The Breast 79 (2025) 103853

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Safety profile of sacituzumab govitecan in patients with breast cancer: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Sacituzumab govitecan
Antibody-drug conjugates
TROP-2
IMMU-132
Breast cancer
Safety

ABSTRACT

Background: Sacituzumab Govitecan (SG), a first-in-class anti-trophoblast cell surface antigen-2-directed antibody-drug conjugate (ADC), has shown clinically meaningful improvement in outcomes of patients with breast cancer (BC). However, it has also been accompanied by significant toxicity. Thus, we conducted a systematic review and meta-analysis to evaluate the safety and tolerability of SG in this patient population.

Methods: We comprehensively searched PubMed, Embase, and Cochrane databases, and ASCO and ESMO websites for clinical trials (CTs) assessing the safety of SG in BC patients. All analyses were performed in R software (v.4.2.2) using random effects models. Heterogeneity was assessed using I^2 test.

Results: Seven studies – three randomized clinical trials (RCTs) and four single-arm phase I/II – were included, comprising 928 patients receiving SG and 576 on treatment of physician's choice (TPC). Most patients had triple negative BC (54.4 %, n = 505), metastatic disease (89.8 %, n = 833), and were heavily pretreated (at least two lines of prior therapy). Most common all-grade adverse events (AEs) were: neutropenia (70 %, 95 % CI, 64–76 %), followed by nausea (62 %, 95 % CI, 55–68 %), diarrhea (54 %, 95 % CI 47–60 %) and anemia (51 %, 95 % CI, 38–65 %). Regarding high-grade AEs, 46 % of patients developed grade ≥3 neutropenia. Compared to TPC, we observed a higher risk of neutropenia (OR 3.11, 95 % CI 1.62–5.99, $I^2 = 81$ %; $p < 0.001$), diarrhea (OR 6.82, 95 % CI 3.99–11.66, $I^2 = 64$ %; $p < 0.001$) and anemia (OR 2.26, 95 % CI 1.20–4.27, $I^2 = 78$ %; $p = 0.012$) for those on SG. Dose reductions and treatment discontinuation were reported in 22 % and 4 % of patients, respectively, and 19 deaths (2 %) were documented. Most of them were not deemed to be treated-related.

Conclusion: This systematic review and meta-analysis provides extensive data on the safety and management of SG toxicity in BC patients across clinical trials. Concerning rates of neutropenia, nausea diarrhea, and anemia were reported. We highlight the need for protocols establishing prophylactic measures and strategies to mitigate SG-related toxicity.

1. Introduction

For several decades, conventional chemotherapy has been the

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https://doi.org/10.1016/j.breast.2024.103853
Received 31 July 2024; Received in revised form 8 November 2024; Accepted 22 November 2024
Available online 23 November 2024

Abbreviations

SG	sacituzumab govitecan
BC	breast cancer
ADCs	antibody-drug conjugates
AEs	adverse events
FDA	Food and Drug Administration
HR	hormone receptor
HER2	human epidermal growth factor receptor 2
NV	nausea and vomit
TEAEs	treatment-emergent adverse events
TRAEs	treatment-related adverse events
RCT	randomized clinical trial
TPC	treatment of physicians' choice
TNBC	triple-negative breast cancer
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis

cornerstone treatment of patients with a wide range of tumors, including breast cancer (BC) [1]. From DNA-interacting agents (*e.g.* cisplatin) to tubulin inhibitors (*e.g.* paclitaxel), cytotoxic agents were refined over the years [1]. However, most of them demonstrated limited efficacy and concerning toxicity. The risk of specific adverse events (AEs) varies according to anti-cancer agents but can be very often long-lasting and debilitating [2]. Thus, there has been an incessant effort to develop treatments with a more favorable risk-benefit ratio [3].

Emerging novel therapies have redefined the treatment paradigm of BC in recent years [4]. Among them, antibody-drug conjugates (ADCs), composed of a complex structure of a monoclonal antibody (mAB) linked with a cytotoxic payload, have drawn attention due to their high selectivity and potent cytotoxic effect [5]. To illustrate, trastuzumab emtansine (T-DM1), the first ADC approved for metastatic BC, was shown to significantly improve survival in human epidermal growth factor 2 (HER2) metastatic BC patients in the EMILIA trial [6]. This was soon followed by studies on other ADCs, such as the trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) [7,8]. SG is composed of the anti-trophoblast cell surface antigen 2 (Trop2) antibody connected through a cleavable linker to a topoisomerase I inhibitor (SN-38) payload [8]. It has first shown activity in triple-negative breast cancer (TNBC) patients, a subgroup that has historically failed to benefit from targeted therapies [8].

The phase III clinical trial (CT) ASCENT explored the clinical benefit and safety of SG on 235 metastatic TNBC patients compared to 233 patients receiving chemotherapy [8]. The authors reported an impressive 59 % reduction in the risk of disease progression or death (hazard ratio [HR] 0.41, 95 % confidence interval [CI], 0.32–0.52; $p < 0.001$) [8]. The phase III TROPiCS-02 trial further expanded the benefit of SG to hormone receptor (HR)-positive and HER2-negative metastatic BC, with a consistent improvement in survival rates (HR for death 0.79, 95 % CI 0.65–0.96; $p = 0.020$) [9]. Based on these findings, SG was approved by the Food and Drug Administration (FDA) for advanced/metastatic TNBC and HR+ and HER2-negative BC patients who received at least two prior lines of therapy [10–12].

Despite its impressive targeting ability and potent antitumor activity, SG is associated with important treatment-related AEs (TRAEs) [8,9]. Studies have registered a risk of TRAEs in up to 100 % of patients receiving SG [13]. Particularly, concerning rates of hematotoxicity and gastrointestinal (GI) symptoms were seen, with frequencies of grade ≥3 neutropenia reaching up to 60 % [13]. SG toxicity may be highly debilitating and affect treatment compliance [8,9,13]. We, therefore, performed a systematic review and meta-analysis to explore safety and toxicity management of SG in BC patients in any setting across CTs.

