential mechanisms of action for SG in the CNS and included quantification of tumor expression for Trop-2 (a marker of antigen expression), γH2AX (a marker of DNA damage), and CAIX (a marker of intratumoral hypoxia).[9]

In the BCBM cohort, 12 samples were sufficient for Trop-2 analysis, and all had an H-score of 3+. Trop-2 expression did not correlate with % SN-38 tissue-to-serum ratio (Pearson r^2, 0.018; 95% CI: -0.23 to 0.81; *P*=0.18). Expression of γH2AX (n=11) ranged from 33.1% to 81.2% (mean, 54.4%), and 5 of the 11 samples indicated high CAIX expression.[9]

Use of SG in Patients With BrM: Real-World Studies in mBC

Retrospective, observational cohort study in mTNBC[10]

A US retrospective, observational cohort study assessed SG data from the Flatiron Health database to evaluate outcomes of patients with mTNBC who received SG in the 2L+ setting (N=381). The median (IQR) age of patients was 61 (52–69) y; 61% and 18% identified as White and as Black/African American, respectively. Patients received a median (IQR) of 2 (1–3) prior LoT in the metastatic setting. SG LOT was 2L in 118 patients (31%) and 3L+ in 263 patients (69%). Of 291 patients with ≥1 metastatic site recorded in the database, 68 (23%) had BrM; a subgroup analysis was conducted for OS in these patients.

mOS (95 % CI) in the overall population was 11.3 (10–12.9) mo; in the group of patients with BrM, mOS (95% CI) was 9 (6.6–11.3) mo. Safety data was not reported for patients with BrM.

Retrospective, Observational Study in mTNBC[11]

Study design and demographics

A retrospective, observational study evaluated the effectiveness and safety of SG in 159 patients with mTNBC treated in southern Spain. A prespecified subgroup analysis included 22 patients (13.8%) with CNS metastases (Table9). Patients with CNS metastases had a higher prevalence of visceral disease and de novo Stage IV disease compared to the overall population (95.2% vs 75.5% and 22.7% vs 17.6%, respectively). All patients with CNS metastases had received prior RT.

Table 9. Subgroup Analysis in Patients With CNS Metastases: Baseline Patient and Disease Characteristics[11]

Key Demographics and Characteristics		SG (n=22)
Age, median (IQR), y		45 (30–67)
Premenopausal, n (%)		11 (50)
HER2 status, 0/low, n (%)		11 (50)/11 (50)
ECOG PS, 0/1/2/3, %		63.6/22.7/9.1/4.5
Visceral metastases, n (%)		21 (95.2)
Disease stage at diagnosis, n (%)	De novo Stage IV	5 (22.7)
	Localized or Stage I–III	17 (77.3)
Previous lines of therapy, median (IQR)		2.4 (2–4)
SG cycles, median (IQR)		4.68 (1–27)
Line of SG, 1L/2L/≥3L, n (%)		0/15 (68.2)/7 (31.8)
(Neo)adjuvant chemotherapy in early disease, n (%)		13 (59.1)[a]
First-line immunotherapy, n (%)		4 (18.2)

Abbreviations: 2L=second-line; 3L=third-line

[a]Twelve patients (54.5%) achieved pathological complete response with (neo)adjuvant chemotherapy in early disease.

Results

Effectiveness

After a median follow-up of 11.6 mo, mPFS (95% CI) was 4.6 (3.7–6.3) mo, and mOS (95% CI) was 10.9 (7.6–14.2) mo in the overall population. ORR was 31.2%, and DCR was 68.9%.

After a median follow of 6 mo, mPFS (95% CI) was 2.3 (1.3–3.2) mo in patients with CNS metastases, vs 5.1 (4.1–5.9) mo in patients without CNS metastases. ORR was 13.6%, and DCR was 36.3%. OS was not reported in this subgroup.

Safety

In patients with CNS metastases, the most common AE was neutropenia (45.5%; Grade 3–4: 27.2%); other AEs included diarrhea (36.8%; Grade 3–4: 9.1%), ALT/AST elevation (30%; Grade 3–4: 0%), and nausea (21.1%; Grade 3–4: 5.3%). G-CSF was administered as primary prophylaxis in 18.2% of patients and as secondary prophylaxis in 18.2% of patients. At least one dose reduction occurred in 31.8% of patients, and no patients discontinued SG due to AEs.

