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Sacituzumab govitecan in HR$^+$HER2$^-$ metastatic breast cancer: the randomized phase 3 EVER-132-002 trial

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Sacituzumab govitecan (SG) significantly improved progression-free survival (PFS) and overall survival (OS) versus chemotherapy in hormone receptor-positive human epidermal growth factor receptor 2-negative (HR$^+$HER2$^-$) metastatic breast cancer (mBC) in the global TROPiCS-02 study. TROPiCS-02 enrolled few Asian patients. Here we report results of SG in Asian patients with HR$^+$HER2$^-$ mBC from the EVER-132-002 study. Patients were randomized to SG (n = 166) or chemotherapy (n = 165). The primary endpoint was met: PFS was improved with SG versus chemotherapy (hazard ratio of 0.67, 95% confidence interval 0.52–0.87; P = 0.0028; median 4.3 versus 4.2 months). OS also improved with SG versus chemotherapy (hazard ratio of 0.64, 95% confidence interval 0.47–0.88; P = 0.0061; median 21.0 versus 15.3 months). The most common grade ≥3 treatment-emergent adverse events were neutropenia, leukopenia and anemia. SG demonstrated significant and clinically meaningful improvement in PFS and OS versus chemotherapy, with a manageable safety profile consistent with prior studies. SG represents a promising treatment option for Asian patients with HR$^+$HER2$^-$ mBC (ClinicalTrials.gov identifier no. NCT04639986).

Breast cancer (BC) is the most frequently diagnosed cancer in women around the world, including in South Korea and Taiwan, and is the second most commonly diagnosed cancer in women in China[1–4]. The most common type of BC is hormone receptor-positive human epidermal growth factor receptor 2-negative (HR$^+$HER2$^-$), which accounts for approximately 70% of BC cases[5,6]. Current standard-of-care therapy for HR$^+$HER2$^-$) metastatic BC (mBC) is endocrine therapy combined with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) as first line, followed by sequential lines of single-agent chemotherapy once endocrine resistance develops[7–10]. Single-agent chemotherapy is associated with limited efficacy and high toxicity, highlighting the unmet need for additional treatment options in patients with HR$^+$HER2$^-$ mBC[11–15].

Sacituzumab govitecan (SG) is a trophoblast cell surface antigen 2 (Trop-2)-directed antibody–drug conjugate. SG selectively targets cells expressing Trop-2, which is commonly expressed in BC[16]. It is then internalized and delivers SN-38, an active metabolite of irinotecan,

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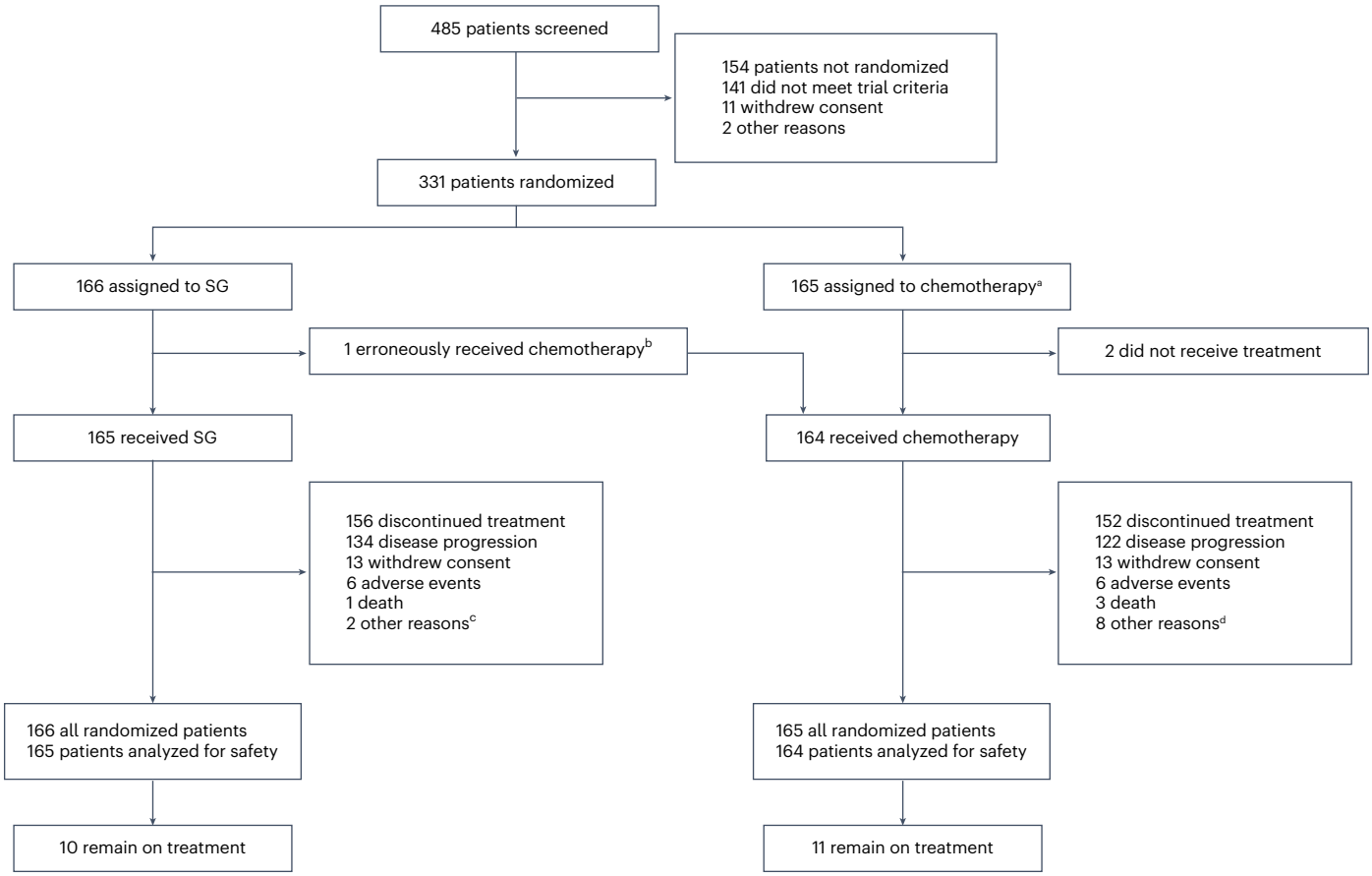

Fig. 1 | CONSORT diagram. Of 485 patients screened, 154 were not randomized to a treatment group. The remaining 331 patients were randomized to the SG or chemotherapy groups. [a]Chemotherapy selected at randomization: eribulin (n = 131), vinorelbine (n = 13), capecitabine (n = 11) or gemcitabine (n = 10). [b]One patient was randomized to the SG group but was erroneously administered chemotherapy. [c]Other reasons included clinical deterioration, pregnancy or administrative problems. [d]Other reasons included clinical deterioration, pregnancy, administrative problems or patient nonadherence/protocol violations.

via a hydrolysable linker[17–19]. SG is approved in the United States and in multiple other countries for the treatment of HR$^+$HER2$^-$ mBC following endocrine therapy and at least two additional systemic chemotherapies in the metastatic setting based on the global phase 3 TROPiCS-02 study[20,21]. SG is also approved in multiple countries for the treatment of triple-negative mBC for patients who have received at least two prior systemic therapies, including at least one in the metastatic setting[20,21]. SG has also received accelerated approval in the United States for the treatment of metastatic urothelial cancer following chemotherapy and immunotherapy[20].

