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ORIGINAL RESEARCH

The efficacy of sacituzumab govitecan and trastuzumab deruxtecan on stable and active brain metastases in metastatic breast cancer patients—a multicenter real-world analysis

D. Dannehl[1*], D. Jakob[2], F. Mergel[3], A. Estler[4], T. Engler[1], L. Volmer[1], M.-L. Frevert[2], S. Matovina[1], A. Englisch[1], C. M. Tegeler[1], A. Rohner[1], A. Seller[1], M. Hahn[1], K. Pfister[3], A. Fink[3], I. Popp[5], S. Lorenz[6], G. Tabatabai[7], I. Juhasz-Böss[2], W. Janni[3], S. Brucker[1], F.-A. Taran[2], A. Hartkopf[1,3] & H. Schäffler[3]

[1]Department of Women's Health, Tuebingen University, Tuebingen; [2]Department of Gynecology and Obstetrics, University Medical Center Freiburg, Freiburg; [3]Department of Gynecology and Obstetrics, Ulm University, Ulm; [4]Department of Radiology, Section for Diagnostic and Interventional Neuroradiology, Tuebingen; [5]Department of Radiation Oncology, University Medical Center Freiburg, Freiburg; [6]Department of Radiology, Ulm University, Ulm; [7]Center for Neurooncology, Comprehensive Cancer Center, Tuebingen University, Tuebingen, Germany

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Background: Fifteen to thirty percent of all patients with metastatic breast cancer (MBC) develop brain metastases (BCBMs). Recently, the antibody—drug conjugates (ADCs) sacituzumab govitecan (SG) and trastuzumab deruxtecan (T-DXd) have shown to be highly effective in the treatment of MBC. However, there are only limited data whether these macromolecules are also effective in patients with BCBMs. We therefore aimed to examine the efficacy of SG and T-DXd in patients with stable and active BCBMs in a multicenter real-world analysis.

Patients and methods: Female patients with stable or active BCBMs who were treated with either SG or T-DXd at three breast centers in Germany before 30 June 2023 were included. As per local clinical praxis, chemotherapy efficacy was evaluated by whole-body computed tomography and cranial magnetic resonance imaging at baseline and at least every 3 months according to local standards. Growth dynamics of BCBMs were assessed by board-certified neuroradiologists.

Results: Of 26 patients, with a median of 2.5 prior therapy lines in the metastatic setting (range 2-15), 12 (43%) and 16 (57%) patients received SG and T-DXd, respectively. Out of the 12 patients who received SG, 2 (17%) were subsequently treated with T-DXd. Five out of 12 (42%) and 5 out of 16 (31%) patients treated with SG and T-DXd, respectively, had active BCBMs at treatment initiation. The intracranial disease control rate was 42% [95% confidence interval (CI) 13% to 71%] for patients treated with SG and 88% (95% CI 72% to 100%) for patients treated with T-DXd. After a median follow-up of 12.7 months, median intracranial progression-free survival was 2.7 months (95% CI 1.6-10.5 months) for SG and 11.2 months (95% CI 7.5-23.7 months) for T-DXd.

Conclusions: SG and T-DXd showed promising clinical activity in both stable and active BCBMs. Further prospective clinical studies designed to investigate the efficacy of modern ADCs on active and stable BCBMs are urgently needed.

Key words: breast cancer, brain metastasis, antibody—drug conjugates, real-world data

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, with 20%-30% of patients developing distant metastatic disease.[1] Breast cancer is the second most common solid tumor to cause brain metastases, affecting up to 30% of patients.[2-4] However, a clinical benefit of screening for breast cancer brain metastases (BCBMs) has not been demonstrated, and BCBMs are typically detected by the occurrence of neurological symptoms.[5,6] Patients with metastatic breast cancer (MBC) that is human epidermal growth factor receptor 2 (HER2) positive (HER2+) or hormone receptor negative (HR−) and HER2 negative (HER2−) are at a higher risk of developing BCBMs, with rates up to 30%. In comparison, HR+/HER2− patients may develop BCBMs in up to 15% of cases.[7]

With the use of modern drugs and targeted treatment, prognosis of MBC has improved over recent years.[8-17] However, in addition to radiation therapy (whole-brain irradiation or stereotactic radiosurgery) or surgical removal, only a few systemic treatments are available to specifically treat BCBMs.[18] Thus, the prognosis for patients with BCBMs

*Correspondence to: Dr Dominik Dannehl, Department of Women's Health, Tuebingen University, Calwerstraße 7, 72070 Tuebingen, Germany. Tel: +49-7071-29-82211

E-mail: Dominik.Dannehl@med.uni-tuebingen.de (D. Dannehl).

is limited when compared to those with extracranial breast cancer metastases.[7,15,19,20] This limited prognosis may be attributed to the blood—brain barrier (BBB) formed by cerebral blood vessels and astrocytes, which can impede the delivery of systemic therapies to brain tumors.[21] Nevertheless, recent studies have demonstrated antitumor activity even of therapeutic macromolecules. As an explanation, the BBB may be disrupted as abnormal vessels grow during tumor progression, leading to the formation of a blood—tumor barrier (BTB).[22]

