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Trodelvy® (sacituzumab govitecan-hziy) Use of SG Monotherapy With Radiation Therapy in Patients With mBC

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

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Trodelvy is not indicated for use with RT. 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: Use of SG Monotherapy + RT in Patients With mBC

In SG monotherapy studies (ASCENT-03 in 1L PD-[L]1 inhibitor-ineligible mTNBC,[1] ASCENT in 2L+ mTNBC,[2] TROPiCS-02 in pre-treated HR+/HER2- mBC,[3] and IMMU-132-01 in various metastatic epithelial cancers, including mBC[4]), RT was to be discontinued ≥2 wk prior to study participation. Prior to study enrollment, AEs associated with previous treatment(s), including RT, were required to have recovered to Grade ≤1 (or Grade ≤2 in ASCENT-03). During SG studies, palliative procedures were permitted at the discretion of the study investigator. Palliative RT was not permitted for tumor progression across the studies.[5,6]

Retrospective and Real-World Studies: Use of SG Monotherapy + RT in Patients With mBC

In a multicenter TNBC study of SG with (n=66) or without RT (n=237), the median PFS was similar between groups: SG + RT, 4.2 mo; SG, 5.1 mo (*P*=0.42). The median OS was numerically shorter in the SG + RT group than in the SG group: 9.3 vs 11.9 mo, respectively; *P*=0.14. The rates of all-grade TRAEs, treatment discontinuation, and SG dose reduction were similar between treatment groups.[7]

In a retrospective analysis in patients with mTNBC treated with SG, with (n=28) or without (n=40) RT, no significant association between RT and Grade >2 AEs was observed (*P*=0.096). SG dose reductions occurred in 5 patients (17.9%) who received RT and in 9 patients (22.5%) who did not receive RT, with permanent discontinuation of SG due to toxicity occurring in 4 (14.3%) vs 3 (7.5%) patients.[8]

In a BC study of SG + concurrent or sequential RT in France, 37 RT courses were administered concurrently with SG, and 26 were administered sequentially. Of the 36 RT courses administered for symptomatic control, the overall response rates per course were as follows: CR, 16 (25%); PR, 50 (80%). Of the 27 RT courses administered for oligoprogressive disease (n=27), RECIST data from 12 wk were available for 10 courses:

CR, 8 (29.6%); PR, 20 (74.1%); and PD, 1. Seventeen cases (27%) of Grade 1 to 2 AEs were observed, and no Grade ≥3 AEs were reported among those who received concomitant SG + RT.[9]

In an observational mBC study of SG in 33 patients with CNS metastases (treated/stable BrM, n=18; active BrM, n=7; LMD, n=8), the overall median (95% CI) CNS-PFS and extra-CNS-PFS was 2.9 (2–4.3) mo and 2.6 (1.9–4) mo, respectively; CNS-PFS was similar across patient subgroups. Three patients (TNBC, n=2; HR+/HER2-, n=1) had bicompartmental PFS that was >10 mo; each had surgery and brain RT. No safety data were reported.[10]

In a multicenter HER2- BCBM study of SG + SRS (patients, N=26; lesions, n=277 over 36 courses; 135 of the lesions [47%] received SRS + SG administered concurrently), the 12- and 24-mo LC rates were 94% and 84%, respectively. The median (95% CI) CNS-PFS and systemic PFS were 5.4 (2.8–7.3) mo and 4.4 (2.2–7.3) mo, respectively. The median (95% CI) OS was 8.4 (5.4–13.4) mo. No SRN was reported, and 2 cases (8%) of LMD were reported.[11]

A multicenter cohort TNBC study evaluated SG and concurrent (sequential, n=9; simultaneous, n=8) palliative RT in female patients (N=17). Prior to SG administration, 12 patients received RT, while 17 patients received 34 local RT series concurrently with SG. At the first follow-up (4–8 wk post-RT), the response rate per treatment course was 82.1%. RT response was not available in 6 lesions. The most common AEs were neutropenia and fatigue; 3 and 4 patients who received simultaneous and sequential RT administration, respectively, reported acute Grade 2 to 3 AEs.[12]