In the TROPiCS-02 study (NCT03901339), SG was compared with chemotherapy treatment of physician's choice. At the primary progression-free survival (PFS) analysis (data cutoff date 3 January 2022), SG demonstrated statistically significant improvement in the primary endpoint of PFS versus chemotherapy, with a 34% reduction in risk of disease progression or death (hazard ratio (HR) of 0.66, 95% confidence interval (CI) 0.53–0.83; P = 0.0003) and median of 5.5 versus 4.0 months[22]. At a subsequent prespecified interim analysis (data cutoff date 1 July 2022), SG demonstrated statistically significant and clinically meaningful improvement in overall survival (OS), with a median of 14.4 versus 11.2 months (HR of 0.79, 95% CI 0.65 to 0.96; P = 0.020), for SG versus chemotherapy[23]. Treatment with SG also resulted in higher objective response rate (ORR) and median duration of response (DoR) versus chemotherapy, which were 21% versus 14% and 8.1 versus 5.6 months, respectively[23]. The safety profile of SG was manageable and similar to earlier clinical trials in BC and other tumors[22–26]. The patients treated with SG experienced grade ≥3 treatment-emergent adverse events (TEAEs) at higher rates than with chemotherapy (74% versus 60%), but the rates of TEAEs leading to treatment discontinuation were similar (6% versus 4%)[23].

TROPiCS-02 primarily enrolled non-Asian patients, with Asian patients making up 3% of the study population[22]. Thus, the benefit–risk profile for SG in Asian patients with HR$^+$HER2$^-$ mBC has not been adequately characterized. The phase 3, randomized EVER-132-002 study (NCT04639986) was initiated to determine the efficacy and safety of SG in Asian patients with endocrine-resistant, pretreated HR$^+$HER2$^-$ mBC.

Results

Patient characteristics

Of the 485 patients screened between 9 December 2020 and 2 December 2022, 331 were randomized at 41 study sites in China, Republic of Korea and Taiwan to receive SG (n = 166) or chemotherapy (n = 165; eribulin, n = 131 (79%); vinorelbine, n = 13 (8%); capecitabine, n = 11 (7%); gemcitabine, n = 10 (6%); Fig. 1). Two patients were randomized to the chemotherapy group but did not receive any study drug. One patient was randomized to the SG group but was erroneously administered chemotherapy; this patient was included in the SG group for efficacy outcomes and the chemotherapy group for safety outcomes. At the data cutoff date of 30 April 2023, 21 patients were continuing study drug, 6% (n = 10) in the SG group and 7% (n = 11) in the chemotherapy group.

Patient demographics and baseline characteristics were generally well balanced across treatment groups. The median age was 52 years. Most patients had visceral metastases at baseline (88% SG, 89% chemotherapy). Approximately half of patients had received prior CDK4/6i

therapy in the metastatic setting (49% SG, 48% chemotherapy). In both treatment groups, 56% of patients had received two prior chemotherapy regimens for treatment of metastatic disease, and 44% had received three to four prior regimens (Table 1).

Most patients had received prior endocrine therapy in the metastatic setting (92% SG, 90% chemotherapy), and 37% of patients in the SG group and 41% in the chemotherapy group had previously received targeted therapy in the metastatic setting (Extended Data Table 1).

Efficacy

Median follow-up duration was 13.4 months (range 0.1–28.7) in all randomized patients, 14.5 months (range 1.3–27.8) in the SG group and 12.7 months (range 0.1–28.7) in the chemotherapy group. The primary endpoint of PFS per blinded independent central review (BICR) was met, with a 33% reduction in the risk of disease progression or death (HR of 0.67, 95% CI 0.52 to 0.87; $P = 0.0028$) (Fig. 2a). The median PFS per BICR was 4.3 months (95% CI 4.1 to 5.7) in the SG group versus 4.2 months (95% CI 2.8 to 4.2) in the chemotherapy group. The PFS rate at 6 months was 41% versus 24% and at 12 months was 17% versus 9% with SG versus chemotherapy, respectively. The results for PFS per investigator (INV) were generally consistent with the respective results per BICR (HR of 0.61, 95% CI 0.48 to 0.79; $P = 0.0001$), with a longer median PFS demonstrated in the SG group (5.7 months (95% CI 4.3 to 7.9)) versus the chemotherapy group (4.2 months (95% CI 2.9 to 4.3)) (Fig. 2b). PFS benefit was generally consistent across multiple prespecified subgroups, including by age, baseline Eastern Cooperative Oncology Group performance status, HER2 status, presence of visceral metastasis, number of prior chemotherapy regimens for treatment of metastatic disease and prior CDK4/6i treatment (Fig. 3).

A 36% reduction in the risk of death was observed with SG versus chemotherapy (HR of 0.64, 95% CI 0.47 to 0.88; $P = 0.0061$). The median OS with SG versus chemotherapy was 21.0 (95% CI 16.5 to not estimable) versus 15.3 months (95% CI 13.2 to 18.4). The OS rate for SG versus chemotherapy was 76% versus 62% at 12 months and 41% versus 30% at 24 months (Fig. 2c). The ORR per BICR was 20% with SG and 15% with chemotherapy. Median DoR per BICR was 5.3 months (SG) versus 5.2 months (chemotherapy). Responses per INV assessment were consistent with responses per BICR (Table 2). SG generally provided consistent OS benefit versus chemotherapy across prespecified subgroups (Extended Data Fig. 1).

When patients were divided by Trop-2 H-score (<100 versus ≥100), the HR for PFS per BICR with SG versus chemotherapy was 0.91 (95% CI 0.65 to 1.28) in the Trop-2 <100 subgroup and was 0.44 (95% CI 0.29 to 0.68) in the ≥100 subgroup. The HR for OS with SG versus chemotherapy was 0.72 (95% CI 0.47 to 1.10) for Trop-2 < 100 and 0.61 (95% CI 0.37 to 1.01) for ≥100 (Fig. 3 and Extended Data Fig. 1).

Safety

Among patients in the safety population, the median duration of treatment with SG was 5.1 months (range 0.03–24.9) and with chemotherapy was 3.3 months (range 0.03–28.1). The patients were administered a median of seven cycles of SG compared with five cycles with chemotherapy, and the median relative dose intensity for SG was 100% (Extended Data Table 2).