Retrospective cohort study in mTNBC[12]

A retrospective study assessed data from 16 centers in the UK in patients (N=132) with mTNBC. Median (range) age of patients was 56 (28–91) y. Median prior LOT in the metastatic setting was 2; SG LOT was 2L (28%), 3L (31%) and 3L+ (41%). Of 24 patients (18%) with CNS metastases, 8 were diagnosed with BrM while on treatment with SG. Median age of patients with CNS disease was 53 y and median prior LOT in the metastatic setting was 2.

mPFS (95% CI) and mOS (95% CI) in the overall population were 5.2 (4.5–6.6) mo and 8.7 (6.8–NA) mo, respectively. In patients with CNS disease, mPFS (95% CI) was 5.1 (1.6–6.6) mo and mOS was NR.

In patients with CNS disease who did not receive radiotherapy (RT) at any point (n=12) mOS (95% CI) was 2.5 (1.7–NA) mo. Of the 12 patients with CNS disease who were treated with RT to the CNS before or during treatment with SG, a significantly longer mOS was observed vs those who were not treated with RT (*P*=0.0025). Of the 13 patients with brain metastasis who remained on treatment long enough to have brain imaging to assess disease response, 5 had a PR, 1 had SD and 7 had PD.

Ambispective, Bicentric Cohort Study in mTNBC[13]

An ambispective, bicentric cohort study assessed effectiveness and safety of SG in patients with mTNBC treated through a French Early Access Program. Of the 103 patients enrolled, median (range) age at baseline was 55 (26–89) y, 80.6% of patients had an ECOG PS of 0 to 1, 64.1% of patients had 1 to 2 prior lines of treatment in the advanced setting, and 31.1% (n=32) were BMPos.

Effectiveness outcomes in the BMPos population are summarized below (Table 1010).

Table 10. Effectiveness Outcomes in the BMPos Population[13]

Outcome	SG (n=32)
mPFS (95% CI), mo	3.7 (2.6–6.2)
mOS (95% CI), mo	6.7 (56.3–NR)
ORR, %	19.8%[a]

[a]n=6 patients

SG treatment discontinuation was reported in 26 patients (81.2%) and was mostly due to disease progression. AEs that led to SG dose reduction were reported in 4 patients (12.5%).

Observational Study in aTNBC[14]

An observational study in Italy evaluated the effectiveness and safety of SG in patients aged ≥65 y with aTNBC. Of the 69 patients included, 11 (15.9%) had BrM, the median (range) age was 70 (65–85) y, and the median (range) number of previous anticancer therapies for metastatic disease was 2 (1–10).

Among the patients who had available data, no significant differences in PFS were observed between the 7 patients with BrM and the 48 patients without BrM (HR, 1.36; 95% CI: 0.47–3.95; *P*=0.6). OS was significantly shorter in patients with BrM than in those without BrM (HR, 5.58; 95% CI: 1.82–17.11; *P*=0.003).

Safety data were not reported specifically in patients with BrM.

Multicenter Study in HER2- mBC[15]

A multicenter study evaluated the effectiveness and safety of SG in 58 patients with HER2- mBC, including 12 (20.69%) with BrM (TNBC, n=11; HR+/HER2- mBC, n=1). Of the 58 patients included, median (range) age was 52.9 (30–77) y, and median (range) previous LOT for metastatic disease was 3 (1–10).

Effectiveness outcomes in patients with BrM are summarized in Table 11. Two patients with BrM received concomitant RT during SG treatment; 1 patient achieved CNS-CR and the other achieved CNS-PR.

Table 11. Effectiveness Outcomes in Patients With BrM[15]

Outcome	SG (n=12)
ORR, %	25
CNS-ORR, %	41.6
DCR, %	91.6
mPFS, (95% CI), mo	5.43 (2.73–NR)
CNS-PFS, median (95% CI), mo	14.87 (10.16–NR)
mOS (95% CI), mo	17.5 (17.5–NR)

Safety data were not reported specifically for patients with BrM.

Retrospective Study in mTNBC and CNS Metastases[16]

Study design and demographics

A retrospective study evaluated the effectiveness of SG in patients with mTNBC and CNS metastases and were treated in Italy. Overall, 54 patients were included (Table 12); 46 (85.2%) had treated/stable disease, 4 (7.4%) had active CNS metastases, and 4 (7.4%) had LMD.