2. Materials and methods

2.1. Search strategy

This study was performed following the guidelines from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [14]. It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the protocol number CRD42024501630 [15].

In January of 2024, a systematic search with no restriction regarding the publication date was performed in PubMed, Embase, and Cochrane databases and the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) conference proceedings. The search was last updated on June 20, 2024. The terms used include "breast cancer" and "sacituzumab govitecan". The full search used in each database is described on Table S2.

2.2. Eligibility criteria

We included CTs reporting safety data of SG monotherapy in patients with BC in any setting, regardless of tumor subtype. Abstracts were considered for inclusion. No restrictions were made to the sample size. Main exclusion criteria were as follows: (1) retrospective cohort studies; (2) reviews, case-report, or case-series; (3) SG-combined therapy; (4) tumors other than BC; (5) studies lacking safety data; and (5) studies assessing prophylaxis strategies for SG toxicity.

2.3. Study selection and data extraction

Two authors (MID and IM) independently screened the articles, extracted data on baseline characteristics and outcomes from all included studies and performed the risk of bias. All inconsistencies between the authors were resolved by consensus or consulting other authors (MV and RLBC).

2.4. Outcomes and subgroup analyses

The outcomes of interest were absolute risk (AR) of all-grade and grade ≥3 TRAEs: neutropenia; nausea; diarrhea; anemia; febrile neutropenia; alopecia; fatigue; vomiting; constipation; leukopenia; febrile neutropenia; and thrombocytopenia, according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) [21]. We also evaluated the proportion of patients who had undergone dose reduction, treatment discontinuation, serious TRAE, number of deaths, and health-related quality of life.

We explored the AR of all-grade and grade ≥3 AEs (neutropenia, nausea, diarrhea, and anemia) in patients treated with SG compared to those on treatment of physician choice (TPC). Moreover, subgroup analyses were performed according to the setting (early stage *versus* metastatic). We also explored rates of neutropenia, diarrhea, anemia, and

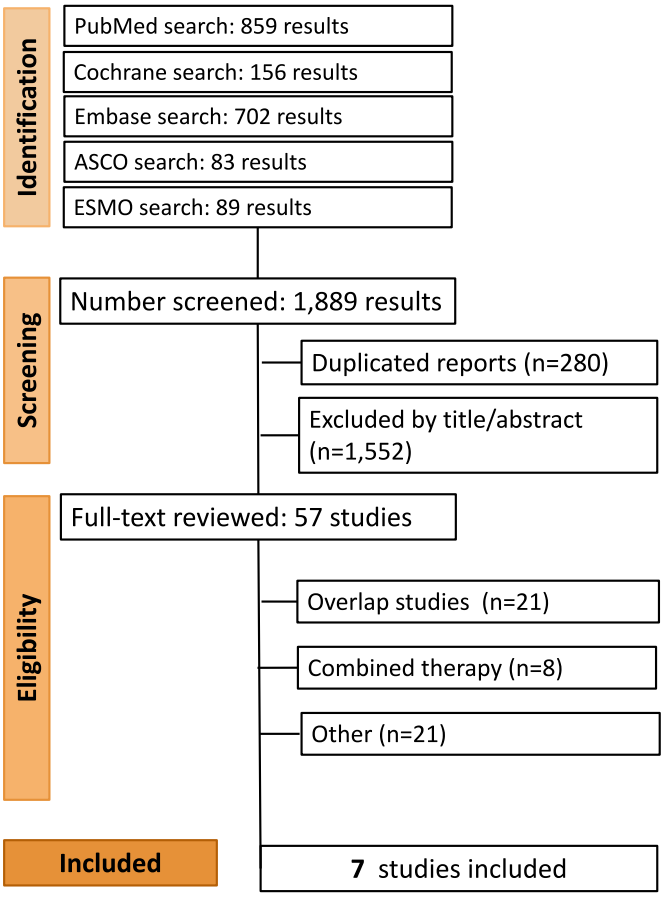


Fig. 1. PRISMA flow diagram of study screening and selection [17].
Blue vertical boxes indicate each screening stage, and the horizontal boxes show detailed information on the selection process, including the steps performed in each stage.
ASCO: American Society of Medical Oncology; ESMO: European Society for Medical Oncology.

febrile neutropenia according to the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) polymorphisms (1*/1* *versus* 1*/28* *versus* 28*/28*).

2.5. Quality assessment

For randomized studies, we used the Cochrane risk-of-bias tool for randomized trials (RoB 2) [16]. According to this protocol, studies are categorized as low, high, or unclear risk of bias across five domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, and (5) incomplete outcome data. On the other hand, non-randomized phase I or II CTs were assessed through the Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool [17]. This tool covers bias due to (1) confounding, (2) selection of participants, (3) deviations from intended interventions, (4) missing data, (5) measurement of outcomes, and (6) selection of the reported result. Based on these domains, studies are further classified as low, moderate, serious, critical risk of bias, or with insufficient information. Publication bias was explored using a funnel plot and the Egger test [20].

2.6. Sensitivity analyses and exploring heterogeneity

Besides performing a subgroup analysis according to disease setting (early *versus* metastatic), we also explored heterogeneity through leave-one-out analyses and the Baujat plot. The latter illustrates the contribution of each study to the overall heterogeneity. For both, we carried out analyses using the AEs with the higher frequency (*i.e.,* all all-grade neutropenia, nausea diarrhea, and anemia). We also carried out leave-one-out analyses for the comparative analyses of SG *versus* TPC for all-grade AEs (*i.e.,* all all-grade neutropenia, nausea diarrhea, and anemia).

2.7. Statistical analysis

Proportional meta-analyses were performed for dichotomous outcomes and reported in percentages (rates), with 95 % CI. Logit-transformation of data was used when the individual study proportion was smaller than 0.2 or higher than 0.8. For analysis including studies with zero events, we used the doubled-arcsine transformation. Comparative analyses were carried out using the number of events in each group (SG and TPC) and reported in odds ratio (OR) with 95 % CI. R software (version 4.2.2) was used to perform all statistical analyses. The following packages were used: "metafor"; "meta"; and "weight". I^2 statistics were used to assess the heterogeneity; I^2>25 % were considered significant for heterogeneity. DerSimonian and Laird random-effects models were used in all analyses. P values < 0.05 were considered statistically significant.