All patients in both treatment groups experienced any-grade TEAEs. Grade ≥3 TEAEs in the SG versus chemotherapy groups were reported in 82% versus 70% of patients, respectively. The most common TEAEs of any-grade with SG versus chemotherapy were neutropenia (88% versus 78%), anemia (71% versus 55%) and leukopenia (68% versus 63%). The most common grade ≥3 TEAEs with SG versus chemotherapy were neutropenia (69% versus 62%), leukopenia (42% versus 37%) and anemia (18% versus 6%) (Table 3). Febrile neutropenia (any grade and grade ≥3) was observed in 5% of patients in the SG group and 4% in the chemotherapy group. TEAEs leading to dose interruption with SG versus chemotherapy occurred at a rate of 68% versus 40%, and TEAEs leading to treatment discontinuation 3% versus 4%. TEAEs leading to dose reduction were reported in 25% of patients in the SG group and 32% in the chemotherapy group, and treatment-emergent serious AEs

Table 1 | Patient demographics and baseline characteristics

	SG (*n*=166)	Chemotherapy (*n*=165)
Sex, *n* (%)		
Female	166 (100)	163 (99)
Male	0	2 (1)
Median age (range), years	53 (32–72)	51 (28–79)
<65, *n* (%)	151 (91)	142 (86)
≥65, *n* (%)	15 (9)	23 (14)
Region, *n* (%)		
Mainland China	118 (71)	114 (69)
Taiwan	17 (10)	12 (7)
Republic of Korea	31 (19)	39 (24)
ECOG PS, *n* (%)		
0	33 (20)	41 (25)
1	133 (80)	124 (75)
Visceral metastases at baseline[a], *n* (%)		
Yes	146 (88)	147 (89)
No	20 (12)	18 (11)
Median time from initial metastatic diagnosis to randomization (range), months	39.1 (1.4–156.2)	36.9 (0.8–171.0)
Prior endocrine therapy in metastatic setting for at least 6 months, *n* (%)		
Yes	131 (79)	126 (76)
No	35 (21)	39 (24)
Prior chemotherapy in neoadjuvant or adjuvant setting, *n* (%)		
Yes	120 (72)	118 (72)
No	46 (28)	47 (28)
Prior CDK4/6i in metastatic setting[a], *n* (%)		
Yes	81 (49)	80 (48)
No	85 (51)	85 (52)
Prior CDK4/6i duration[b], *n* (%)		
Treatment duration ≤12 months	56 (34)	53 (32)
Treatment duration >12 months	25 (15)	27 (16)
Median prior chemotherapy regimens in the metastatic setting[c], *n* (range)	2 (1–4)	2 (1–4)
Number of prior chemotherapy regimens for treatment of metastatic disease[a], *n* (%)		
2	93 (56)	93 (56)
3–4	73 (44)	72 (44)
Trop-2 H-score[d], *n* (%)		
<100	94 (57)	90 (55)
≥100	59 (36)	63 (38)

[a]Stratification factor data from interactive web-based response system. [b]Summary of prior CDK4/6i duration accounted for the three patients who were mis-stratified for the stratification factor 'prior CDK4/6i in metastatic setting'. Prior CDK4/6i treatment duration was unknown for one (1%) patient in the chemotherapy group. [c]Number of prior chemotherapy regimens in metastatic setting does not include chemotherapy received in the neoadjuvant or adjuvant setting, which may have been counted as a line of therapy in patients with early relapse for purposes of randomization and eligibility. [d]Missing, SG, *n*=13; chemotherapy, *n*=12. ECOG PS, Eastern Cooperative Oncology Group performance status.

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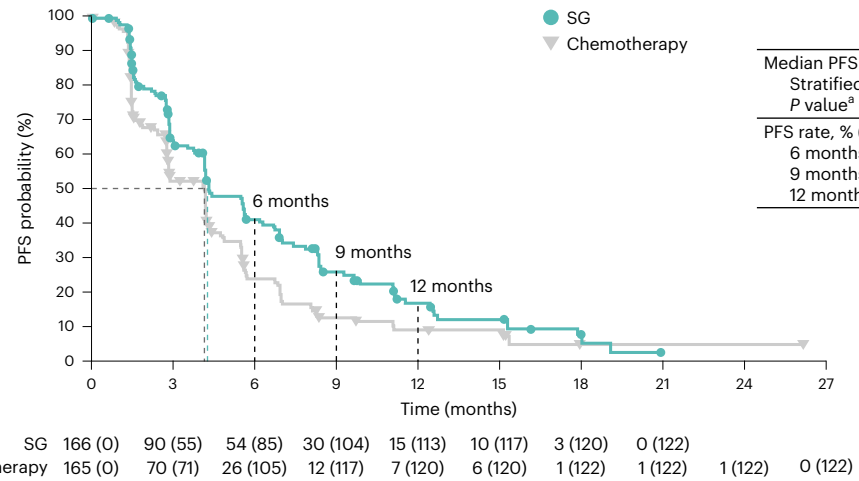
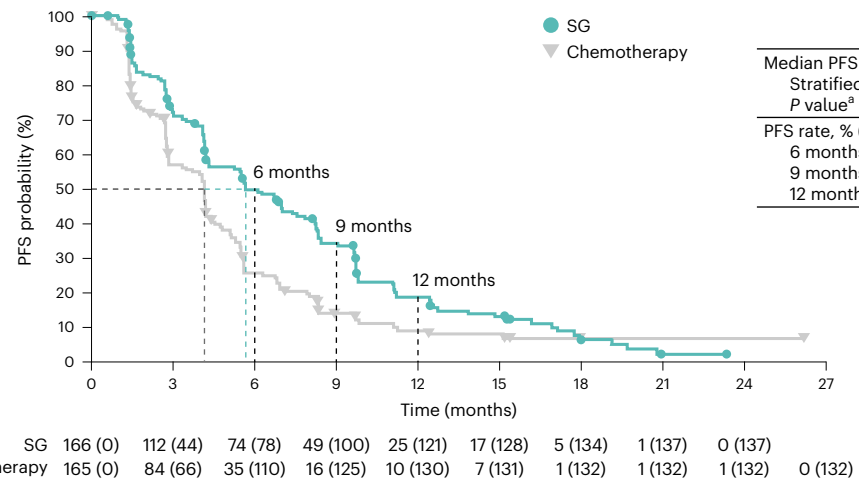
a



	SG group (*n* = 166)	Chemotherapy group (*n* = 165)
Median PFS (95% CI), months	4.3 (4.1–5.7)	4.2 (2.8–4.2)
Stratified HR (95% CI)	**0.67** (0.52–0.87)	
P value[a]	0.0028	
PFS rate, % (95% CI)		
6 months	41.4 (33.2–49.4)	24.2 (17.1–32.0)
9 months	26.2 (19.0–33.9)	12.9 (7.5–19.8)
12 months	17.2 (10.9–24.6)	9.2 (4.6–15.8)

SG	166 (0)	90 (55)	54 (85)	30 (104)	15 (113)	10 (117)	3 (120)	0 (122)		
Chemotherapy	165 (0)	70 (71)	26 (105)	12 (117)	7 (120)	6 (120)	1 (122)	1 (122)	1 (122)	0 (122)