In a study of SG + SRS in patients with active BCBM in the US (N=14; lesions, n=121), the median (95% CI) OS was 8.4 (4.2–NR) mo. The median (95% CI) CNS-PFS and EC-PFS were 4.2 (1.9–6.3) mo and 4.4 (1.4–8.1) mo, respectively. LMD occurred in 2 patients, and SRN was reported in 1 patient who had received SRS before SG treatment.[13]

In a single-center mBC study in patients (N=13; 19 metastatic lesions) treated with SG + concurrent EBRT, 10 sites received SBRT, and 9 sites received conformal VMAT. The median (95% CI) OS at Months 6 and 12 was 45.1% (22.9–88.9%) and 16.9% (3.27–87.5%), respectively. Most SG-related AEs were Grade 1 or 2 in severity and included nausea/vomiting, asthenia, alopecia, diarrhea, and anemia. No patients had RT-induced AEs, and none required disruption of SG.[14]

In a subgroup analysis of a real-world mTNBC study that evaluated patients who had received ≥1 dose of SG, 11 of 24 patients with CNS disease received RT for BrM prior to or during SG treatment. Compared with patients with CNS disease who had not been treated with RT, PFS was significantly longer in RT-treated patients (HR, 0.27; 95% CI: 0.1–0.71; *P*=0.006). No safety data were reported.[15]

In an observational study that evaluated early toxicity of ADCs with concurrent RT in 23 patients with Stage IV BC (SG, n=5; T-DXd, n=18), no RT courses were suspended, and all-grade AEs were reported in 11 patients (47.8%). Of the 5 SG-treated patients, 1 had Grade 2 brain radionecrosis (the patient had received multiple brain SRT courses); 3 had Grade 1 fatigue, and 1 had Grade 1 pneumonitis.[16]

Clinical Studies: Use of SG Monotherapy + RT in Patients With mBC

Use of RT Prior to and During SG Study Participation

In SG monotherapy studies (ASCENT-03 in 1L PD-[L]1 inhibitor-ineligible mTNBC,[1] ASCENT in 2L+ mTNBC,[2] TROPiCS-02 in HR+/HER2- mBC,[3] and IMMU-132-01 in various metastatic epithelial cancers, including mBC[4]), RT was to be discontinued ≥2 wk prior to study participation, as described in the protocols. Prior to study enrollment, AEs associated with previous treatment(s), including RT, were required to have recovered to Grade ≤1 (or Grade ≤2 in ASCENT-03).[5,6]

During SG studies, palliative procedures were permitted at the discretion of the study investigator. Palliative RT was permitted in ASCENT, for the treatment of BrM, and in ASCENT-03, for non-target lesions; these studies required that SG be interrupted 1 wk before the procedure and reinstated 2 wk after the procedure. Palliative RT was permitted in TROPiCS-02, for the treatment of a symptomatic solitary non-target lesion or to the brain, and in ASCENT, for the treatment of bone metastases; there was no requirement to interrupt SG treatment in these instances.[5,6]

Palliative RT was not permitted for tumor progression across the four studies.[5,6]

Retrospective and Real-World Studies: Use of SG Monotherapy + RT in Patients With mBC

Retrospective Analysis of SG ± RT in TNBC in Europe[7]

A retrospective analysis compared efficacy and safety outcomes in female patients treated with SG with (n=66) or without RT (n=237) at centers in the Czech Republic, Poland, and Slovakia. RT administration occurred before or during SG (n=33 patients each). Baseline demographics were not provided. Of the 83 RT treatments delivered across 10 treatment sites, the brain was the most frequently treated (33.7%; n=28). Other RT sites were as follows: breast/chest wall ± lymph nodes, 18.1% (n=15); thoracic spine, 13.3% (n=11); pelvis, 8.4% (n=7); lumbar spine and other bones (skull, extremities, ribs), each 7.2% (n=6); other locations (lymph nodes, retroperitoneum), 4.8% (n=4); and cervical spine, lung, and liver, each 2.4% (n=2). Significantly more patients in the SG + RT group had CNS metastases than in the SG group (27.3% vs 4.6%, respectively; $P<0.001$).