Table 12. Baseline Demographics and Disease Characteristics[16]

Key Demographics and Characteristics		SG (N=54)
Age, median (range), y		54 (31–75)
ECOG PS, n (%)	0–1/2	48 (94.2)/ 3 (5.8)
TNBC at initial diagnosis, n (%)		44 (81.5)
HER2 low, n (%)		12 (33.2)
BRCA1 or *BRCA2* mutation, n (%)		11 (20.4)
Number of metastatic sites, median (range)		3 (2–7)
Number of prior anticancer regimens for metastatic disease, median (range)		3 (0–5)
Lines of therapy before CNS metastases, median (range)		2 (0–4)
Prior PARPi, n (%)		10 (18.5)
Prior PD-(L)1, n (%)		16 (29.6)
Prior surgery for CNS metastases, n (%)		4 (10.3)
Prior RT for CNS metastases, n (%)		50 (92.6)

Results

The median time from diagnosis of CNS metastases to SG initiation was 5 mo. After a median follow-up of 18.2 mo, mPFS (95% CI) in the overall population was 3.75 (3.06–7.89) mo, while OS was immature. Additional effectiveness outcomes in the overall population and by subgroup are summarized in Table 13.

Table 13. Effectiveness Outcomes in the Overall Population and by Subgroup[16]

Outcome	Overall (N=54)	Treated/Stable BrM (n=46)	Active BrM (n=4)	LMD (n=4)
CNS-PFS, median (95% CI), mo	9.26 (4.8–16.2)	12.1 (4–16.2),	4.8 (2–NA)	4.1 (2.79–NA)
ORR, n (%)	11 (20.4)	9 (19.6)	1 (25)	1 (25)
DCR, n (%)	20 (48.8)	16 (34.8)	1 (25)	3 (75)
CBR at 6 mo, n (%)	18 (14.8)	8 (17.4)	0	0
SD, n (%)	9 (16.6)	7 (15.2)	0	2 (50)
PD, n (%)	20 (37)	16 (34.8)	3 (75)	1 (25)
Not evaluable, n (%)	14 (26)	14 (30.4)	0	0

Safety was not reported.

Retrospective, Observational Study[17]

Study design and demographics

A retrospective, observational study evaluated clinical outcomes with SG (≥1 dose) treatment in patients with HER2- mBC and CNS metastases. Of the 33 patients included, 23 and 10 had TNBC and HR+/HER2- mBC, respectively. Overall, 18 patients had treated/stable BrM (defined as lesions that had been previously treated with CNS-specific therapies), 7 had active BrM (defined as those with new BrM or progressed BrM that had not been treated with CNS-specific therapies since progression), and 8 had LMD (defined as metastases in the leptomeningeal space with or without BrM). One patient had CNS metastases without extra-CNS involvement. Additional baseline characteristics are shown in Table 14.

Table 14. Baseline Demographics and Disease Characteristics: Overall and by Subgroup[17]

Key Demographics and Disease Characteristics		Overall (N=33)	Treated/Stable BrM (n=18)	Active BrM (n=7)	LMD (n=8)
Age at start of SG, median (range), y		56.7 (51.3–65.7)	59.59 (42.9–75.1)	59.1 (52.9–72.8)	50.88 (41.4–68.3)
Diagnosis of BrM to SG, median (range), mo		7.5 (0.6–94.8)	4.6 (0.7–94.8)	9.3 (0.6–21)	9.3 (2.7–21.5)
HER2 status at SG start, n (%)	HER2-0	22 (66.7)	9 (50)	7 (100)	6 (75)
	HER2-low	11 (33.3)	9 (50)	0 (0)	2 (25)
Metastatic lines prior to SG, median (range), n		3 (0–10)	3 (0–9)	5 (2–10)	3.5 (2–6)

Results

The overall median (95% CI) duration of follow-up was 6.7 (3.1–10) mo; responses were evaluable in 30 patients in the CNS metastases subgroup and 29 patients in the extra-CNS metastases subgroup. The CNS PFS was 2 (1.2–7.7) mo and 3.2 (2.2–5.1) mo in patients with HR+/HER2- and TNBC, respectively. In patients with >3 and ≤3 prior lines, the CNS PFS was 2.7 (1.2–4.8) mo and 3.2 (2–7.1) mo, respectively; additional results are found in Table 15. The CNS ORR by mBC type was as follows: HR+/HER2-, 11.1%; TNBC, 14.3%.