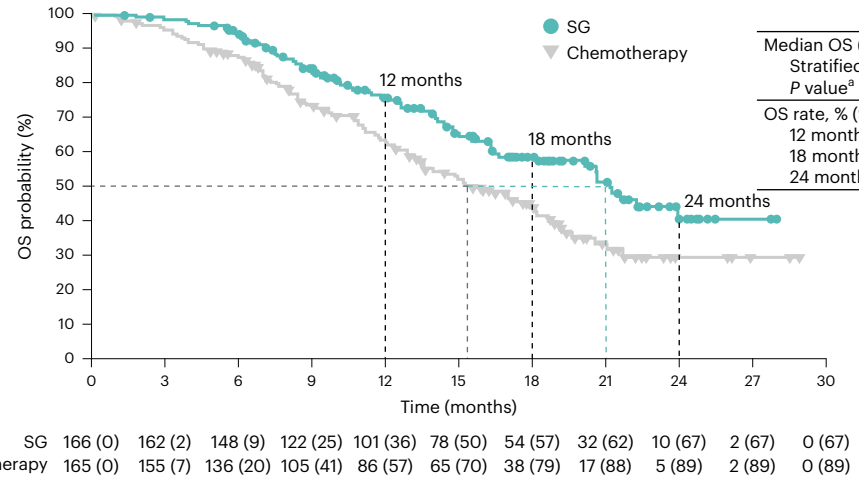
b



	SG group (*n* = 166)	Chemotherapy group (*n* = 165)
Median PFS (95% CI), months	5.7 (4.3–7.9)	4.2 (2.9–4.3)
Stratified HR (95% CI)	**0.61** (0.48–0.79)	
P value[a]	0.0001	
PFS rate, % (95% CI)		
6 months	49.9 (41.8–57.5)	26.2 (19.3–33.6)
9 months	34.6 (27.1–42.2)	14.6 (9.2–21.1)
12 months	19.0 (13.0–25.9)	9.7 (5.3–15.8)

SG	166 (0)	112 (44)	74 (78)	49 (100)	25 (121)	17 (128)	5 (134)	1 (137)	0 (137)	
Chemotherapy	165 (0)	84 (66)	35 (110)	16 (125)	10 (130)	7 (131)	1 (132)	1 (132)	1 (132)	0 (132)

c



	SG group (*n* = 166)	Chemotherapy group (*n* = 165)
Median OS (95% CI), months	21.0 (16.5–NE)	15.3 (13.2–18.4)
Stratified HR (95% CI)	**0.64** (0.47–0.88)	
P value[a]	0.0061	
OS rate, % (95% CI)		
12 months	76.0 (68.3–82.1)	62.1 (53.8–69.4)
18 months	58.6 (49.7–66.5)	43.9 (35.2–52.2)
24 months	40.6 (28.8–52.1)	29.5 (20.3–39.2)

SG	166 (0)	162 (2)	148 (9)	122 (25)	101 (36)	78 (50)	54 (57)	32 (62)	10 (67)	2 (67)	0 (67)
Chemotherapy	165 (0)	155 (7)	136 (20)	105 (41)	86 (57)	65 (70)	38 (79)	17 (88)	5 (89)	2 (89)	0 (89)

Fig. 2 | Kaplan–Meier estimates of PFS and OS. a, Kaplan–Meier curve of PFS per BICR in patients treated with SG (*n* = 166) versus chemotherapy (*n* = 165). **b**, Kaplan–Meier curve of PFS per INV in patients treated with SG versus chemotherapy. **c**, Kaplan–Meier curve of OS in patients treated with SG versus chemotherapy. The median PFS and OS were calculated using the Kaplan–Meier method. The HR values were estimated using a stratified Cox proportional-hazards model, and the *P* values were calculated using a stratified log-rank test. Dashed blue and grey lines indicate median values, and dashed black lines indicate landmark time points. [a]Stratified log-rank *P* value. NE, not estimable.

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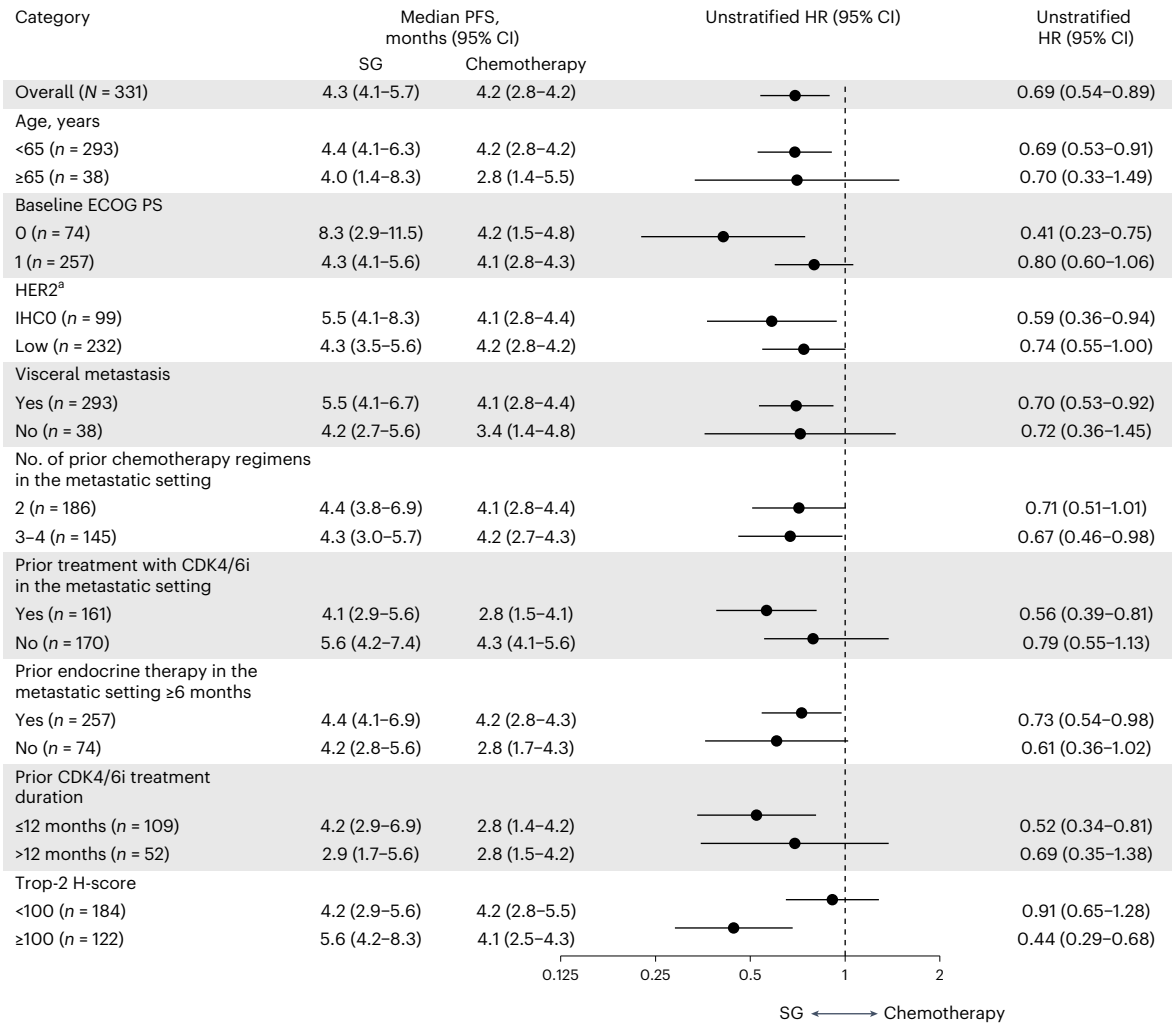