Current treatment options for BCBMs include classic chemotherapy regimens and HER2-targeted treatment approaches.[18,23] The HER2-Climb and the recently presented HER2Climb02 studies have shown that combination therapy involving trastuzumab and capecitabine with tucatinib, or the antibody—drug conjugate (ADC) trastuzumab emtansine with tucatinib, can significantly enhance overall survival (OS) in patients with BCBMs.[24,25] These trials also included patients with active, progressing or newly diagnosed BCBMs. In contrast to the HER2Climb trials, regulatory approval of the modern ADCs sacituzumab govitecan (SG) and trastuzumab deruxtecan (T-DXd) was based on large phase III trials that solely enrolled patients with asymptomatic BCBMs not requiring immediate local therapy.[10,12,13] For patients with progressing BCBMs, prospective data only exist from the TUXEDO-1 phase II trial, demonstrating the effectiveness of T-DXd in a small cohort of 15 patients.[26]

This retrospective study aims to characterize the patient population with BCBMs who received SG and/or T-DXd treatment and to evaluate the efficacy of these ADCs on active and stable BCBMs in real-world treatment scenarios.

MATERIALS AND METHODS

All patients included in this retrospective study received T-DXd or SG treatment at Ulm University Hospital's Department of Gynecology and Obstetrics, the University Medical Center Freiburg's Department of Gynecology and Obstetrics, and the Department of Women's Health at Tuebingen University Hospital in Germany between 1 November 2020 and 30 June 2023. The data cut-off date of 31 November 2023 was used for data analysis. Patients with solely extracranial disease or patients displaying leptomeningeal disease were excluded from this analysis. Additionally, patients who did not receive complete SG or T-DXd therapy at a single study site as well as patients who developed BCBMs during ongoing SG or T-DXd therapy were excluded. The study adhered to the guidelines outlined in the Declaration of Helsinki and received approval from the ethics committees of Ulm University (158/23), Freiburg University (23-1506-S1-AV), and Tuebingen University (380/2020BO).

As per local clinical praxis, chemotherapy efficacy was evaluated by whole-body computed tomography and cranial magnetic resonance imaging (MRI) at baseline and at least every 3 months according to local standards. Growth dynamics of BCBMs were assessed by board-certified neuroradiologists. HR and HER2 receptor expression was assessed by board-certified pathologists according to local standards as previously described.[27-29]

BCBMs were classified as active if they were newly diagnosed or if they were progressing and did not require local treatment before the first application of SG or T-DXd.[24,30] Preexisting treated and asymptomatic BCBMs without intracranial disease progression or preexisting or newly diagnosed BCBMs that had been treated by surgery and/or radiation therapy up to 45 days prior or concomitant to SG or T-DXd therapy and demonstrated disease stabilization were considered as stable.[12,13,30] If patients received radiation therapy concurrently with the beginning of ADC administration, patients were classified as stable.

Intracranial disease control rate (icDCR) was defined as the percentage of patients with at least intracranial stable disease at the first follow-up MRI. Median treatment duration was defined as the period between the first application of SG or T-DXd and intracranial disease progression or treatment cessation due to the patients' will or the onset of intolerable toxicity or death. Intracranial progression-free survival (icPFS) was determined as the period between the first application of SG or T-DXd and intracranial disease progression. OS was defined as the period between the first application of SG or T-DXd and death. Therapy lines were reported as the number of chemotherapies after the first breast cancer diagnosis. The treatment-emergent adverse events (TEAEs) recorded included a decline in left ventricular ejection fraction, hematologic toxicities, and interstitial pneumonia. These events were measured using the Common Terminology Criteria for Adverse Events (CTCAE) V5.0 by incidence, type, and severity.

Data processing and statistical analyses were carried out using Jupyter Notebook on Anaconda, with the Python extension packages pandas, numeric Python, and lifelines as previously described.[27-29] Comparative statistics of survival analyses were carried out using the log-rank test with a significance level of $\alpha = 0.05$. Affinity Publisher 2 (Serif Europe Ltd., Nottingham, UK) was used for data visualization.

RESULTS

Eighty-two patients with MBC were treated with SG or T-DXd at three participating centers. Of the patients treated with SG, 12 out of 37 (32%) displayed BCBMs while 18 out of 45 (40%) treated with T-DXd had the same condition. All patients with BCBMs receiving SG ($n = 12$) were included in this analysis. Of all patients treated with T-DXd, 16 out of 18 patients (89%) initiated therapy at our centers and were also included. The starting dose for SG was 10 mg/kg body weight in 10 out of 12 patients (83%), while for T-DXd it was 5.4 mg/kg body weight in 11 out of 16 patients (69%). Table 1 shows patient characteristics for both cohorts.