Efficacy and safety results

The median PFS was similar between groups: SG + RT, 4.2 mo; SG, 5.1 mo ($P=0.42$); the 6-mo PFS (95% CI) rates were 36.9% (24.5–49.3%) in the SG + RT group and 42% (35.3–48.5%) in the SG group. The median OS was numerically shorter in the SG + RT group than in the SG group: 9.3 vs 11.9 mo, respectively; $P=0.14$. The 12-mo OS (95% CI) rates were as follows: SG + RT, 36.2% (23.7–48.8%); SG, 49.5% (42.1–56.4%).

The incidence of all-grade TRAEs was not significantly different between the SG + RT and SG groups: neutropenia (74.2% vs 67.5%, respectively; $P=0.37$); diarrhea (15.2% vs 20.7%; $P=0.38$); anemia (47% vs 37.6%; $P=0.2$); thrombocytopenia (16.9% vs 8%; $P=0.06$); and

fatigue (43.3% vs 39.1%; *P*=0.56). In both groups, most patients discontinued SG due to disease progression. Similar rates of treatment discontinuation (SG + RT, 1.5%; SG, 2.1%; *P*=1) and SG dose reductions (SG + RT, 34.9%; SG, 38.4%; *P*=0.35) were observed between groups.

Retrospective, Multicenter Analysis of SG ± RT in mTNBC in Europe[8]

A retrospective analysis compared safety outcomes in 68 patients with mTNBC treated with SG with (n=28) or without (n=40) RT across three European countries. The primary objective was to evaluate the association between RT and Grade >2 AEs.

The median (range) age at SG initiation was 64 (36–84) y, and the median (range) follow-up from SG initiation was 12 (1–50) mo. RT was administered within 2 wk before, or concurrently with, uninterrupted SG treatment, accounting for a total of 39 RT courses. Seventeen patients (60.7%) received RT with ablative intent, defined as a minimum EQD2 dose of 50 Gy delivered in ≤12 fractions, whereas 11 patients (39.3%) received palliative RT only. The most common target site of RT was bone (40.1%; n=16 RT courses).

The median (range) total RT dose was 25 (8–54) Gy delivered over 8 (1–18) fractions, with median (range) EQD2 and biologically effective doses of 28 (12–83) Gy and 34 (14–100) Gy, respectively.

No significant association between RT and Grade >2 AEs was observed (*P*=0.096). Dose reductions of SG occurred in 5 patients (17.9%) who received RT vs 9 patients (22.5%) who did not receive RT, with permanent discontinuation of SG due to toxicity occurring in 4 (14.3%) vs 3 (7.5%) patients.

Retrospective, Multicenter French mBC Study of SG + RT[9]

A retrospective study evaluated the safety and efficacy of SG given concurrently or sequentially with RT in female patients with various types of BC (N=55; 63 lesions; 63 RT courses) at six French institutions. Data were collected via an online questionnaire completed by the healthcare provider who was the most familiar with the patient's course. The primary endpoint was safety, and the secondary endpoint was efficacy (per RECIST).

The median (range) age was 56 (37–82) y; most patients (30%) had HER2-/HR- BC, 27% had HER2-/HR+ BC, 24% had HER2-low/HR+ BC, 18% had HER2-low/HR- BC, and 2% had HER2+/HR- BC. RT techniques included 3D-CRT (52%), SBRT (40%), and IMRT/VMAT (8%). Six RT courses (9.5%) occurred in the same field; 36 courses (57.1%) of RT were initiated for symptomatic control, and 27 courses (42.8%) of RT were initiated for oligometastatic control. Target sites of RT included the following: bone, 49.2% (n=31); brain, 31.7% (n=20); thorax, 14.3% (n=9); and eye, liver, and lymph node (each, n=1). Sixty patients received SG 10 mg/kg, and 3 received 8 mg/kg. A median (IQR) of 5 (3–13.5) doses of SG were administered before RT, and 14 RT courses were administered on the same day as SG. SG + RT was administered concurrently (defined as a ≤4 d interval between SG and RT treatments) in 37 courses (58.7%; median, 3 d) and sequentially (defined as a >5 d interval between treatments) in 26 courses (42.3%; median [range], 6 [5–30] d).