Fig. 3 | Subgroup analysis of PFS. PFS per BICR with SG versus chemotherapy was analyzed across multiple subgroups. The median PFS was calculated using the Kaplan–Meier method, and HR values were estimated using a Cox proportional-hazards model. [a]HER2-low was defined as IHC score of 1+ or score of 2+ with a negative fluorescence in situ hybridization result; HER2 IHC0 was defined as an IHC score of 0.

occurred in 23% and 20% of patients, respectively. There was one TEAE leading to death observed in both treatment groups, one instance of septic shock (SG) and one of asphyxia (chemotherapy). Neither of these events were assessed as treatment-related by the INV. The patient with septic shock had been receiving central parenteral nutrition due to a bowel obstruction starting approximately 4 months before initiation of SG, and central parenteral nutrition-related infection was considered the reason for septic shock by the INV.

Exposure-adjusted incidence rate (EAIR) was similar between the SG and chemotherapy groups for any-grade and grade ≥3 TEAEs. EAIR was also similar between the treatment groups for serious TEAEs, TEAEs leading to treatment discontinuation and TEAEs leading to death. EAIR for TEAEs leading to dose interruption was higher with SG than chemotherapy (EAIR difference versus chemotherapy 1.18; 95% CI 0.51 to 1.86). EAIR for TEAEs leading to dose reduction was lower with SG versus chemotherapy (EAIR difference versus chemotherapy −0.58; 95% CI −1.00 to −0.20; Extended Data Table 3).

Polymorphisms in uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) have been associated with an increased incidence of specific AEs during treatment with some systematic anticancer agents[27–30]. In this study, the most common *UGT1A1* genotypes in patients receiving SG were *1/*1 (wild type; $n = 77$), *1/*6 ($n = 40$) and *1/*28 ($n = 18$). Patients in the *1/*1 subgroup experienced numerically lower rates of grade ≥3 TEAEs, TEAEs leading to treatment interruption and TEAEs leading to dose reduction when compared with *1/*6 and *1/*28. Patients with heterozygous genotypes (*1/*6, *1/*28) had increased rates of any-grade neutropenia, anemia and diarrhea compared with *1/*1, and grade ≥3 neutropenia and diarrhea were also more common in heterozygous patients (Extended Data Table 4). Rates of febrile neutropenia were similar for *1/*1 versus *1/*6 versus *1/*28 (4% versus 5% versus 6%, respectively, for any-grade and grade ≥3 AEs).

QoL

Most patients (96%, $n = 318$) were evaluable for quality of life (QoL) assessments using European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30 v3.0) and European Quality of Life (EuroQOL) five-dimension five-level (EQ-5D-5L) questionnaire. The median time to deterioration (TTD) was longer with SG than with chemotherapy across the EORTC QLQ-C30 global health status/QoL, pain, fatigue and physical functioning measures (Extended Data Table 5). SG demonstrated a significant extension in TTD over chemotherapy on the physical functioning and pain measures when death was censored. However, when considering death as an event, a significant extension in TTD was observed only in the physical functioning measure; for the other three measures, the TTD was longer for SG, though the differences were not significant between SG and chemotherapy. In EQ-5D-5L patient responses, mobility, self-care, usual activities, pain/discomfort and anxiety/depression scores decreased for

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Table 2 | Objective response summary

	BICR-assessed		INV-assessed	
	SG (*n*=166)	Chemotherapy (*n*=165)	SG (*n*=166)	Chemotherapy (*n*=165)
ORR, *n* (%)	34 (20)	25 (15)	31 (19)	26 (16)
95% CI	(15 to 27)	(10 to 22)	(13 to 25)	(11 to 22)
Odds ratio (95% CI)	1.46 (0.82 to 2.61)		1.24 (0.69 to 2.22)	
P value	0.1994		0.4742	
CR	2 (1)	0	0	0
PR	32 (19)	25 (15)	31 (19)	26 (16)
SD	93 (56)	82 (50)	103 (62)	89 (54)
PD	36 (22)	45 (27)	29 (17)	39 (24)
Not evaluable	3 (2)	13 (8)	3 (2)	11 (7)
CBR, *n* (%)	63 (38)	37 (22)	77 (46)	48 (29)
95% CI	(31 to 46)	(16 to 30)	(39 to 54)	(22 to 37)
Odds ratio (95% CI)	2.17 (1.33 to 3.55)		2.11 (1.34 to 3.33)	
P value	0.0018		0.0012	
Median DoR,[a] months (95% CI)	5.3 (4.1 to 9.8)	5.2 (4.2 to 9.7)	8.2 (5.7 to 9.4)	4.2 (2.9 to 5.6)

[a]In patients with confirmed objective response with SG (BICR-assessed, *n*=34; INV-assessed, *n*=31) and chemotherapy (BICR-assessed, *n*=25; INV-assessed, *n*=26).

Table 3 | Safety summary

TEAEs	SG (*n*=165)		Chemotherapy (*n*=164)	
Any TEAE	165 (100)		164 (100)	
Grade ≥3	135 (82)		114 (70)	
TEAEs leading to treatment discontinuation	5 (3)		6 (4)	
TEAEs leading to dose interruption	112 (68)		66 (40)	
TEAEs leading to dose reduction	42 (25)		53 (32)	
TE SAEs	38 (23)		32 (20)	
TEAEs leading to death	1 (1)		1 (1)	
Treatment-related	0		0	
	SG (*n*=165)		Chemotherapy (*n*=164)	
Most common TEAEs[a]	Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic TEAEs				
Neutropenia[b]	145 (88)	114 (69)	128 (78)	101 (62)
Anemia[c]	117 (71)	30 (18)	91 (55)	10 (6)
Leukopenia[d]	113 (68)	69 (42)	104 (63)	60 (37)
Thrombocytopenia[e]	33 (20)	7 (4)	58 (35)	8 (5)
Nonhematologic TEAEs				
Alopecia	103 (62)	0	66 (40)	0
Nausea	95 (58)	3 (2)	52 (32)	1 (1)
Diarrhea	84 (51)	11 (7)	22 (13)	0
Decreased appetite	68 (41)	3 (2)	50 (30)	2 (1)
Alanine amino-transferase increased	61 (37)	1 (1)	53 (32)	2 (1)
Vomiting	60 (36)	3 (2)	27 (16)	1 (1)
Constipation	59 (36)	0	40 (24)	0
Fatigue	57 (35)	12 (7)	29 (18)	3 (2)
Aspartate amino-transferase increased	54 (33)	1 (1)	58 (35)	2 (1)
Hypokalemia	40 (24)	16 (10)	28 (17)	5 (3)
Hypoalbuminemia	39 (24)	1 (1)	32 (20)	0
Abdominal pain	36 (22)	1 (1)	17 (10)	1 (1)
Blood alkaline phosphatase increased	31 (19)	0	43 (26)	1 (1)
Hyperglycemia	31 (19)	0	35 (21)	1 (1)
Gamma-glutamyl transferase increased	28 (17)	1 (1)	41 (25)	10 (6)