The median age of the patients treated with SG was 50.5 years. All SG-treated patients had HR−/HER2− tumor biology (100%). Patients received between 2 and 5 prior chemotherapies, with a median of 2.5 prior chemotherapies. Before SG treatment, 11 out of 12 patients (92%) had

Table 1. Patient characteristics of patients treated with SG and T-DXd

	SG	Percentage	T-DXd	Percentage
Overall	12	100	16	100
Median age (IQR) in years	50.5 (42-60)		58 (52.5-62)	
Histology				
NST	11	92	14	88
ILC	0	0	0	
Other	1	8	2	12
Receptor status				
HR				
Positive	0	0	10	63
Negative	10	83	6	37
N/a	2	17	0	0
HER2				
Positive	0	0	11	69
Low	4	33	5	31
0	8	67	0	0
Treatment indication				
TNBC	12	100	—	—
HR+/HER2−	0	0	—	—
HER2+	—	—	11	69
HER2 low	—	—	5	31
Median prior chemotherapies (range)	2.5 (2-5)		2.5 (2-15)	
Previous HER2-directed therapies				
Trastuzumab	0	0	11	69
Pertuzumab	0	0	11	69
T-DM1	0	0	9	56
Tucatinib	0	0	3	19
Prior local therapy				
Radiation therapy	11	92	14	88
WBRT	9	75	6	38
Stereotaxis	1	8	4	25
Both	4	33	4	25
Surgery	2	17	4	25
Brain metastasis status				
Active	5	42	5	31
Stable	7	58	11	69

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ILC, invasive-lobular carcinoma; IQR, interquartile range; N/a, not applicable; NST, non-special type; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; WBRT, whole-brain radiation therapy.

Table 2. Therapy duration, efficacy, and reasons for discontinuation of patients treated with SG and T-DXd

	SG	T-DXd
Intracranial disease control rate (95% CI)	42% (13% to 71%)	88% (72% to 100%)
Median treatment duration (IQR) in days	71 (37-154)	281 (229-328)
Treatment discontinuation, *n* (%)	12 (100)	11 (69)
Intracranial disease progression, *n* (%)	5 (42)	4 (36)
Extracranial disease progression, *n* (%)	3 (25)	2 (18)
TEAEs, *n* (%)	1 (8)	3 (27)
Patients' wish, *n* (%)	0 (0)	1 (9)
Death, *n* (%)	3 (25)	1 (9)
Death within the observation period, *n* (%)	7 (58)	6 (38)

CI, confidence interval; IQR, interquartile range; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.

previously undergone cerebral radiation therapy, while 2 out of 12 patients (17%) had undergone surgery for BCBMs. Of the 12 BCBM patients who received SG, 5 (42%) were classified as active and 7 (58%) as stable.

Patients who received T-DXd had a median age of 58 years and underwent a median of 2.5 prior chemotherapy treatments, with a range of 2-15. Eleven out of 16 patients (69%) treated were HER2+ while 5 patients (31%) exhibited HER2-low tumor biology. Accordingly, most patients had undergone HER2-targeted therapy before T-DXd was given. Specifically, 11 were treated with trastuzumab and pertuzumab (69%), 9 patients received trastuzumab emtansine (56%), and 3 received tucatinib (19%). Of the 16 patients, 14 had undergone radiation therapy at least once before the initiation of T-DXd treatment, and 4 had undergone surgery for BCBMs. BCBMs were classified as active in 5 out of 16 cases (31%) and deemed stable in 11 out of 16 (69%).

Table 2 and Figure 1 present key information on immediate local therapy before ADC administration, median treatment duration, duration of icPFS, and reasons for therapy discontinuation. The median duration of SG treatment lasted 71 days, and treatment was discontinued for all patients at the time of analysis. Three (25%) patients underwent radiation therapy of the brain at least 45 days before the initial application of SG, and two patients (18%) received radiation therapy simultaneously with SG application. Before the data cut-off, five patients discontinued SG treatment due to intracranial disease progression (42%), three patients due to extracranial disease progression (25%), one patient due to treatment-induced adverse events (8%), and three patients had deceased (25%). Overall, 7 out of 12 patients treated with SG died before the data cut-off (58%).

The median duration of T-DXd treatment was 281 days, with 11 out of 16 patients (69%) discontinuing treatment before the data cut-off. Three patients (19%) received brain radiation therapy at least 45 days before the initial application of T-DXd. Before the data cut-off, four patients discontinued T-DXd treatment due to intracranial disease progression (36%), two patients discontinued due to extracranial disease progression (18%), three patients discontinued due to TEAEs (27%), one patient discontinued treatment due to personal preference, and one patient died (9%). Overall, 6 out of 16 patients treated with T-DXd had died by the time of data cut-off (38%).