Table 1
Baseline characteristics of studies included in this systematic review and meta-analysis.

Study (trial ID)	Year	Design	Location	Population	SG dose and schedule	SG (N)	Control	Total (N)	Patients on SG		Median follow-up in months[a]
									Median age (range) in years	Prior lines of treatment[a]	
ASCENT (NCT02574455) [8,18]	2021	phase III RCT	USA	mTNBC	10 mg/kg IV D1, D8 Q3W	267	TPC[b] (N = 262)	529	54 (27–82)	2–3, N (%): 184 (69) >3, N (%): 83 (31)	17.7 (range, 5.8–28.1).
TROPiCS-02 (NCT03901339) [9]	2023	phase III RCT	Multicenter	mHR+/ HER2-negative[c]	10 mg/kg IV D1, D8 Q3W	272	TPC[b] (N = 271)	543	56 (48–65)	median (IQR): 3 (2–3)	12·5 (IQR, 6.4–18.8)
SASCIA* **(NCT04595565)** [19]	2022	phase III RCT	Austria	HER2-negative[d]	10 mg/kg IV D1, D8 Q3W	45	TPC[b] (N = 43)	88	46 (24–71)	NA	NA
SACI-IO*,[e] (NCT04448886) [20]	2024	randomized phase II	USA	mHR+/ HER2-negative	10 mg/kg IV D1, D8 Q3W	52	SG + Pembro (N = 52)[e]	104	57 (27–81)	None, N (%): 26 (50) 1 line, N (%): 26 (50)	12.5 (NA)
EVER-132–001 (NCT04454437) [13]	2023	phase IIb	China	mTNBC	10 mg/kg IV D1, D8 Q3W	80	NA	80	47 (24–69)	Median (range): 4 (2–8)	14.7 (range, 1.2–25.3)
IMMU-132–01 (NCT01631552) [21,22]	(A) 2020	phase I/II	USA	mHR+/ HER2-negative	10 mg/kg IV D1, D8 Q3W	54	NA	54	54 (33–79)	At least two	1.5 (range, 0.7–38.4)
	(B) 2019	phase I/II	USA	mTNBC	10 mg/kg IV D1, D8 Q3W	108	NA	108	55 (31–80)	Median (range): 3 (2–10)	16.6 (NA)
NeoSTAR trial (NCT04230109) [23]	2023	phase II	USA	localized TNBC	10 mg/kg IV D1, D8 Q3W	50	NA	50	48.5 (31–77)	NA	18.9 (95 % CI, 16.3–21.9)

CI: confidence interval; D: day; ID: identification; HR: hormone receptor; HER2: human epidermal growth factor receptor; IQR: interquartile range; IV: intravenous; m: metastatic; N: number of patients; Pembro: pembrolizumb; Q3W: every three weeks; RCT: randomized controlled trial; SG: Sacituzumab govitecan; TPC: treatment of physician's choice; TNBC: triple-negative breast cancer; USA: United States of America.
Abstracts from conferences.

[a] prior lines of treatment and follow-up time were given according to the information available in each study.

[b] TPC refers to eribulin, vinorelbine, capecitabine, or gemcitabine in ASCENT and TROPiCS-02 and capecitabine, platinum or observation in SASCIA.

[c] the population of TROPiCS-02 consisted of HER2- BC and residual disease after neoadjuvant chemotherapy (NACT).

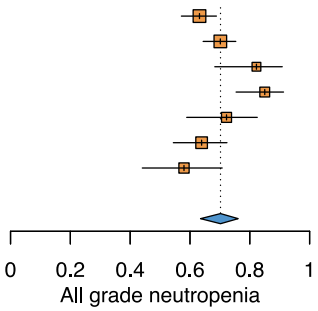
[d] the population of SASCIA consisted of HR-positive/HER2-negative tumors with a clinical and pathological stage (CPS) and histological grade (EG) score of >3 or 2 and ypN + after NACT.

[e] for all analyses, we included only the SG monotherapy arm of SACI-IO, and the SG-Pembro arm was not used in any of the analyses.

(A) Neutropenia

Study	Cases	Total	Weight	Proportion	95% C.I.
ASCENT	163	258	19.3%	0.63	[0.57; 0.69]
TROPiCS–02	188	268	19.1%	0.70	[0.64; 0.75]
SASCIA	37	45	9.2%	0.82	[0.68; 0.91]
EVER–132–001	68	80	11.6%	0.85	[0.75; 0.91]
IMMU–132–01 (A)	39	54	12.0%	0.72	[0.59; 0.83]
IMMU–132–01 (B)	69	108	16.2%	0.64	[0.54; 0.72]
NeoSTAR	29	50	12.6%	0.58	[0.44; 0.71]
Random effects model			**100.0%**	**0.70**	**[0.64; 0.76]**

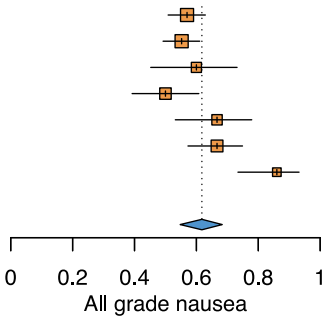
Heterogeneity: $I^2 = 71\%$, $\tau^2 = 0.1063$, $\chi^2_6 = 20.65$ ($p < 0.01$)



(B) Nausea

Study	Cases	Total	Weight	Proportion	95% C.I.
ASCENT	147	258	19.0%	0.57	[0.51; 0.63]
TROPiCS–02	148	268	19.2%	0.55	[0.49; 0.61]
SASCIA	27	45	11.4%	0.60	[0.45; 0.73]
EVER–132–001	40	80	14.7%	0.50	[0.39; 0.61]
IMMU–132–01 (A)	36	54	12.0%	0.67	[0.53; 0.78]
IMMU–132–01 (B)	72	108	15.5%	0.67	[0.57; 0.75]
NeoSTAR	43	50	8.2%	0.86	[0.73; 0.93]
Random effects model			**100.0%**	**0.62**	**[0.55; 0.68]**