Efficacy results

Of the 36 RT courses for symptomatic control, 24 courses (66.7%) resulted in symptom improvement, 6 (16.6%) resulted in complete disappearance of symptoms, and 6 (16.6%) maintained a stable response to symptom control. Efficacy data, per RECIST, from 12 wk were available for 10 courses, which resulted in 1 CR, 6 PRs, and 3 SDs. The overall response rate (via imaging or symptom relief) per course was as follows: CR, 25% (n=16); PR, 80% (n=50). The median (95% CI) OS after SG treatment was 12.6 (7.97–17.77) mo, and the 12-mo OS rate was 32.7%.

Twelve weeks post-RT, all patients in the oligoprogressive cohort (n=27; 27 courses) had imaging, with the following results (per RECIST): CR, n=8 (29.6%); PR, n=20 (74.1%); and PD, n=1 (mediastinal lymph node).

Safety results

After RT (median [range] follow-up, 7.9 [1.7–35.4] mo), AEs were noted in 8 SBRT courses, 7 3D-CRT courses, and 3 IMRT courses. Seventeen cases (27%) of Grade 1 to 2 AEs were observed, including 4 cases of esophagitis/odynophagia, 3 cases of RD, and 1 case of SBRT-associated Grade 2 brain radionecrosis. Other safety events included the following in 1 patient each: seizure, moderate headache, aphasia during RT, and Grade 3 nausea (patient received SBRT for mediastinal lymph node). Among patients who received concomitant SG, all AEs were Grade 1 or 2 (in 9 courses; 14%) and were localized to the irradiated volume in 7 cases (esophagitis, n=2; RD, n=1). Among patients who received RT for symptom control, 5 acute in-field AEs occurred (each, Grade 1 or 2). Acute AEs did not increase during the 14 RT courses in which RT and SG were administered on the same day. No RT cycles were interrupted due to SG, and 1 SG cycle was postponed due to RT.

Of the 6 cases of re-irradiation or overlapping of prior RT fields, 4 occurred in instances during which SG was administered concomitantly (SBRT, n=2; 3D-CRT, n=2). Two AEs occurred during concurrent SG and re-irradiation: Grade 2 odynophagia (palliative 3D-CRT; 20 Gy in 5 fractions) and Grade 1 nausea (SBRT; 27 Gy in 3 fractures).

Retrospective, Observational Real-World mBC Study in US[10]

A retrospective, observational real-world mBC study evaluated clinical outcomes with SG treatment in patients with CNS metastases. Of the 33 patients included (median [range] age at SG initiation, 56.7 [51.3–65.7] y), 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.

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Table 1. Select Baseline Patient and Treatment Characteristics: Overall and by Subtype (Grinda et al)[10]

Select Patient and Treatment Characteristics		Overall (N=33)	Treated/Stable BrM (n=18)	Active BrM (n=7)	LMD (n=8)
Time between events, median (range), mo	Diagnosis of BrM to SG	7.5 (0.6–94.8)	4.6 (0.7–94.8)	9.3 (0.6–21)	9.3 (2.7–21.5)
	Prior RT for BrM to SG	2 (0.2–44)	1 (0.2–44)	7.4 (5–17.5)	8.8 (1.2–15.2)
Prior RT for BrM, n (%)		28 (84.8)	17 (94.9)	6 (85.7)	5 (62.5)
Type of prior RT for BrM, n (%)	SRS	16 (57.1)	10 (58.8)	3 (50)	3 (60)
	WBRT	7 (25)	4 (23.5)	2 (33.3)	1 (20)
	SRS and WBRT	4 (14.3)	3 (17.6)	1 (16.7)	0

Abbreviation: WBRT=whole brain radiation therapy.