For patients treated with SG, the icDCR was 42% [95% confidence interval (CI) 13% to 71%]. As demonstrated in Figure 2A, median icPFS for patients treated with SG was 2.7 months (95% CI 1.6-10.5 months). Patients with active BCBMs who were treated with SG had a median icPFS of 2.7 months (95% CI 1.9-10.5 months), while those with stable BCBMs had a median icPFS of 2.1 months (95% CI 0.4-14.1 months). The icPFS for active BCBMs compared to stable ones (Figure 2B) showed no significant difference ($P = 0.86$, pairwise log-rank test). Patients who received SG had a median OS of 6.4 months (Figure 2C) (95% CI 1.2 months-not reached). Patients with active BCBMs had a median OS duration of 8.1 months (95% CI 5.3 months-not reached), while patients with stable BCBMs had a median OS duration

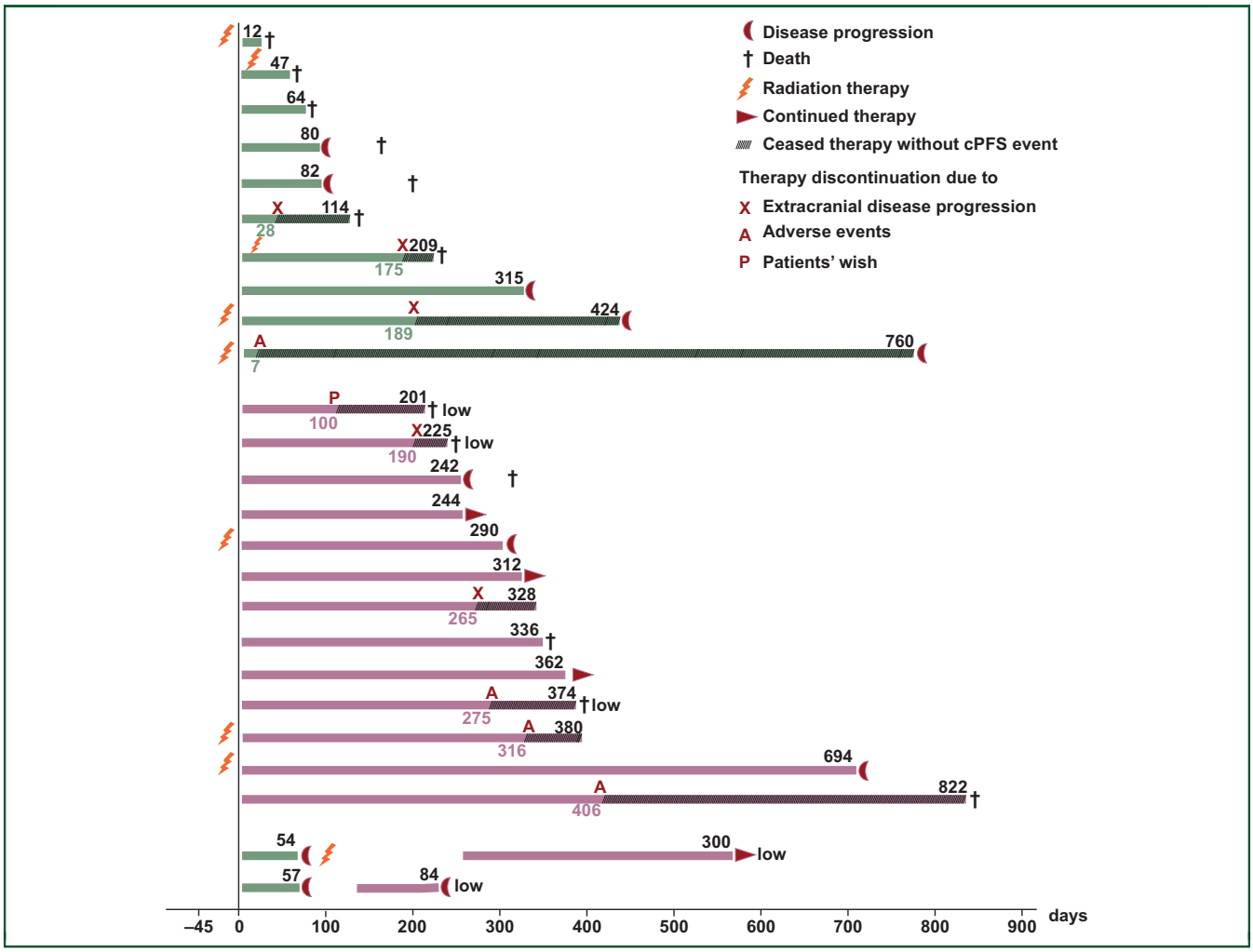

Figure 1. Breast cancer patients with BCBMs were treated with either sacituzumab govitecan (green) or trastuzumab deruxtecan (purple) for a specified number of days, and icPFS was observed. Sequential treatment using both drugs was also a viable option. If the therapy ended before an icPFS event occurred, the interval without ADC application is indicated by black hatching. An icPFS event is denoted by a red sickle. Therapy cessation due to extracranial disease progression is indicated by the letter 'X'. Therapy cessation due to treatment-emergent adverse events is indicated by the letter 'A'. Therapy cessation due to patients' wish is indicated by the letter 'P'. Continued treatment is indicated by a red triangle, and patient death is indicated by a cross. Patients who underwent radiation therapy before or during ADC treatment are identified by a yellow lightning bolt. Patients with an HER2-low status are labeled as 'low.'
ADC, antibody—drug conjugate; BCBMs, breast cancer brain metastases; icPFS, intracranial progression-free survival.

of 2.2 months (95% CI 0.4 months-not reached). The OS for active versus stable BCBMs (Figure 2D) did not differ significantly ($P = 0.63$, pairwise log-rank test).