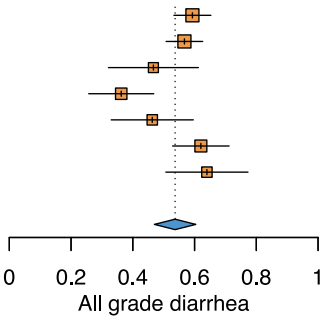
Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.0986$, $\chi^2_6 = 21.25$ ($p < 0.01$)



(C) Diarrhea

Study	Cases	Total	Weight	Proportion	95% C.I.
ASCENT	153	258	18.3%	0.59	[0.53; 0.65]
TROPiCS–02	152	268	18.4%	0.57	[0.51; 0.63]
SASCIA	21	45	10.7%	0.47	[0.32; 0.61]
EVER–132–001	29	80	14.0%	0.36	[0.26; 0.47]
IMMU–132–01 (A)	25	54	11.6%	0.46	[0.33; 0.60]
IMMU–132–01 (B)	67	108	15.3%	0.62	[0.53; 0.71]
NeoSTAR	32	50	11.6%	0.64	[0.51; 0.77]
Random effects model			**100.0%**	**0.54**	**[0.47; 0.60]**

Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.0055$, $\chi^2_6 = 21.31$ ($p < 0.01$)



(D) Anemia

Study	Cases	Total	Weight	Proportion	95% C.I.
ASCENT	89	258	15.6%	0.34	[0.29; 0.41]
TROPiCS–02	91	268	15.6%	0.34	[0.29; 0.40]
SASCIA	36	45	12.6%	0.80	[0.66; 0.89]
EVER–132–001	66	80	13.7%	0.82	[0.73; 0.89]
IMMU–132–01 (A)	20	54	13.9%	0.37	[0.25; 0.51]
IMMU–132–01 (B)	54	108	15.0%	0.50	[0.41; 0.59]
NeoSTAR trial	20	50	13.8%	0.40	[0.27; 0.54]
Random effects model			**100.0%**	**0.51**	**[0.38; 0.65]**

Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.4958$, $\chi^2_6 = 77.97$ ($p < 0.01$)

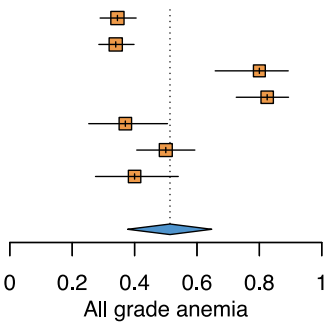


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Fig. 2. Absolute risk of all-grade (A) neutropenia; (B) nausea; (C) diarrhea; and (D) anemia.
Proportions for each trial are represented by a square and the horizontal line crossing the squares indicates the 95 % confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects. CI: confidence interval; IMMU-132-01 (A) refers to the hormone receptor (HR)-positive and human epidermal growth factor 2 (HER2)-negative population; IMMU-132-01 (B) refers to the triple-negative breast cancer (TNBC) population.

3. Results

3.1. Systematic review and baseline characteristics

Initially, 1889 studies were identified through the search and 57 studies were included for a comprehensive review. Finally, seven studies (four randomized CTs and three phase I/II studies) with nine related reports met our eligibility criteria (Fig. 1) [8,9,13,18–23]. A list of studies excluded after a comprehensive assessment is available in Table S3.

Overall, 928 patients received SG, and 576 were treated with TPC. In the phase II randomized SASCI-IO study, the comparator arm included 58 patients who received SG plus pembrolizumab. In this meta-analysis, SG-combined therapy was an exclusion criteria. Therefore, this trial was seen as a single-arm study, as only the SG-monotherapy arm was considered in our analyses. Most patients had TNBC (54.4 %, n = 505), metastatic disease (89.8 %, n = 833), and were heavily pretreated (at least two lines of prior therapy). SG dose and schedule were consistent in all studies. Median age and follow-up time, and other baseline characteristics of studies are presented in Table 1.

3.2. Main safety analyses

All studies graded AEs severity according to the CTCAE, most commonly using version 5.0 [8,9,13,18–23]. Safety outcomes description and criteria used in studies are detailed in Table S4. Information about preventive measures was available in three studies [8,9,18,21,22]. In two, GI symptoms prophylaxis was recommended according to established institutional guidelines whereas no specific recommendation was made in one study. As to neutropenia, studies recommended strategies for high-risk patients but lacked routine prophylaxis for all patients. Details about preventive measures are shown in Table S5. Over 45 % and 50 % of patients required concomitant growth-factor support and antidiarrheals, respectively, across studies (Table S6).

The pooled analysis of all-grade AEs including 863 patients revealed a high AR of neutropenia (70 %, 95 % CI, 64–76 %), followed by nausea (62 %, 95 % CI, 55–68 %), diarrhea (54 %, 95 % CI 47–60 %) and anemia (51 %, 95 % CI, 38–65 %) (Fig. 2). Regarding severe toxicity, 46 % (95 % CI, 39–53 %) of patients developed grade ≥3 neutropenia (Fig. 3A). Grade ≥3 diarrhea and anemia were reported in 7 % and 10 % of patients, respectively, whereas nausea was less frequent (3 % of patients).

Other important all-grade AEs include alopecia (50 %, 95 % CI 40–59 %), fatigue (48 %, 95 % CI 36–60 %); vomiting (35 %, 95 % CI 25–47 %); and constipation (31 %, 95 % CI, 20–45 %) (Figs. S1A–D). For all these AEs except for constipation (10 %, 95 % CI 5–16 %), grade ≥3 toxicity was seen in 5 % or less of patients (Figs. S2A–D). Important rates of all-grade and grade ≥3 hematotoxicity were registered (Figs. S1E–G and S2E-G).

The ASCENT study documented one case of grade 3 pneumonitis on SG but no cases of grade 2 or 3 interstitial lung disease (ILD) [8]. The case involved a 52-year-old patient with previous history of extensive lung involvement and metastases. The episode was deemed to be treatment-related and the patient discontinued the treatment. The event was resolved a week after management with antibiotics and steroids.