The data are presented as *n* (%). [a]Includes any-grade TEAEs observed in at least 20% of patients or grade ≥3 TEAEs observed in at least 10% of patients in either treatment group. [b]Combined preferred terms of neutropenia and neutrophil count decreased. [c]Combined preferred terms of anemia, red blood cell count decreased and hemoglobin decreased. [d]Combined preferred terms of leukopenia and white blood cell count decreased. [e]Combined preferred terms of thrombocytopenia and platelet count decreased. TE SAE, treatment-emergent serious adverse event.

patients in both treatment groups from baseline to end of treatment. The percentage of patients with severe problems was generally numerically higher in the chemotherapy group versus the SG group at end of treatment, and the percentage of patients with no problems was higher in the SG group versus the chemotherapy group (Extended Data Fig. 2).

Discussion

Due to the limited options available and poor outcomes for patients with previously treated HR$^+$HER2$^-$ mBC, an unmet need exists for treatments that improve outcomes in this patient population. SG demonstrated statistically significant improvement in PFS and clinically meaningful improvement in OS compared with chemotherapy in Asian patients with endocrine-resistant, chemotherapy-pretreated HR$^+$HER2$^-$ mBC in the phase 3 EVER-132-002 trial. The primary endpoint of PFS per BICR was met, with a 33% reduction in risk of disease progression or death (HR of 0.67, P = 0.0028). The median PFS values were similar between SG (4.3 months) and chemotherapy (4.2 months) due to a convergence of the curves at the median time point and do not reflect the overall benefit that patients in the SG group received as measured by the HR. Importantly, nearly twice as many patients were alive and progression free in the SG group compared with the chemotherapy group at all prespecified landmark time points of 6, 9 and 12 months. PFS per INV review was generally consistent with PFS per BICR. SG also demonstrated a clinically meaningful improvement in OS versus chemotherapy, with a 36% reduction in the risk of death (HR of 0.64, P = 0.0061). Median OS was 5.7 months longer in the SG group (21.0 months) compared with the chemotherapy group (15.3 months). The Kaplan–Meier curves separated early and widened over time with a higher proportion of patients alive in the SG group at both landmark time points of 12 and 24 months. ORR and clinical benefit rate (CBR) per BICR were numerically higher in patients treated with SG, and BICR assessment was generally consistent with INV assessment results.

PFS and OS benefit with SG was observed across most predefined subgroups, including for each stratification factor (visceral metastases, prior treatment with CDK4/6i in the metastatic setting and number of prior chemotherapy regimens for treatment of metastatic disease). Notably, 49% of patients had received prior CDK4/6i in this study. This reflects the treatment landscape in China, South Korea and Taiwan at the time of trial design, in which first-line CDK4/6i treatment was less accessible for patients with HR$^+$HER2$^-$ mBC. As current cancer care guidelines in Asia include first-line use of CDK4/6i for advanced HR$^+$HER2$^-$ BC[9,10], it is expected that the majority of patients in this population are likely to have received prior CDK4/6i treatment.

The patients in EVER-132-002 experienced clinical benefit regardless of whether prior treatment with a CDK4/6i was received.

Safety in this trial was consistent with the safety profile observed in previous global studies of SG[23,24,26], and TEAEs were generally manageable. No new safety signals were identified. Grade ≥3 TEAEs were higher in the SG group compared with the chemotherapy group. The incidence of TEAEs leading to dose reduction was lower in the SG versus chemotherapy group, and the incidence of TEAEs leading to discontinuation and death was similar in the SG and chemotherapy groups.

TTD was numerically improved with SG versus chemotherapy for global health status/QoL, pain, fatigue and physical functioning scales, and this improvement was significant for physical functioning and for pain when death was censored. EQ-5D-5L patient responses showed decreases in all dimensions analyzed from baseline to end of treatment in both treatment groups; however, patients in the SG group generally had numerically higher rates of no problems and lower rates of severe problems compared with the chemotherapy group.

The results of EVER-132-002 were consistent with the results of TROPiCS-02, a global phase 3 study that evaluated SG as a treatment for HR$^+$HER2$^-$ mBC and was conducted primarily in non-Asian patients. The eligibility criteria were generally comparable between these studies, with similar median age and a majority of patients with visceral metastases at baseline. One exception to this was the percentage of patients who had received previous CDK4/6i treatment. In TROPiCS-02, 99% of patients had received prior CDK4/6i, compared with 49% of patients in EVER-132-002, which reflected the local treatment paradigm for HR$^+$HER2$^-$ mBC at the time of the study enrollment. In an indirect comparison, PFS benefit of SG versus chemotherapy between EVER-132-002 and TROPiCS-02 was comparable with HR 0.67 and HR 0.66, respectively[22]. OS benefit from SG versus chemotherapy was also comparable between the studies, with HRs of 0.64 and 0.79, respectively[23]. Patients in EVER-132-002 experienced clinical benefit regardless of whether prior treatment with a CDK4/6i was received. Efficacy data from patients who received prior CDK4/6i in EVER-132-002 were also consistent with those in the overall study population of TROPiCS-02, all of whom had received prior CDK4/6i treatment. Overall, efficacy results from the intent-to-treat population were consistent between EVER-132-002 and TROPiCS-02. Additional OS follow-up is ongoing in the EVER-132-002 study.

Subgroup analyses of EVER-132-002 were also generally consistent with previous results from TROPiCS-02. While SG is targeted to Trop-2, previous studies have indicated that SG provided clinical benefit versus chemotherapy in patients with previously treated HR$^+$HER2$^-$ mBC and low Trop-2 expression. In a post hoc analysis of TROPiCS-02, PFS and OS benefit were observed with SG versus chemotherapy in both the Trop-2 <100 and ≥100 subgroups[31,32]. In EVER-132-002, OS benefit was observed with SG versus chemotherapy in both Trop-2 subgroups. PFS HR values numerically favored SG over chemotherapy in both Trop-2 expression subgroups, indicating that SG provided benefit even in patients with low Trop-2 expression. The sample size in these subgroups was small and the study was not powered to detect differences between subgroups, which limits the interpretation of this analysis.