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 subgroup and 29 patients in the extra-CNS subgroup. The CNS-PFS was similar across patient subgroups; additional results are found in Table 2. The CNS objective response rate by mBC type was as follows: HR+/HER2-, 11.1%; TNBC, 14.3%.

Table 2. Outcomes Overall and by Subgroup (Grinda et al)[10]

Response, n (%)	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]	4 (13.3)	1 (3.4)	2[d] (12.5)	0	0	0	2 (28.6)	1 (14.3)
SD	16 (53.3)	12 (41.4)	10 (62.5)	6 (40)	3 (42.9)	4 (57.1)	3 (42.9)	2 (28.6)
PD	10 (33.3)	16 (55.2)	4 (25)	9 (60)	4 (57.1)	3 (42.9)	2 (28.6)	4 (57.1)
DCR	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	8 (26.7)	4 (13.8)	6 (37.5)	2 (13.3)	1 (14.3)	1 (14.3)	1 (14.3)	1 (14.3)
PFS,[e] median (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)
OS, median (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)	

Abbreviations: CBR=clinical benefit rate; DCR=disease control rate.
[a]n=29. [b]n=15. [c]CR or PR for CNS response. [d]Both received RT <2 mo before SG began.
[e]Bicompartmental median (95% CI) PFS 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 AEs; 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.

No safety data were reported.

Retrospective, Multicenter HER2- BCBM Study in US[11]

A multicenter, retrospective HER2- BC study evaluated the efficacy and safety of SG + SRS (patients, N=26; lesions, n=277 over 36 courses). Eligible patients had active BCBM before

SG initiation. All patients received SG 10 mg/kg, and data for those who later had an SG dose reduction were included in the analysis. The median (range) age was 57 (30–72) y, 85% (n=22) had HR- BC, 77% (n=20) did not have neurological symptoms, and the median (range) Breast GPA was 1 (0.5–2). There was a median (range) of 1 (1–4) lesion per patient, with a median (range) of 6 (1–38) lesions treated per course. Patients received a median (range) of 3 (1–11) prior systemic therapies and had 3 (1–5) extracranial metastatic sites. The median (range) follow-up from the beginning of SG treatment was 23.3 (0.3–32.9) mo; see Table 3 for RT characteristics.

Table 3. RT Treatment Characteristics (N=26; Khatri et al)[11]

RT Characteristics		Results	RT Characteristics		Results
Dose, median (range), Gy		24 (16–30)	SRS, n (%)		168 (61)
Fractions, median (range)		1 (1–5)	Dose, median (range)		24 (16–24)
SRS timing, n (%)	Before SG	129 (48.7)	fSRS, n (%)		109 (39)
	Concurrent[a]	135 (46.6)	Dose, median (range)		24 (20–30)
	After SG	13 (4.7)	Fractions, median (range)		3 (3–5)
GTV, median (range), cc		0.05 (0.01–11.26)	Timing of lesion treatment, n (%)	Preoperative	2 (0.7)
PTV, median (range), cc		0.34 (0.03–17.92)		Postoperative	1 (0.4)

[a]Defined as SRS administered during SG treatment and up to the last day of the last SG dose.

Efficacy and safety outcomes

By lesion, 16 local failures (6%) occurred in 6 patients; local failure was defined as a ≥20% increase in lesion size that remained consistent or continued to progress on subsequent imaging per Response Assessment in Neuro-Oncology Brain Metastases criteria. On univariate analysis, there was a significant association between distant intracranial progression and neurological symptoms (HR, 4.15; 95% CI: 1.44–11.95; *P*=0.008) and between CNS-PFS and the number of extracranial metastatic sites (≥3 vs <3; HR, 5.6; 95% CI: 1.53–20.54; *P*=0.009). There was no association between OS and Breast GPA. Extracranial progression was observed in 17 patients (65%), and 18 patients (59%) had died at the time of analysis. See Table 4 for a summary of treatment outcomes.