3.3. Subgroup analyses

The pooled analysis of three RCTs included 571 patients on SG compared to 516 patients on TPC. The analyses indicated a remarkably higher AR of neutropenia (OR 3.11, 95 % CI 1.62–5.99, $I^2 = 81$ %; $p < 0.001$), diarrhea (OR 6.82, 95 % CI 3.99–11.66, $I^2 = 64$ %; $p < 0.001$) and anemia (OR 2.26, 95 % CI 1.20–4.27, $I^2 = 78$ %; $p = 0.012$) for those on SG (Fig. 4). AR of all grade nausea was similar between groups (OR 1.94, 95 % CI 0.64–5.90, $I^2 = 94$ %, $p = 0.242$). A similar pattern was seen for grade ≥3 AEs when comparing both groups (Fig. S3).

Patients with early-stage or metastatic disease had a comparable risk of AEs, although only two studies with 95 patients were included in the early-stage group (Fig. S4).

The subgroup analysis of two studies stratified by UGT1A1 genotype comprised 216, 215, and 59 patients on the following groups: 1*/1*, 1*/28*, and 28*/28*, respectively (Figs. S5 and S6). For both all-grade and grade ≥3 AEs, numerically higher ARs were observed for patients with 28*/28* status. Yet, the test for subgroup difference was nonsignificant ($p > 0.05$) and likely limited by the small sample size.

3.4. Serious TRAE, dose reduction, treatment discontinuation and death

About 18 % (95 % CI, 9–33 %) of patients developed serious TRAEs (Fig. S7A). Dose reductions and treatment discontinuation were reported in 22 % (95 % CI, 15–30 %) and 4 % (3–6%) of patients, respectively (Figs. S7B–C). All studies except SASCIA specified that treatment discontinuation was due to AEs. Across six studies with 813 patients, 19 deaths (2 %) were documented. Most of them were not deemed to be treated-related (Fig. S7D). A narrative of deaths according to the information available in each study is shown in Table S7.

Overall, diarrhea was managed with the administration of loperamide and other supportive measures. Growth factors were allowed when necessary during treatment (*i.e.* patients with a higher risk of poor outcomes). A detailed description of AEs management is shown in Table S8. Infusion-related toxicity management and dose modification criteria are also available for reference (Table S9).

3.5. Health-related quality of life

Two phase III CTs were found to report health-related quality of life data [24,25]. Both studies used the criteria by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). In the ASCENT trial, SG was superior in regards to global health status, physical functioning, fatigue, and pain compared to TPC. Only for nausea, vomiting, and diarrhea, TPC was associated with more favorable changes from baseline. Median time to first clinically worsen was also superior in the SG-arm for physical and role functioning, fatigue, and pain. In TROPiCS-02, better changes from baseline were observed in favor of SG for physical functioning and dyspnea, and worse values were reported for diarrhea. Median time to first clinically worsen was also longer for the SG group in most domains. Overall, both ASCENT and TROPiCS-02 trials reported a better health-related quality of life in symptoms and functioning compared to chemotherapy.

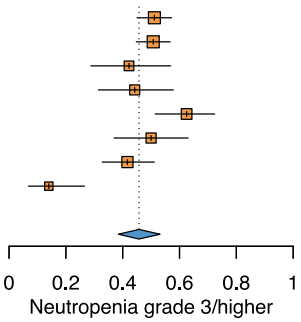
3.6. Quality assessment

A wide but symmetrical distribution of studies was seen in the funnel plot analysis (Fig. S8). No indication of publication bias was detected by the Egger test ($t = 1.35$, $p = 0.236$). Yet, the test's reliability might be affected by the inclusion of only seven studies [26]. All RCTs were judged to be at low risk of bias [8,9,18,19]. Non-randomized studies lacked adjustments for cofounders and thus failed to meet criteria for the first domain. Therefore, they were judged at moderate risk of bias [13,21–23].

(A) Neutropenia

Study	Cases	Total	Weight	Proportion	95% C.I.
ASCENT	132	258	16.1%	0.51	[0.45; 0.57]
TROPiCS–02	136	268	16.2%	0.51	[0.45; 0.57]
SASCIA	19	45	10.5%	0.42	[0.29; 0.57]
SACI–IO	23	52	11.2%	0.44	[0.31; 0.58]
EVER–132–001	50	80	12.7%	0.62	[0.51; 0.72]
IMMU–132–01 (A)	27	54	11.4%	0.50	[0.37; 0.63]
IMMU–132–01 (B)	45	108	13.9%	0.42	[0.33; 0.51]
NeoSTAR	7	50	7.8%	0.14	[0.07; 0.27]
Random effects model			**100.0%**	**0.46**	**[0.39; 0.53]**

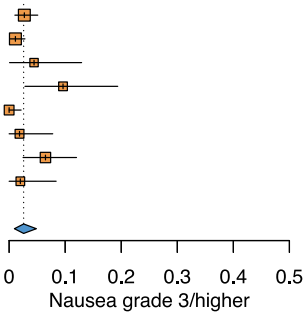
Heterogeneity: I^2 = 76%, τ^2 = 0.1272, χ^2_7 = 29.06 (p < 0.01)



(B) Nausea

Study	Cases	Total	Weight	Proportion	95% C.I.
ASCENT	7	258	17.9%	0.03	[0.01; 0.05]
TROPiCS–02	3	268	18.0%	0.01	[0.00; 0.03]
SASCIA	2	45	8.9%	0.04	[0.00; 0.13]
SASCI–IO	5	52	9.7%	0.10	[0.03; 0.19]
EVER–132–001	0	80	12.1%	0.00	[0.00; 0.02]
IMMU–132–01 (A)	1	54	9.9%	0.02	[0.00; 0.08]
IMMU–132–01 (B)	7	108	13.8%	0.06	[0.02; 0.12]
NeoSTAR	1	50	9.5%	0.02	[0.00; 0.08]
Random effects model			**100.0%**	**0.03**	**[0.01; 0.05]**