Table 15. Outcomes Overall and by Subgroup[17]

Outcome	Overall (n=30)		Treated/Stable BrM (n=16)		Active BrM (n=7)		LMD (n=7)	
	CNS	Extra-CNS[a]	CNS	Extra-CNS[b]	CNS	Extra-CNS	CNS	Extra-CNS
Response[c], n (%)	4 (13.3)	1 (3.4)	2[d] (12.5)	0	0	0	2 (28.6)	1 (14.3)
SD, n (%)	16 (53.3)	12 (41.4)	10 (62.5)	6 (40)	3 (42.9)	4 (57.1)	3 (42.9)	2 (28.6)
PD, n (%)	10 (33.3)	16 (55.2)	4 (25)	9 (60)	4 (57.1)	3 (42.9)	2 (28.6)	4 (57.1)
DCR, n (%)	20 (66.7)	13 (44.8)	12 (75)	6 (40)	3 (42.9)	4 (57.1)	5 (71.4)	3 (42.9)
CBR at 6 mo, n (%)	8 (26.7)	4 (13.8)	6 (37.5)	2 (13.3)	1 (14.3)	1 (14.3)	1 (14.3)	1 (14.3)
mPFS[e] (95% CI), mo	2.9 (2–4.3)	2.6 (1.9–4)	3.4 (2.2–10)	2.7 (1.9–4.2)	1.9 (1.2–16.5)	1.9 (1.5–10.1)	2.1 (0.4–7.7)	2 (0.4–6.9)
mOS (95% CI), mo	6.9 (3.1–10.2)		10 (4.3–15.9)		3.1 (1.9–21.6)		3.8 (1.7–11.9)	

[a]n=29. [b]n=15. [c]CR or PR for CNS response. [d]Both received RT <2 mo before SG began.
[e]Bicompartmental mPFS (95% CI) by subgroup was as follows: overall, 2.6 (1.9–4) mo; treated/stable BrM, 2.7 (1.9–4.1) mo; active BrM, 1.8 (1.5–10.1) mo; LMD, 2.4 (0.4–5.1) mo.

Overall, 32 patients discontinued treatment due to disease progression (53.1% had both CNS and extra-CNS progression), and 1 discontinued SG due to toxicity; 5 patients died during SG treatment.

Three patients had bicompartmental PFS that was >10 mo; each had surgery and brain RT. Two of these patients had TNBC with stable BrM and received SG early (≤2 prior therapies); the third patient with HR+/HER2- mBC had 95 mo between BrM diagnosis and SG initiation.

Safety data were not reported.

Retrospective Study in mBC[18]

A single-center, retrospective study evaluated the effectiveness of SG in 30 patients with mBC (HR+/HER2- mBC: n=16 [53.3%]; TNBC: n=14 [46.7%]) and CNS metastases (BrM, n=22 [73.3%]; BrM + LMD, n=5 [16.7%]; and LMD, n=3 [10%]). All patients were female and had a median (range) age of 57 (36–76) y. Patients with HR+/HER2- mBC had a median of 3 prior lines of chemotherapy, and patients with TNBC had a median of 2 prior lines. Overall, 27 patients (90%) had received prior CNS-directed RT (SRS, n=17; SRS + WBRT, n=7; or WBRT/craniospinal RT, n=3). Among patients with BrM (n=27), 74.1% had stable BrM and a median of 1.2 mo since RT, and 25.9% had active BrM. Among patients with LMD (n=8), 50% received prior LMD-directed RT and had a median of 2.1 mo since RT.

Effectiveness outcomes are summarized in Table 16. All CNS responses were PRs and occurred in patients who had received CNS-directed RT <1 mo prior to SG initiation (BrM, n=4; BrM + LMD, n=2). No CNS ORRs were observed in patients with active BrM or LMD.

Table 16. Effectiveness Outcomes Overall and by Type of mBC[18]

Outcome	SG		
	HR+/HER2- mBC	TNBC	Overall
CNS ORR, n/N (%)	4/16 (25)	2/14 (14.3)	6/30 (20)
Extra-CNS ORR, n/N (%)	0/16 (0)	2/13 (15.4)	2/29 (6.9)
CNS CBR at 6 mo, n/N (%)	3/16 (18.8)	5/14 (35.7)	8/30 (26.7)
Extra-CNS CBR at 6 mo, n/N (%)	3/16 (18.8)	5/13 (38.5)	8/29 (27.6)
TTF, median (IQR), mo	3.2 (2–6.2)	4.5 (1.6–9.4)	3.7 (2–6.7)
CNS-PFS, median (IQR), mo	4.4 (0.8–4.9)	5.1 (2.3–8.5)	4.5 (2.3–8.5)

Outcome	SG		
	HR+/HER2- mBC	TNBC	Overall
Extra-CNS PFS, median (IQR), mo	2.5 (1.6–5.7)	4.5 (2.1–9.3)	3.6 (1.9–9)
mOS (IQR), mo	8.2 (5.9–24)	11.8 (6.7–39.1)	11.7 (6.2–24)

Abbreviation: TTF=time to treatment failure.