Differences in rates of TEAEs by *UGT1A1* genotype were observed in patients with previously treated HR$^+$HER2$^-$ mBC in an exploratory analysis of TROPiCS-02. Patients with the *28/*28 genotype for *UGT1A1* experienced numerically higher rates of grade ≥3 TEAEs, TEAEs leading to discontinuation, any-grade anemia and diarrhea or neutropenia of grade ≥3, when compared with patients with *1/*1 (wild type) or *1/*28 genotypes[33]. The most common *UGT1A1* genotypes differed between the studies, with *1/*1, *1/*6 and *1/*28 being the most common in EVER-132-002, while *1/*1, *1/*28 and *28/*28 were the most common in TROPiCS-02 (ref. 33). Patients with heterozygous genotypes consistently experienced higher rates of grade ≥3 TEAEs, TEAEs leading to dose reduction and grade ≥3 neutropenia and diarrhea than those with *1/*1 (wild type) genotypes. However, the number of patients with heterozygous genotypes was relatively small, which may limit interpretation of these results.

The results of HRQoL analyses from EVER-132-002 generally aligned with those from TROPiCS-02. In both trials, median TTD was numerically higher with SG than chemotherapy across all categories analyzed. This difference was significant in global health status/HRQoL and fatigue in TROPiCS-02, while in EVER-132-002, it was significant in pain and physical functioning[23]. These differences may be explained due to differences in the patient population between the two trials.

One potential limitation of this study is the open-label design. Despite this, only two patients who were assigned to the chemotherapy group withdrew from the study before receiving any study treatment.

The patients in EVER-132-002 are representative of a real-world Asian patient population. This is the first clinical trial of SG to show substantial improvement in both PFS and OS in this patient population. The efficacy benefit of SG versus chemotherapy and the manageable safety profile in the pivotal EVER-132-002 study are consistent with findings of the global TROPiCS-02 study and support the use of SG as a new treatment option for Asian patients with endocrine-resistant, previously treated HR$^+$HER2$^-$ mBC.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-03269-z.

References

1. International Agency for Research on Cancer. Global Cancer Observatory, GLOBOCAN 2022, World fact sheet. *World Health Organization* https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf (2022).
2. International Agency for Research on Cancer. Global Cancer Observatory, GLOBOCAN 2022, China fact sheet. *World Health Organization* https://gco.iarc.who.int/media/globocan/factsheets/populations/160-china-fact-sheet.pdf (2022).
3. International Agency for Research on Cancer. Global Cancer Observatory, GLOBOCAN 2022, Republic of Korea fact sheet. *World Health Organization* https://gco.iarc.who.int/media/globocan/factsheets/populations/410-korea-republic-of-fact-sheet.pdf (2022).
4. Incidence and mortality rates for the top 10 cancers in Taiwan. *Taiwan Cancer Registry Center* https://twcr.tw/wp-content/uploads/2023/04/Top-10-cancers-in-Taiwan-2020.pdf (2023).
5. Surveillance Epidemiology and End Results Program. Cancer stat facts: female breast cancer subtypes. *National Cancer Institute* https://seer.cancer.gov/statfacts/html/breast-subtypes.html (2022).
6. Si, W. et al. Epidemiological and clinicopathological trends of breast cancer in chinese patients during 1993 to 2013: a retrospective study. *Medicine* **94**, e820 (2015).
7. Gennari, A. et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann. Oncol.* **32**, 1475–1495 (2021).
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Breast Cancer, version 1.2024. *National Comprehensive Cancer Network* https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (2024).
9. National Health Commission Of The People's Republic Of China. National guidelines for diagnosis and treatment of breast cancer 2022 in China (English version). *Chin. J. Cancer Res.* **34**, 151–175 (2022).

10. Im, S. A. et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, staging and treatment of patients with metastatic breast cancer. *ESMO Open* **8**, 101541 (2023).
11. Twelves, C. et al. Subgroup analyses from a phase 3, open-label, randomized study of eribulin mesylate versus capecitabine in pretreated patients with advanced or metastatic breast cancer. *Breast Cancer* **10**, 77–84 (2016).
12. Cortes, J. et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* **377**, 914–923 (2011).
13. Yuan, P. et al. Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: a randomised clinical trial. *Eur. J. Cancer* **112**, 57–65 (2019).
14. Burstein, H. J. et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. *J. Clin. Oncol.* **39**, 3959–3977 (2021).
15. Twelves, C. et al. The place of chemotherapy in the evolving treatment landscape for patients with HR-positive/HER2-negative MBC. *Clin. Breast Cancer* **22**, 223–234 (2022).
16. Goldenberg, D. M., Stein, R. & Sharkey, R. M. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. *Oncotarget* **9**, 28989–29006 (2018).
17. Goldenberg, D. M., Cardillo, T. M., Govindan, S. V., Rossi, E. A. & Sharkey, R. M. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody–drug conjugate (ADC). *Oncotarget* **6**, 22496–22512 (2015).
18. Shih, L. B., Xuan, H., Aninipot, R., Stein, R. & Goldenberg, D. M. In vitro and in vivo reactivity of an internalizing antibody, RS7, with human breast cancer. *Cancer Res.* **55**, 5857s–5863s (1995).
19. Cardillo, T. M., Govindan, S. V., Sharkey, R. M., Trisal, P. & Goldenberg, D. M. Humanized anti-Trop-2 IgG-SN-38 conjugate for effective treatment of diverse epithelial cancers: preclinical studies in human cancer xenograft models and monkeys. *Clin. Cancer Res.* **17**, 3157–3169 (2011).
20. Gilead Sciences, Inc. Trodelvy (sacituzumab govitecan-hziy) [prescribing information]. *Drugs@FDA* (2023); https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761115
21. Trodelvy [summary of product characteristics]. *The Electronic Medicines Compendium*. (2023); https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf
22. Rugo, H. S. et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J. Clin. Oncol.* **40**, 3365–3376 (2022).
23. Rugo, H. S. et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. *Lancet* **402**, 1423–1433 (2023).
24. Bardia, A. et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N. Engl. J. Med.* **384**, 1529–1541 (2021).
25. Bardia, A. et al. Sacituzumab govitecan, a Trop-2-directed antibody–drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. *Ann. Oncol.* **32**, 746–756 (2021).
26. Loriot, Y. et al. TROPHY-U-01, a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors: updated safety and efficacy outcomes. *Ann. Oncol.* **35**, 392–401 (2024).
27. Liu, X., Cheng, D., Kuang, Q., Liu, G. & Xu, W. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians. *Pharmacogenomics J.* **14**, 120–129 (2014).
28. Motzer, R. J. et al. Hyperbilirubinemia in pazopanib- or sunitinib-treated patients in COMPARZ is associated with *UGT1A1* polymorphisms. *Ann. Oncol.* **24**, 2927–2928 (2013).
29. Giles, F. J. et al. Nilotinib population pharmacokinetics and exposure-response analysis in patients with imatinib-resistant or -intolerant chronic myeloid leukemia. *Eur. J. Clin. Pharm.* **69**, 813–823 (2013).
30. Rugo, H. S. et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. *NPJ Breast Cancer* **8**, 98 (2022).
31. Tolaney, S. M. et al. Final overall survival (OS) analysis from the phase 3 TROPiCS-02 study of sacituzumab govitecan (SG) in patients (pts) with hormone receptor–positive/HER2-negative (HR+HER2–) metastatic breast cancer (mBC). *J. Clin. Oncol.* **41**, Abst 1003 (2023).
32. Rugo, H. S. et al. Sacituzumab govitecan vs treatment of physician's choice: efficacy by Trop-2 expression in the TROPiCS-02 study of patients with HR+HER2– metastatic breast cancer. *Cancer Res.* **83**, Abst GS1-11 (2023).
33. Marmé, F. et al. 194P Safety outcomes by UGT1A1 status in the phase III TROPiCS-02 study of sacituzumab govitecan (SG) in HR+HER2– metastatic breast cancer (mBC). *ESMO Open* **8**, Abst 194P (2023).