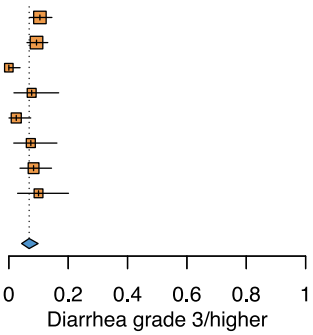
Heterogeneity: I^2 = 60%, τ^2 = 0.0035, χ^2_7 = 17.46 (p = 0.01)



(C) Diarrhea

Study	Cases	Total	Weight	Proportion	95% C.I.
ASCENT	27	258	18.6%	0.10	[0.07; 0.15]
TROPiCS–02	25	268	18.8%	0.09	[0.06; 0.13]
SASCIA	0	45	8.6%	0.00	[0.00; 0.04]
SASCI–IO	4	52	9.4%	0.08	[0.02; 0.17]
EVER–132–001	2	80	12.0%	0.03	[0.00; 0.07]
IMMU–132–01 (A)	4	54	9.6%	0.07	[0.02; 0.16]
IMMU–132–01 (B)	9	108	13.8%	0.08	[0.04; 0.14]
NeoSTAR trial	5	50	9.2%	0.10	[0.03; 0.20]
Random effects model			**100.0%**	**0.07**	**[0.04; 0.10]**

Heterogeneity: I^2 = 55%, τ^2 = 0.0029, χ^2_7 = 15.51 (p = 0.03)



(D) Anemia

Study	Cases	Total	Weight	Proportion	95% C.I.
ASCENT	20	258	14.2%	0.08	[0.05; 0.11]
TROPiCS–02	17	268	14.2%	0.06	[0.04; 0.10]
SASCIA	1	45	11.2%	0.02	[0.00; 0.09]
SACI–IO	19	52	11.6%	0.37	[0.24; 0.50]
EVER–132–001	17	80	12.6%	0.21	[0.13; 0.31]
IMMU–132–01 (A)	6	54	11.7%	0.11	[0.04; 0.21]
IMMU–132–01 (B)	12	108	13.1%	0.11	[0.06; 0.18]
NeoSTAR trial	0	50	11.5%	0.00	[0.00; 0.03]
Random effects model			**100.0%**	**0.10**	**[0.05; 0.16]**

Heterogeneity: I^2 = 87%, τ^2 = 0.0157, χ^2_7 = 53.39 (p < 0.01)

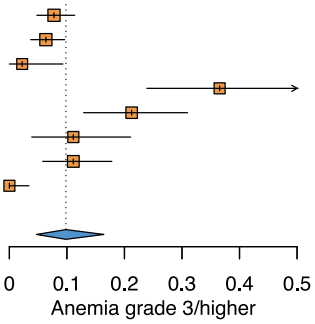


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Fig. 3. Absolute risk of grade ≥3 (A) neutropenia; (B) nausea; (C) diarrhea; and (D) anemia.
Proportions for each trial are represented by a square and the horizontal line crossing the squares indicates the 95 % confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects. CI: confidence interval; IMMU-132-01 (A) refers to the hormone receptor (HR)-positive and human epidermal growth factor 2 (HER2)-negative population; IMMU-132-01 (B) refers to the triple-negative breast cancer (TNBC) population.

3.7. Sensitivity analyses and exploring heterogeneity

Fairly similar results were observed in the leave-one-out sensitivity analyses for single-arm all-grade neutropenia, nausea, diarrhea, and anemia (Fig. S9). Moreover, considerable heterogeneity persisted across all outcomes explored. The Baujat plot showed that NeoSTAR and EVER-132-001 studies remarkably contributed to the overall heterogeneity of these outcomes (Fig. S10). This was probably linked to the slightly different eligibility criteria of both studies: NeoSTAR included only early-stage BC patients, whereas EVER-132-001 was conducted exclusively on Chinese patients. As to the effect on the overall result, TROPiCS-02 was the study that predominantly influenced effect sizes of analyses. This is expected as this is the study with the largest population included in this meta-analysis.

In the sensitivity analyses of pair-wise outcomes, the pooled effect size varied for all four outcomes when leaving each study out (Fig. S11). Yet, all analyses sustained an increased risk of AEs for the SG-arm compared to TPC. A low heterogeneity was observed when omitting SASCIA in the analyses of anemia and neutropenia, and when omitting ASCENT of nausea. Likely, this variability reflects different scenarios and population characteristics in which studies were performed.

4. Discussion

This comprehensive systematic review and meta-analysis included 928 BC patients in any setting treated with SG and 571 patients treated with TPC. The AEs most frequently reported were all-grade neutropenia, nausea, diarrhea, and anemia in 70 %, 62 %, 54 %, and 51 % of patients, respectively. Remarkably, grade ≥3 neutropenia was seen in 47 % of patients. Other important AEs include all-grade alopecia (50 %), fatigue (48 %), and vomiting (35 %). Concerning rates of mild and severe (*i.e.* grade ≥3) hematotoxicity were also reported. A significantly increased risk of neutropenia, diarrhea, and anemia was observed for the SG group compared to chemotherapy. Most studies lacked preventive measures and routine prophylaxis for neutropenia. The subgroup analysis stratified by UGT1A1 genotype revealed a numerically higher but nonsignificant risk of AEs for patients with 28* homozygosis.

SG is currently the only ani-Trop2 ADC available in clinical practice and exhibits a distinct toxicity profile, primarily due to its targeted delivery mechanism and cytotoxic payload, SN-38 – the active metabolite of irinotecan [27]. The antibody component works by binding to specific cell membrane antigens, and it is internalized into targeted cells [28,29]. The payload is then released into the tumor cell microenvironment and exhibits its cytotoxic effects [28,29]. Combining the mAB selectivity and payload lethality, SG was designed to optimize on-site cytotoxicity while minimizing systemic exposure [27–29]. Nevertheless, this can also lead to unique safety challenges.