For patients treated with T-DXd, icDCR was 88% (95% CI 72% to 100%). As shown in Figure 3A, the median duration of icPFS for patients receiving T-DXd was 11.2 months (95% CI 7.5-23.7 months). Patients who had stable BCBMs had a median icPFS of 11.2 months (95% CI 6.7-23.7 months), while in patients with active BCBMs median icPFS was not reached (Figure 3B). The difference between icPFS of patients with active versus stable BCBMs was not statistically different ($P = 0.86$, pairwise log-rank test). Median OS for patients receiving T-DXd was 27.1 months (95% CI 9.6-27.1 months) (Figure 3C). Patients with stable BCBMs had a median OS duration of 27.1 months (95% CI 5.4-27.1 months), while in patients with active BCBMs median OS was not reached (Figure 3D). There was no significant difference between the OS of active and stable BCBMs ($P = 0.74$, pairwise log-rank test). When stratified after treatment indication, patients with HER2+ breast cancer and brain metastases had a median icPFS of 12.7 months (95% CI 7.7-27.4 months), while the median icPFS of HER2-low patients with brain metastases was 7.5 months (95% CI 2.8-12.5 months) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.102995).

Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.102995, displays the recorded TEAEs of SG and T-DXd. The most prominent adverse event was neutropenia in patients receiving SG (5/12; 42%). Four out of 12 patients (33%) had severe adverse events (grade ≥3) due to neutropenia and 1 out of 12 patients (8%) due to anemia. During SG therapy, four dose reductions occurred in three patients: two due to neutropenia and two due to fatigue. Treatment was discontinued due to therapy-associated neutropenia in 1 out of 12 patients (8%). The most prevalent adverse event in patients treated with T-DXd was neutropenia (7/16; 44%). Severe adverse events (grade ≥3) were documented in 1 out of 16 patients for