Table 4. Treatment Outcomes in SG + SRS-Treated Patients (Khatri et al)[11]

LC and DIC		Results	PFS and OS		Results
LC, (95% CI), %	12-mo	94 (87–97)	CNS-PFS, median (95% CI), mo		5.4 (2.8–7.3)
	24-mo	84 (71–92)	12-mo CNS-PFS, (95% CI), %		18 (7–40)
LC with concurrent[a] SRS, (95% CI), %	12-mo	94 (81–98)	Systemic PFS, median (95% CI), mo		4.4 (2.2–7.3)
	24-mo	83 (61–94)	Systemic PFS rates, (95% CI), %	12-mo	17 (7–37)
				24-mo	4 (1–24)
DIC, median (95% CI), mo		6.1 (2.3–17.4)	OS, median (95% CI), mo		8.4 (5.4–13.4)
DIC, (95% CI), %	12-mo	37 (20–59)	OS rates, (95% CI), %	12-mo	38 (21–60)
	24-mo	9 (1–42)		24-mo	16 (5–41)

[a]Concurrent was defined as SRS administered during SG treatment and up to the last day of the last SG dose.

No SRN or other unexpected AEs were reported. Two cases (8%) of LMD were reported. One patient developed LMD 2.8 mo after SG was initiated. The patient had several SRS courses (one was 9 mo before SG for 8 lesions, one was 4.4 mo before SG for 13 lesions, two were concurrent with SG for 10 and 3 lesions, and one was 8.4 mo after SG discontinuation). This patient did not undergo intracranial surgery and died 14.2 mo after SG initiation, which was 11.4 mo after LMD diagnosis. The second patient was diagnosed with LMD 8.1 mo after SG initiation and received 2 SRS courses (one was 2.2 mo before SG to

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2 lesions, and one was concurrent with SG). The second course occurred postoperatively (27 Gy in 3 fractions), and the patient died 13.4 mo after SG started.

Retrospective, Multicenter Cohort TNBC Study of SG + RT in Germany[12]

A retrospective, multicenter cohort TNBC study assessed the efficacy and safety of SG and concurrent (sequential or simultaneous) palliative RT in female patients (N=17). The median (range) patient age was 48 (33–73) y, and most had an ECOG PS of 0 to 1. Patients had previously received a median (range) of 2.5 (1–6) prior lines of treatment and a median (range) of 5 (2–26.5) treatment cycles of SG, which was mostly administered using a dose of 10 mg/kg. The median (range) total dose and dose per fraction of RT was 36 (8–50.4) Gy and 3 (1.8–20) Gy, respectively. See Table 5 for further treatment characteristics.

Table 5. RT Treatment Characteristics (N=17; Krug et al)[12]

RT Technique,[a] n (%)	Patients	RT Target Volume,[a] n or n (%)	Targets
Intensity-modulated RT	13 (38.2)	Lymph node metastases	9 (26.5)
Electrons	8 (23.5)	Brain metastases	8 (23.5)
SRT	7 (20.6)	Skin metastases	8 (23.5)
3D-conformal RT	4 (11.8)	Bone metastases	6 (17.6)
Unknown	2 (5.9)	Breast/thoracic wall	2 (5.9)
		Lung metastasis	1 (2.9)
		Target volumes with re-irradiation[b]	12

[a]Individual RT courses and target volumes.
[b]Targets that had partial overlap of irradiated volumes.

Timing of RT

Prior to SG administration, 12 patients had received RT, while 17 patients received 34 local RT series concurrently with SG; sequential and simultaneous SG and RT were administered in 9 and 8 patients, respectively. The median (range) time between sequential SG and RT was 7 (1–33) d. SG was resumed after a median (range) of 6 (1–68) d. In most patients, concomitant RT was used to treat local progressive metastases; other reasons included palliation of symptoms or ulcerations (n=2), treatment of a local relapse or postoperative irradiation after resection of a brain metastasis (each, n=1). There was an overlap with prior RT in 12 RT courses. The median (range) time between concurrent SG and RT with prior RT courses was 2 (1–7) y. The median (range) dose of cumulative RT was 79 (65–102) Gy.

Efficacy and safety results

At the first follow-up (4–8 wk post-RT), the response rate per treatment course was 82.1%. RT response was not available in 6 lesions. After the first SG dose, OS ranged from 2.5 to 36 mo; post-RT, the OS ranged from 1.6 to 12 mo.