Mechanisms behind SG toxicity rely on the linker's stability, ADC's internalization, but specially on the payload's release [29,30]. ADC toxicity can be classified based on the target expression of affected cells. On-target off-tumor toxicity occurs when SG binds and delivers SN-38 to healthy Trop2-expressing tissues, and manifests as localized effects (mucositis and skin reactions) [29,30]. Yet less than 1 % of the administered ADC dose is delivered to targeted tumor cells [30]. The linker instability or catabolism results in the premature release of SN-38 in the circulation, causing systemic effects, including fatigue, GI and hematotoxicity, (off-target off-tumor toxicity) [3,29–31].

Another rationale to explain SG toxicity correlates directly with its payload mechanism of action [29,30,32]. SN-38 inhibits the topoisomerase I enzyme leading to persistent double-strand breaks in DNA and, consequently, cell arrest and apoptosis [32]. This phenomenon is remarkably relevant in cells with a high proliferation rate such as hematopoietic progenitors [29,30,32]. Accordingly, in this meta-analysis, we found high ARs of neutropenia, febrile neutropenia, anemia, and leukopenia, among patients treated with SG.

A similar pattern of hematotoxicity was previously seen in patients on T-DXd, which also contains a topoisomerase inhibitor payload [33,34]. Neutropenia was frequently reported in patients treated with T-DXd, affecting over 30 % of patients in DESTINY-Breast03 and DESTINY-Breast04 [33,34]. However, the frequency of febrile neutropenia with T-DXd was notably lower (less than 2 %) [33,34]. In this meta-analysis, about 15 % of patients experienced febrile neutropenia, and 6 % had grade ≥3 events. We also explored differences in AEs frequencies between patients treated with SG and TPC across three RCTs. Although GI and hematotoxicity are not uncommon in chemotherapy agents (eribulin, vinorelbine, capecitabine, and gemcitabine) we found even higher ARs for those in the SG group [35–38].

Important GI AEs of SG include nausea and vomiting (NV) and diarrhea [27]. The mechanisms relating ADCs and NV are complex and involve both peripheral and central emesis pathways [29,30]. For diarrhea, off-tumor off-target toxicity is thought to play a major role in its pathophysiology [29,30]. A key factor influencing SG toxicity, particularly diarrhea and neutropenia, is UGT1A1 polymorphisms [39,40]. This enzyme plays a crucial role in the glucuronidation and clearance of SN-38. The UGT1A1 28* homozygosis implies in reduced enzymatic activity, thus, increasing SN-38 exposure and toxicity [39,40]. In this meta-analysis, the group of 59 patients harboring UGT1A1 28* genotype experienced numerically higher risks of AEs. Current guidelines have not established specific dose recommendations for those with UGT1A1 polymorphisms. Nevertheless, close safety vigilance should be followed for these patients [39,40].

Other than impacting the quality of life, SG-related toxicity may lead to severe and life-threatening complications, including metabolic imbalances, dehydration, bleeding, sepsis, and shock [8,9,13]. In this scenario, prophylactic measures are as essential as careful monitoring and timely management [41]. For prevention of chemotherapy-induced neutropenia, myeloid growth factors are often indicated [42]. On the other hand, a variety of options are available for chemotherapy-induced NV. They are usually given based on the emetogenic potential of specific agents, but two/three-drug combination regimens (*i.e.,* 5-HT_3 receptor antagonists, NK_1 receptor antagonists, and corticosteroids) are suggested by ESMO and ASCO guidelines [43,44]. Although there is a paucity of formal recommendations for preventive measures for most ADCs regimens, an expert panel focusing on antiemetic regimens supports the prophylactic use of two/three-drug combination regimens for patients treated with SG [45].

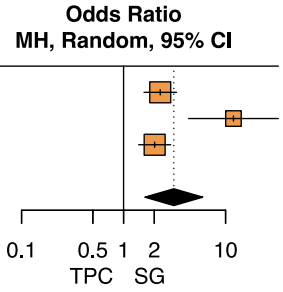
Most of the studies included in this meta-analysis only addressed preventive measures for specific high-risk groups and lacked indications for the general population [8,9,21]. Future research should focus on establishing effective strategies to maximize treatment tolerance and efficacy. An ongoing phase II CT is currently assessing the impact of prophylactic treatment on SG toxicity and will likely provide some directions on this matter (NCT05520723). Despite important toxicity, treatment discontinuation rates were relatively low across studies. Dose reductions were required in about 22 % of patients. A great percentage of patients received concomitant treatment with antiemetics and growth factor support. Moreover, most deaths were not treatment-related. This suggests that aligned with dose adjustments and supportive care, SG may be tolerable for most patients in clinical practice.

Yet, there are still some unanswered questions. For instance, how the

(A) Neutropenia

Study	SG (N)	Total	TPC (N)	Total	Weight	Effect	CI
ASCENT	163	258	96	224	39.2%	2.29	[1.59; 3.30]
SASCIA	37	45	12	43	21.6%	11.95	[4.33; 32.93]
TROPiCS–02	188	268	134	249	39.3%	2.02	[1.41; 2.89]
Total (95% CI)					**100.0%**	**3.11**	**[1.62; 5.99]**

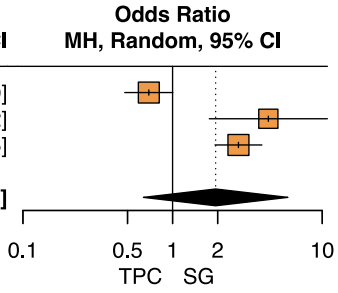
Heterogeneity: $Tau^2 = 0.2503$; $Chi^2 = 10.59$, df = 2 (P < 0.01); $I^2 = 81\%$
Test for overall effect: Z = 3.39 (P < 0.001)



(B) Nausea

Study	SG (N)	Total	TPC (N)	Total	Weight	Effect	CI
ASCENT	147	258	147	224	35.2%	0.69	[0.48; 1.00]
SASCIA	27	45	11	43	29.5%	4.36	[1.76; 10.82]
TROPiCS–02	148	268	77	249	35.3%	2.75	[1.92; 3.95]
Total (95% CI)					**100.0%**	**1.94**	**[0.64; 5.90]**