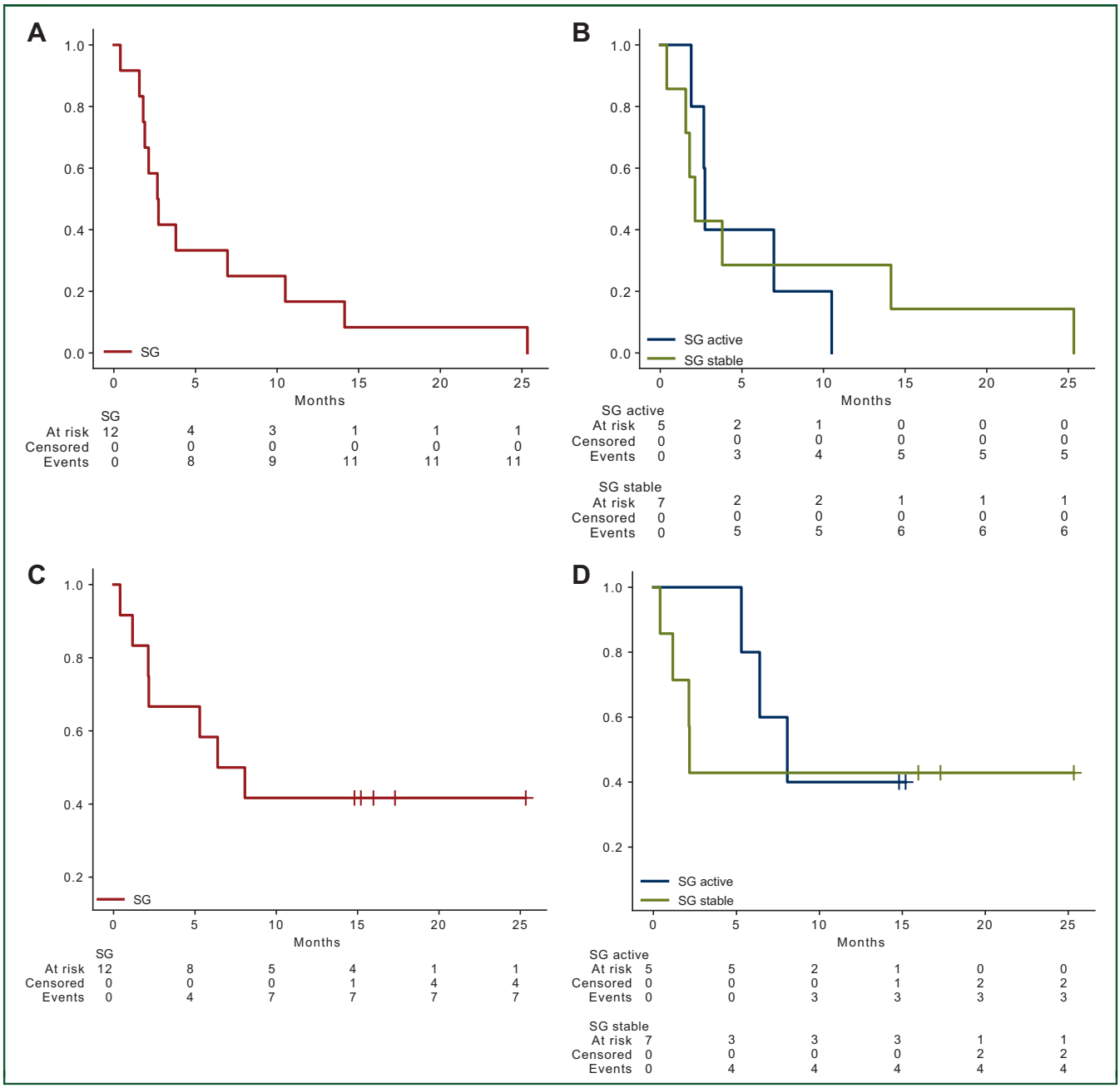

Figure 2. Intracranial progression-free survival and overall survival for patients receiving SG. (A) icPFS of patients with BCBMs who received treatment with SG. (B) icPFS of patients diagnosed with active and stable BCBMs. (C) OS of patients with BCBMs who received treatment with SG. (D) OS of patients diagnosed with active and stable BCBMs.
BCBMs, breast cancer brain metastases; icPFS, intracranial progression-free survival; OS, overall survival; SG, sacituzumab govitecan.

neutropenia (6%), for anemia (6%), and for thrombocytopenia (6%), respectively. Interstitial pneumonitis was seen in three patients (19%), while one patient (6%) developed severe pneumonitis. No cardiac toxicities were observed. During therapy, two dose reductions occurred in two patients due to anemia and fatigue. Adverse events resulted in the discontinuation of treatment in 19% (3/16) of the patients, all of whom developed interstitial pneumonitis.

DISCUSSION

This retrospective analysis highlights the efficacy of the ADCs SG and T-DXd in treating stable and active BCBMs in a real-world scenario. The effectiveness of SG and T-DXd was initially demonstrated in phase III trials (ASCENT, DESTINY-Breast03, and DESTINY-Breast04). However, these trials only involved a small number of patients with asymptomatic or stable BCBMs.[10,12,13] Given that a significant number of patients have active BCBMs or require immediate local therapy before initiating ADC therapy, we believe the results of this study are highly relevant to clinical practice. While the efficacy of T-DXd in active BCBMs has recently been demonstrated in the prospective TUXEDO-1 and DEBBRAH trials, the current analysis is the first to report the efficacy of SG administration in active and stable BCBMs in a real-world setting.[26,31] Furthermore, this study is the first