All patients treated with SG received granulocyte colony-stimulating factor as primary prophylaxis. Safety data were available for 15 patients; the most common AEs were neutropenia and fatigue. Other AEs included infections (enterocolitis, n=2; herpes zoster, n=1), diarrhea, abdominal pain, chest pain, and alopecia. Grade 2 fatigue was reported in 6 patients after RT.

No Grade 4 or 5 AEs were reported with SG and RT used in combination; however, 82.3% of patients experienced AEs, and fatigue and dermatitis were the most commonly reported AEs. In-field Grade 3 AEs included dermatitis (n=2) and esophagitis (n=1). Grade 3 AEs

were only reported by patients with overlap of prior radiation fields. Three patients (37.5%) who received simultaneous RT and 4 patients (44.4%) who received sequential RT administration reported acute Grade 2 to 3 AEs.

Retrospective BCBM Study of SG + SRS in US[13]

A retrospective study evaluated efficacy and safety outcomes in patients with active BCBM (N=14; lesions, n=121) treated with SG who also received SRS for BM within 6 mo of SG treatment. The median (range) age was 60 (30–72) y, 7 patients (50%) had HR+ BC, and 5 patients (36%) had neurologic symptoms. Patients were followed for a median of 28.6 mo and received 25 courses of SRS. Of the 121 lesions that were treated with SRS, 77 (63%) were treated concurrently with SG. Overall, 110 lesions (91%) received single-fraction SRS (median [range] dose, 24 [16–24] Gy), and 11 (9%) received fSRS (median [range] dose, 27 [20–30] Gy; median [range], 5 [3–5] fractions). The median (range) GTV and PTV was 0.047 (0.007–17.4) cc and 0.14 (0.032–30) cc, respectively. Six lesions (5%) received postoperative treatment.

The median (95% CI) OS was 8.4 (4.2–NR) mo; the 12-mo OS rate was 48%. The median (95% CI) CNS-PFS and EC-PFS were 4.2 (1.9–6.3) mo and 4.4 (1.4–8.1) mo, respectively; the 12-mo CNS-PFS and EC-PFS rates were 11% and 17%. The 12-mo LC rate of SRS was 91%. The median (95% CI) DIC was 4.2 (2.1–7.5) mo, and the 12-mo DIC rate was 12%. LMD occurred in 2 patients and SRN was reported in 1 patient who had received SRS before SG treatment.

Retrospective, Single-Center mBC Study in France[14]

A retrospective, single-center mBC study evaluated safety outcomes in patients (N=13) treated with SG + concurrent EBRT. Delivery of EBRT was according to a conventional fractionation or stereotactic technique. Of the included patients (median [range] age of 54 [37–77] y; 12 had invasive ductal carcinoma and 1 had invasive lobular carcinoma), 8 had TNBC, and 5 had HR+/HER2-low/negative mBC. Most tumors (61.5%) were Grade 3, and there was a median (range) Ki67 index of 35% (8–90%). Patients received SG for a median (range) of 7 (2–19) mo. Of the 19 sites of metastases treated with RT, 10 were in the brain, and 9 were in bone; 4 sites in the brain had previously been surgically resected. Ten sites (52.6%) received SBRT and 9 sites (47.4%) received conformal VMAT.

Efficacy and safety results

The median (range) duration of follow-up after completion of RT was 5 (1–19) mo. At the time of data cutoff, 9 patients had died due to disease progression; the time between completion of RT and death ranged from 1 to 19 mo. The overall median OS from the completion of RT was 6 mo, and the median (95% CI) OS rate at Months 6 and 12 was 45.1% (22.9–88.9%) and 16.9% (3.27–87.5%), respectively.