Safety data were not reported.

Retrospective, Multicenter Study in mTNBC and BrM[19]

Study design and demographics

A retrospective, multicenter study evaluated the effectiveness and safety of SG in patients with mTNBC and radiologically confirmed BrM treated at centers in the Czech Republic, Poland, and Slovakia. Overall, 29 patients were included (Table 17). In the palliative setting, prior treatments included the following: platinum compounds (n=19; 65.5%), taxanes (n=15; 51.7%), anthracyclines (n=13; 44.8%), cape (n=9; 31%), gem (n=8; 27.6%), and pembro (n=6; 20.7%). PARPi were administered in 5 patients (17.2%), vinorelbine in 2 (6.9%), hormonal agents in 4 (13.8%), anti-HER2 therapy in 1 (3.4%), and other regimens in 4 (13.8%).

Table 17. Baseline Demographics and Disease Characteristics[19]

Key Demographics and Characteristics		SG (N=29)
Age, median (range), y		48.5 (29.8–69.6)
Premenopausal, n (%)		14 (48.3)
HER2 IHC, 0/1+/2+/unknown, n (%)		15 (51.7)/ 8 (27.6)/ 2 (6.9)/ 4 (13.8)
ECOG PS, 0/1/≥2, (%)		7 (24.1)/ 21 (72.4)/ 1 (3.4)
Previous lines of palliative systemic therapy, median (range)		2 (1–3)
Prior CNS therapy, n (%)	Neurosurgical resection	4 (14.3)
	Brain RT	25 (86.21)
Number of BrM lesions, median (range)		3 (1–20)
Size of largest BrM lesion, median (range), mm		16.5 (2–50)

Results

Effectiveness

After a median (range) follow-up of 6.05 (0.79–27.47) mo, 22 patients (75.9%) had died, and 26 (89.7%) had discontinued treatment with SG; of these, 25 discontinued due to disease progression. Effectiveness outcomes are summarized in Table 18.

Table 186. Effectiveness Outcomes[19]

Outcome	SG (N=29)
mOS (95% CI), mo	8.9 (6.04–10.32)
Estimated OS rates at 3/6/9/12 mo, %	85.2/ 60.3/ 42.3/ 28.2
mPFS (95% CI), mo	3.09 (2.4–4.11)
Estimated PFS rates at 3/6/9/12 mo, %	53.6/ 31.4 /22.5/ 12

Of the 26 patients with evaluable data, ORR was 30.8% (n=8). CNS progression occurred in 6 patients (23.1%), and per univariable Cox proportional hazards model, there was no statistically significant association between the number or size of CNS lesions and PFS or OS (*P*>0.05 for each).

Safety

No unexpected safety signals were reported. Hematological AEs included neutropenia (79.3%; Grade 2: n=7; Grade 3: n=11; Grade 4: n=5), anemia (41.4%; Grade 1: n=4; Grade 2: n=6; Grade 3: n=2), thrombocytopenia (13.8%; Grade 1: n=1; Grade 2: n=1; Grade 3: n=2), and febrile neutropenia (10.3%). Febrile neutropenia included events of Grade 5 severity; however, the total number of events was not reported. Non-hematologic AEs included alopecia (50%), fatigue (48.1%; Grade 1: n=5; Grade 2: n=6; Grade 3: n=2), nausea (25%; Grade 1: n=4; Grade 2: n=3), diarrhea (17.2%; Grade 1: n=3; Grade 2: n=2), and vomiting (10.3%; Grade 1: n=2; Grade 2: n=1). Maximum Grade 2 hepatotoxicity occurred in 6.9% of patients, and Grade 4 allergic reaction to SG occurred in 3.4% of patients.

AEs resulted in dose delays in 15 patients (51.7%), and dose reductions in 11 patients (37.9%), with further reductions seen in 1 patient. Neutropenia was the main reason for dose delay (n=13) or reduction. SG was permanently discontinued due to treatment-related toxicities in 2 patients (7.7%). G-CSF was administered as primary prophylaxis in 11 patients (37.9%) and as secondary prophylaxis in an additional 12 patients (41.4%).