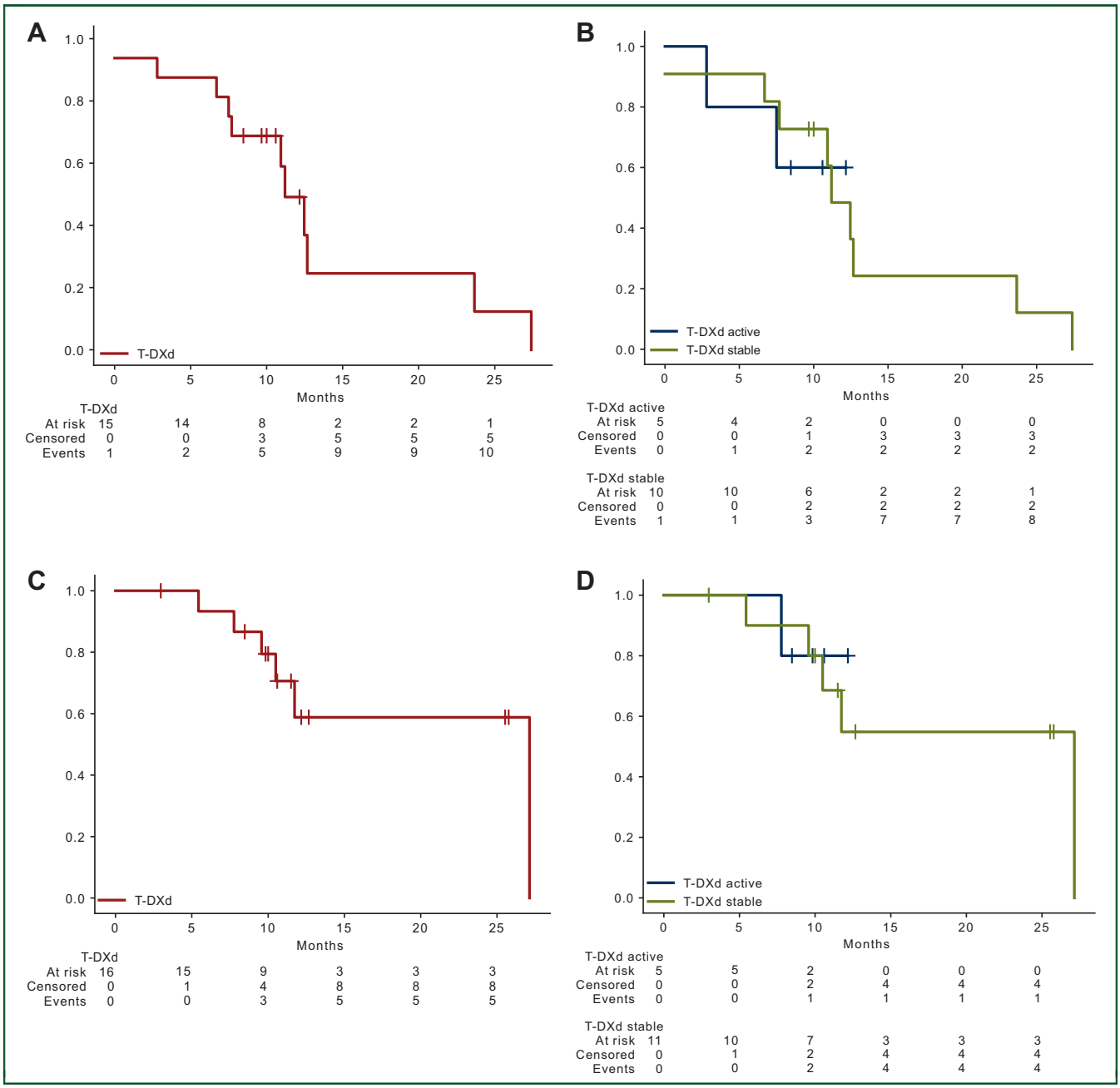

Figure 3. Intracranial progression-free survival and overall survival for patients receiving T-DXd. (A) icPFS of patients with BCBMs who received treatment with T-DXd. (B) icPFS of patients diagnosed with active and stable BCBMs. (C) OS of patients with BCBMs who received treatment with T-DXd. (D) OS of patients diagnosed with active and stable BCBMs.
BCBMs, breast cancer brain metastases; icPFS, intracranial progression-free survival; OS, overall survival; T-DXd, trastuzumab deruxtecan.

to demonstrate the feasibility of administering an ADC after prior ADC treatment for BCBMs, specifically T-DXd after SG in HER2-low patients. In both cases, the median therapy duration was numerically longer with T-DXd compared to SG, even though T-DXd was administered in a higher line of therapy. The safety profile was consistent with published data and no additional safety concerns were identified. Similar proportions of patients experienced hematotoxic adverse events and interstitial pneumonitis, while no case of cardiac toxicity was observed.[12,13,20,26,32,33]

Recent clinical trials are evaluating drug efficacy in BCBMs. To enhance comparability, a classification system for brain metastases was defined by the Food and Drug Administration in 2020 to further the inclusion of patients with BCBMs of any kind in clinical studies.[30] Yet, the proposed definition of active and treated/stable BCBMs is not used consistently. The DESTINY-Breast03 and DESTINY-Breast04 trials enrolled only patients with clinically asymptomatic and untreated or previously treated BCBMs with disease stabilization at least 14 days after completion of local therapy.[12,13] In contrast, the TUXEDO-1 trial evaluated the effectiveness of T-DXd exclusively for patients with active BCBMs, defined as lesions that were newly diagnosed or progressing after previous local therapy but did not

require immediate local treatment.[26] The largest prospective phase III trial to date investigating the efficacy of HER2-directed systemic therapy in patients with active BCBMs is the HER2CLIMB trial. BCBMs were considered active if they had progressed since the last central nervous system (CNS)-directed therapy or if they were untreated and did not require immediate local therapy. Conversely, BCBMs were deemed stable if they were previously treated and had not progressed since the last CNS-directed therapy. Patients with newly diagnosed BCBMs requiring immediate local therapy were also included after local therapy and subsequent disease stabilization and were then classified as stable.[24]

In clinical practice, routine screening for BCBMs is not carried out.[5] As a result, most patients are diagnosed with brain metastases only after experiencing symptoms, requiring local therapy in the majority of cases.[6] However, BCBMs are classified as stable if stabilized at least 14 days after local therapy and the patient does not need anticonvulsive or corticosteroid therapy.[12,13,34] This classification may appear counterintuitive because patients with a high CNS symptom burden are deemed stable after local therapy, whereas those with small, asymptomatic BCBMs are classified as active. In a pooled analysis from the DESTINY-Breast01, -03, and -04 trials, treated and asymptomatic BCBMs were defined as stable and untreated and asymptomatic BCBMs as active. Here, the icPFS of patients with active BCBMs was longer as compared to that of patients with stable BCBMs after T-DXd administration.[35] The prospective DEBBRAH trial improves clinical classification of BCBMs and categorizes patients into five cohorts, including asymptomatic untreated BCBMs that are HER2+, stable HER2+ brain metastases that have undergone local therapy, HER2+ BCBMs that have progressed after local therapy, HER2-low BCBMs that have progressed after local therapy, and HER2+ or HER2-low tumors with leptomeningeal carcinomatosis.[31] In the current real-world analysis, BCBMs were considered active if they were newly diagnosed or locally pretreated and progressing and did not require immediate local therapy or if it was not feasible. In contrast, BCBMs were defined stable when pretreated and asymptomatic or if radiation therapy was administered at least 45 days before or concurrently with ADC administration. Most patients received local therapy directly prior to ADC administration. However, due to high therapeutic pressure, two of the SG treated patients received it concurrently. Therefore, even our group of stable BCBMs is likely to encompass patients with a greater disease burden and more symptoms compared to those in recently published trials.[26,33,35]