No patients had RT-induced AEs, and none required disruption of SG. One (7.7%) Grade 3 and 1 (7.7%) Grade 4 SG-related AE of neutropenia were reported. All other SG-related AEs were Grade 1 or 2 in severity: nausea/vomiting (Grade 1, 30.8%); asthenia (Grade 1, 23.1%; Grade 2, 15.4%); alopecia (Grade 1, 15.4%; Grade 2, 23.1%); diarrhea (each, Grade 1 and 2, 15.4%); anemia (Grade 1, 15.4%); and neutropenia (Grade 2, 7.7%).

Retrospective, Real-World mTNBC Study in UK[15]

A UK retrospective, real-world mTNBC study evaluated safety and efficacy in patients who had received ≥1 dose of SG following ≥2 prior lines of chemotherapy, one of which could have been in the (neo)adjuvant setting. In a subgroup analysis of 24 patients with CNS disease, 11 patients received RT for BrM prior to or during SG treatment.

In the subgroup analysis of patients with CNS disease, PFS was 5.1 mo, which was not significantly different from that in patients without CNS disease (*P*=0.8); OS was not reached. Compared with patients with CNS disease who had not been treated with RT, PFS was significantly longer in RT-treated patients (HR, 0.27; 95% CI: 0.1–0.71; *P*=0.006). Patients with CNS disease that was untreated with RT demonstrated a PFS and OS of 1.6 and 2.6 mo, respectively. No safety data were reported in the subgroup analysis.

Observational BC Study of ADCs + RT in Italy[16]

An observational study evaluated early toxicity in patients with Stage IV BC who received SG (n=5) or T-DXd (n=18) and were candidates for concurrent RT (palliative or curative; administered concurrently or within 1 wk of ADC). The overall median (range) age was 58 (33–81) y. Of the 21 RT courses with SG treatment, 2 (9.5%) were palliative, and 19 (90.5%) were stereotactic fractionated RT, and the mean duration of SG treatment was 11.9 mo.

Overall, no RT courses were suspended, and all-grade AEs were reported in 11 patients (47.8%); 2 patients (8.7%) had Grade ≥2 AEs, and none had Grade 3 AEs. Of the 5 SG-treated patients, 1 had Grade 2 brain radionecrosis (the patient had received multiple brain SRT courses); 3 had Grade 1 fatigue, and 1 had Grade 1 pneumonitis. Of the 9 patients treated for palliation of bone metastasis (ADC treatment[s] not disclosed), all achieved pain relief (numerical rating scores: before, 1.8; after, 0.4; *P*=0.014).

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Abbreviations

1L=first line
2L+=second-line and later
3D-CRT=three-dimensional conformal radiotherapy
ADC=antibody drug conjugate
AE=adverse event
BC=breast cancer
BCBM=breast cancer brain metastasis
BrM=brain metastases
CNS=central nervous system
CR=complete response
DIC=distant intracranial control
EBRT=external beam radiotherapy
EC-PFS=extracranial progression-free survival
ECOG PS=Eastern Cooperative Oncology Group Performance Status
EQD2=equivalent dose in 2-Gy fractions
Extra-CNS=lesions or disease outside of the central nervous system
fSRS=fractionated stereotactic radiosurgery
Gy=Gray
GPA=Graded Prognostic Assessment
GTV=gross tumor volume
HER2=human epidermal growth factor receptor 2
HR=hazard ratio
HR+/-=hormone receptor-positive/-negative
IMRT=intensity-modulated radiotherapy
LC=local control
LMD=leptomeningeal disease
mBC=metastatic breast cancer
mTNBC=metastatic triple-negative breast cancer
NR=not reached
OS=overall survival
PD=progressive disease
PD-(L)1=programmed death (ligand) 1
PFS=progression-free survival
PR=partial response
PTV=planning target volume
RD=radiation dermatitis
RECIST=Response Evaluation Criteria in Solid Tumors
RT=radiation therapy
SBRT=stereotactic body radiotherapy
SD=stable disease
SG=sacituzumab govitecan--hziy
SRN=symptomatic radiation necrosis
SRS=stereotactic radiosurgery
SRT=stereotactic radiotherapy
T-DXd=trastuzumab deruxtecan
TNBC=triple-negative breast cancer
TRAE=treatment-related adverse event
VMAT=volumetric modulated arc therapy

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