Retrospective Study in mBC and BrM[20]

Study design and demographics

A retrospective study evaluated the effectiveness and safety of SG or T-DXd in 12 patients with mBC and active (n=5) or stable (n=7) BCBMs who were treated in Germany. Of the patients with BrM, 12 had TNBC and were treated with SG. Patients with extracranial-only or LMD were excluded. Starting doses of SG 10 mg/kg were administered in 10 patients (83%).

Median (IQR) age was 50.5 (42–60) y in patients treated with SG. SG-treated patients received a median (range) of 2.5 (2–5) prior lines of chemotherapy, 11 (92%) had received prior RT, and 2 (17%) had undergone surgery for BrM.

Three patients (25%) received brain RT ≥45 d before SG initiation, and 2 (18%) received concurrent RT during treatment. Active and stable BrM were present in 5 (42%) and 7 patients (58%) treated with SG, respectively.

Results

Effectiveness

In the SG cohort, median (IQR) duration of treatment was 71 (37–154) d, and intracranial DCR (95% CI) was 42% (13–71%). Intracranial PFS and OS in the overall population and by BrM subtype are summarized in Table 19.

Table 19. Outcomes Overall and by Subgroup in Patients With BrM Treated With SG[20]

Median (95% CI), Mo	SG		
	Overall (N=12)	Active BrM (n=5)	Stable BrM (n=7)
Intracranial PFS	2.7 (1.6–10.5)	2.7 (1.9–10.5)	2.1 (0.4–14.1)
OS	6.4 (1.2–NR)	8.1 (5.3–NR)	2.2 (0.4–NR)

In patients treated with SG, no statistically significant association between BrM status (active vs stable) and intracranial PFS or OS was observed (P=0.86 and P=0.63, respectively).

Before data cut-off, SG was discontinued due to intracranial progression in 5 patients (42%), extracranial progression in 3 (25%), and a treatment-related AE in 1 (8%); overall, 7 patients (58%) died before data cut-off.

Safety

In patients treated with SG, the most common AE was neutropenia (42%). Severe Grade ≥3 AEs included neutropenia (33%) and anemia (8%). Dose reductions occurred in 3 patients due to 4 events: 2 events of neutropenia and 2 of fatigue. Treatment discontinuation occurred in 1 patient due to treatment-associated neutropenia.

Ongoing Clinical Studies

An open-label, phase 2 study (NCT04647916) is evaluating the efficacy and safety of SG in patients with HER2- breast cancer and BrM.

A real-world, multicenter study (NCT07251868) is evaluating the efficacy and safety of SG in patients with BC and BrM.

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Abbreviations

1L=first-line
γH2AX=phosphorylated form of histone H2AX
AE=adverse event
aTNBC=advanced triple-negative breast cancer
BCBM=breast cancer brain metastases
BC=breast cancer
BMNeg=negative for brain metastasis
BMPos=positive for brain metastasis
BRCA=breast cancer gene
BrM=brain metastases
CAIX=carbonic anhydrase IX
cape=capecitabine
CBR=clinical benefit rate
CNS=central nervous system
CR=complete response
CSF=cerebrospinal fluid
DCR=disease control rate
ECOG PS=Eastern Cooperative Oncology Group performance status
ET=endocrine therapy
extra-CNS=lesions or disease outside of the central nervous system
G-CSF=granulocyte colony-stimulating factor

gem=gemcitabine
H-score=histochemical scoring
HER2-=human epidermal growth factor receptor 2-negative
HR=hazard ratio
HR+=hormone receptor-positive
IC_{50}=half maximal inhibitory concentration
IHC=immunohistochemistry
ISH=in situ hybridization
LMD=leptomeningeal disease
mBC=metastatic breast cancer
mOS=median overall survival
mPFS=median progression-free survival
mTNBC=metastatic triple-negative breast cancer
NA=not available
NE=not estimable
NR=not reached
ORR=objective response rate
OS=overall survival
PARPi=poly(ADP-ribose) polymerase inhibitors
PD-(L)1=programmed death (ligand)-1
PD=progressive disease
pembro=pembrolizumab
PFS=progression-free survival
PR=partial response
RT=radiotherapy
SD=stable disease
SG=sacituzumab govitecan
SN-38=active metabolite of irinotecan; topoisomerase I inhibitor
SN-38G=glucuronidation metabolite of SN-38
SRS=stereotactic radiosurgery
T-DXd=trastuzumab deruxtecan
TEAE=treatment-emergent adverse event
TNBC=triple-negative breast cancer
TPC=treatment of physician's choice
Trop-2=trophoblast cell surface antigen 2
WBRT=whole-brain radiotherapy

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