There is an ongoing debate regarding the ability of antibodies, including ADCs, to cross the BTB. As macroscopic tumors undergo neoangiogenesis, causing the BBB to become leaky, the BTB may allow drugs to enter the brain more easily.[18] The CTNI-07 trial examined intratumoral concentrations of SG in BCBMs by administering 10 mg/kg SG to patients before craniotomy and tumor resection. Mass spectrometry demonstrated a significant enrichment of SG in metastatic lesions.[36] In the ASCENT trial, which led to the approval of SG for HR−/HER2− recurrent or metastatic breast cancer, 12% of patients had stable BCBMs at screening and were randomized to SG or chemotherapy.[10] SG showed a numerical superiority for icPFS with a median of 2.8 months compared to 1.6 months for treatment of physicians' choice while no significant difference in OS was observed with a median of 6.8 months versus 7.5 months, respectively.[33] Similarly, in our current real-world analysis, which included patients with both stable and active BCBMs, median icPFS was 2.7 months and median OS was 6.4 months.

T-DXd also demonstrated preclinical and clinical activity in HER2+ and HER2-low BCBMs in several retrospective and prospective studies.[20,26,31,37,38] T-DXd has shown preclinical activity in trastuzumab emtansine-resistant patient-derived xenograft models of HER2+ and HER2-low BCBMs.[37] This suggests that T-DXd also has the ability to cross the BTB. In the pooled analysis of DESTINY-Breast01, -03, and -04, median icPFS was 12.5 months for patients with stable BCBMs and 18.5 months for those with active BCBMs. In our real-world analysis, we found a comparable icPFS rate of 11.2 months for patients with stable BCBMs. The icPFS for patients with active and progressing BCBMs treated with T-DXd was not met in our analysis. Importantly, our analysis of real-world data included patients in later lines of treatment, including those who had previously received tucatinib, and patients with HER2-low disease. The median icPFS for HER2+ patients was numerically longer than that for HER2-low patients (12 months versus 7 months, as shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.102995). Hence, patients derived a more durable disease control if the target of the ADC was a driver of carcinogenesis compared to a surface antigen.

Limitations of our analysis are the small sample size and the heterogeneous patient population, even though it is comparable in size to currently published data.[26,31] Furthermore, it should be noted that the neuroradiological assessments in this study were not standardized according to Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) or RECIST due to the retrospective character of the analysis and data availability, but rather based on routine clinical evaluation by board-certified neuroradiologists. Thus, the data reported in this manuscript should only be carefully compared to prospective clinical trials using standardized neuroradiological assessments. Less than 25% of the patients underwent surgical resection of BCBMs before ADC administration. Thus, tumor biology was rarely determined by histopathologic evaluation of BCBMs, but on the latest available histology. Nevertheless, the multicenter design of this study is a strength of this retrospective real-world analysis. As of today, few data exist on the efficacy of modern ADCs on stable and active brain metastases.

In conclusion, this retrospective, multicenter study illustrates the effectiveness of both SG and T-DXd for the treatment of stable and active BCBMs in a real-world setting with a safety profile that is similar to large phase

III trials. Moreover, there was no significant difference shown in the median icPFS and OS rates between stable and active BCBMs. This emphasizes the efficacy of the newly developed ADCs for the therapy of both stable and active BCBMs. However, it also raises the question of whether the current classification for stable and active BCBMs is appropriate. The growing incidence of BCBMs highlights the urgent need for new systemic treatment alternatives.[15-18] According to our analysis, all patients with BCBMs, whether stable or active, may qualify for testing novel agents in large phase III studies. Future research should also address the question of therapy sequencing in patients with BCBMs and identify those who still require local treatment.[39] Furthermore, preventing BCBMs already at early stages is of utmost importance. While ADCs may be able to pass through the BTB of macroscopic tumor lesions, an intact BBB could provide a sanctuary for breast cancer micrometastases. While post-neoadjuvant trastuzumab emtansine has been shown to effectively prevent distant extracerebral metastases in patients who do not respond to neoadjuvant chemotherapy, it seems not to prevent the development of BCBMs.[40,41] Due to the increasing number of systemic therapies and the heterogeneity of the disease, many of these questions will need to be answered not only by innovative prospective trials that include patients with BCBMs, but also by analysis of real-world registries that include a significant number of patients.

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None declared.

DISCLOSURE

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