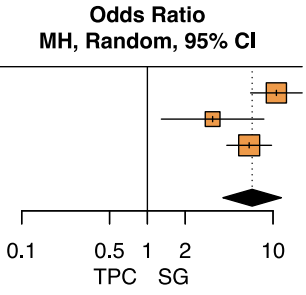
Heterogeneity: $Tau^2 = 0.8766$; $Chi^2 = 32.90$, df = 2 (P < 0.01); $I^2 = 94\%$
Test for overall effect: Z = 1.17 (P = 0.242)



(C) Diarrhea

Study	SG (N)	Total	TPC (N)	Total	Weight	Effect	CI
ASCENT	153	258	27	224	38.3%	10.63	[6.63; 17.06]
SASCIA	21	45	9	43	20.4%	3.31	[1.29; 8.46]
TROPiCS–02	152	268	42	249	41.3%	6.46	[4.28; 9.73]
Total (95% CI)					**100.0%**	**6.82**	**[3.99; 11.66]**

Heterogeneity: $Tau^2 = 0.1373$; $Chi^2 = 5.51$, df = 2 (P = 0.06); $I^2 = 64\%$
Test for overall effect: Z = 7.02 (P < 0.001)



(D) Anemia

Study	SG (N)	Total	TPC (N)	Total	Weight	Effect	CI
ASCENT	89	258	54	224	38.6%	1.66	[1.11; 2.47]
SASCIA	36	45	15	43	22.3%	7.47	[2.85; 19.55]
TROPiCS–02	91	268	62	249	39.1%	1.55	[1.06; 2.27]
Total (95% CI)					**100.0%**	**2.26**	**[1.20; 4.27]**

Heterogeneity: $Tau^2 = 0.2314$; $Chi^2 = 9.14$, df = 2 (P = 0.01); $I^2 = 78\%$
Test for overall effect: Z = 2.51 (P = 0.012)

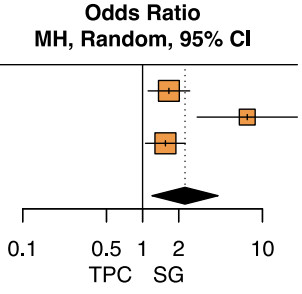


Fig. 4. Absolute risk of grade ≥3 (A) neutropenia; (B) nausea; (C) diarrhea and (D) anemia in patients treated with SG *versus* TPC.
Proportions for each trial are represented by a square and the horizontal line crossing the squares indicates the 95 % confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects. CI: confidence interval; MH: Mantel-Haenszel; SG: Sacituzumab govitecan; TPC: treatment of physician's choice.

SG long-term toxicity behaves and the effect of cumulative toxicity of previous therapies. This is specifically important in the context of ADC sequencing strategies [46]. Despite achieving relevant antitumor responses, many patients will face progression under ADC therapy [47]. Frequently, this is associated with acquired resistance [47]. Current evidence suggests that alterations in the tumor microenvironment - such as disruptions in the payload target - are one of the rationales behind ADC-acquired resistance [47]. Mechanisms involved in this process warrant investigation.

Another scenario in which unraveling toxicity is highly needed is when considering ADC-combining regimens [48]. For instance, the phase Ib/II BEGONIA trial (NCT03742102) is currently studying the combination of durvalumab with other novel agents, including ADCs. Although this association could provide synergistic activity and translate to higher benefit, the resultant toxicity is unknown [48]. The influence of genetic factors, such as UGT1A1 polymorphisms should also be better explored [40]. Advances in predictive biomarkers and improvements in monitoring techniques could further refine safety management and optimize dosing regimens in patients receiving SG [48].

High heterogeneity was seen in our analyses, both in pairwise and single-arm meta-analyses, likely due to the inclusion of studies in different settings (early-stage *versus* metastatic) and with slightly different designs (randomized *versus* non-randomized clinical trials), and populations. However, in the context of proportional analyses, Barker and colleagues previously highlighted in their guide on proportional meta-analysis that high heterogeneity may not translate into data inconsistencies, but it usually arises from certain population characteristics and the nature of proportional estimates [49]. Additionally, our leave-one-out sensitivity analyses showed consistent results even for pair-wise analyses. Therefore, we believe our findings reflect those seen in the overall clinical practice.

This meta-analysis has some limitations. Firstly, it is a study-level meta-analysis; therefore, we did not have access to baseline blood samples of patients. Most patients were previously treated with chemotherapy that could have cumulative toxicities. For some studies, data was not fully matured as only abstracts from conferences were available. Moreover, some subgroup analyses were limited by a small number of studies. Analyses based on important factors such as age could not be performed due to the lack of data from individual studies. To minimize some of these limitations, we used random models and performed multiple sensitivity and subgroup analyses.

5. Conclusion

This comprehensive systematic review and meta-analysis gathers extensive data on safety and management of SG toxicity in BC patients across CTs. Particularly, concerning rates of neutropenia, nausea diarrhea, and anemia were reported. Significantly higher toxicity was observed for patients receiving SG compared to chemotherapy. We highlight the need for protocols on prophylactic measures and strategies to mitigate SG-related toxicity.

CRediT authorship contribution statement

Maria Inez Dacoregio: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Isabella Michelon:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Caio Ernesto do Rego Castro:** Resources, Methodology, Investigation, Data curation, Conceptualization. **Francisco Cezar Aquino de Moraes:** Methodology, Formal analysis, Data curation. **Guilherme Rossato de Almeida:** Resources, Methodology, Data curation, Conceptualization. **Lis Victória Ravani:** Methodology, Investigation, Data curation. **Maysa Vilbert:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Ricardo Lima Barros Costa:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Data availability

All data presented in this study is accessible to the corresponding author upon a reasonable request.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors M.I.D., I.M, C.E.R.C, F.C.A.M., G.R.A, L.V.R., M.V., declare no conflicts of interest. R. L. B. Costa received honorarium from Gilead Sciences, Pfizer, Daiichi Sankyo and Astra Zeneca.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2024.103853.

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