Methods

Ethics statement

EVER-132-002 was compliant with Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines and was approved by national regulatory authorities, as well as each investigational sites' ethics committee or review board. The investigational sites that approved the study protocol were Cancer Hospital Chinese Academy of Medical Science; Chinese PLA General Hospital; Peking University People's Hospital; Jilin Cancer Hospital; The First Hospital of Jilin University; Chongqing University Cancer Hospital; West China Hospital, Sichuan University; Fujian Medical University Union Hospital; Guangdong Provincial People's Hospital; Sun Yat Sen Memorial Hospital of Sun Yat Sen University; Sun Yat Sen University Cancer Center; Sir Run Run Shaw Hospital Zhejiang University School of Medicine; Zhejiang Cancer Hospital; Anhui Provincial Hospital; The Second Hospital of Anhui Medical University; Shandong Cancer Hospital; Yunnan Cancer Hospital; Linyi Cancer Hospital; Jiangsu Province Hospital; Nanjing Drum Tower Hospital; Shanghai General Hospital; Tianjin Medical University Cancer Institute and Hospital; Hubei Cancer Hospital; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; The First Affiliated Hospital of Xi'an Jiaotong University; Henan Cancer Hospital; Cancer Hospital of Xinjiang Medical University; Dong-A University Hospital; Seoul National University Bundang Hospital; Asan Medical Center; Korea University Anam Hospital; Samsung Medical Center; Seoul National University Hospital; Severance Hospital of Yonsei University Health System; Ajou University Hospital; Changhua Christian Medical Foundation Changhua Christian Hospital; Kaohsiung Medical University Chung-Ho Memorial Hospital; China Medical University Hospital; National Cheng Kung University Hospital; National Taiwan University Hospital; Taipei Veterans General Hospital; Tri-Service General Hospital; and Chang Gung Memorial Hospital, Linkou. All patients gave written informed consent.

Patients

Patients from mainland China, Republic of Korea and Taiwan were eligible for enrollment if they had histologically or cytologically confirmed HR^+HER2^- metastatic or locally recurrent inoperable BC, with most recently available or newly obtained tumor biopsy from a locally recurrent or metastatic site. Patient sex was self-reported and recorded by the study site in the study database. Archival or newly acquired tumor tissue in a formalin-fixed, paraffin embedded block or adequate unstained slides from a metastatic or recurrent site was required. HR+ was defined as ≥1% of cells expressing hormonal receptors (estrogen and/or progesterone) by immunohistochemistry (IHC), and HER2− was defined as IHC0, IHC1+ or IHC2+ and in situ hybridization negative. Patients were required to have received two to four prior systemic chemotherapy regimens for mBC and to be eligible for one of the options for chemotherapy of INV's choice. Adjuvant or neoadjuvant chemotherapy was counted as one of the required prior regimens if development of unresectable, locally advanced or mBC occurred within a 12 month period after completion of chemotherapy. Previous treatment included at least one taxane and at least one anticancer endocrine therapy in any setting; prior use of CDK4/6i was not mandatory. Documented measurable disease by Response Evaluation Criteria in Solid Tumors v1.1 (by computed tomography or magnetic resonance imagery) following the most recent anticancer therapy was required. The patients were required to be aged ≥18 years and to provide written informed consent, Eastern Cooperative Oncology Group performance status of 0 or 1 and to be recovered from all prior treatment-related toxicities to grade ≤1 per the Common Terminology Criteria for Adverse Events v5.0 (except alopecia or stable sensory neuropathy, which could be grade ≤2).

Exclusion criteria included previous treatment with topoisomerase 1 inhibitors, known brain metastases, second active malignancy within 3 years before providing informed consent (nonmelanoma skin cancer and histologically confirmed completed excision of carcinoma in situ excepted), human immunodeficiency virus positivity, active hepatitis B or C virus infection, known history of unstable angina/myocardial infarction/congestive heart disease within 6 months before first dose, clinically significant cardiac arrythmia requiring antiarrythmia therapy or left ventricular ejection fraction <50%, known history of clinically significant active chronic obstructive pulmonary disease or other moderate-to-severe chronic respiratory illness within 6 months before first dose, active chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease)/clinically significant gastrointestinal bleeding/intestinal obstruction/gastrointestinal perforation within 6 months before first dose, active serious infection requiring systemic antibiotic use within 7 days before first dose, high-dose systemic corticosteroid use within 2 weeks before first dose, scheduled surgery that would delay study treatment during study, receipt of live vaccine within 30 days before first dose, other concurrent medical or psychiatric conditions that may confound study interpretation or prevent completion of study procedures or follow-up examinations, known hypersensitivity or intolerance to study treatments or any of the excipients, anticancer treatment with chemotherapy/radiation/small molecule targeted therapy/endocrine therapy within 2 weeks before first dose, biological therapy within 4 weeks before first dose, current treatment in another clinical study or use of any investigational drug or device within five half-lives or 4 weeks before first dose (whichever is longer), pregnancy or lactation and women of childbearing potential/fertile men unwilling to use highly effective contraception during the study and up to 6 months after treatment discontinuation for women of childbearing potential and 3 months for fertile men.

Study design

Patients were randomly assigned at 1:1 to receive SG (10 mg kg^{-1} intravenously days 1 and 8 of every 3 week cycle) or chemotherapy treatment of physician's choice (eribulin, capecitabine, gemcitabine or vinorelbine, with dosing and schedule per package insert depending on region). Randomization was stratified according to presence of visceral metastases (yes versus no), number of prior chemotherapy regimens for the treatment of metastatic disease (two versus three/four) and prior CDK4/6i treatment in the metastatic setting (yes versus no). Patients were randomized via an interactive web-based response system. The randomization list was generated by a designated vendor using stratified blocked randomization with a block size of four.

Endpoints

The primary endpoint was PFS per BICR using Response Evaluation Criteria in Solid Tumors v1.1. PFS was defined as time from randomization to progressive disease (PD) or death, whichever occurred earlier.

Secondary endpoints included OS, ORR per BICR, DoR per BICR, CBR per BICR, safety and QoL. Efficacy by INV assessment was not a prespecified endpoint but was a planned supportive analysis per the protocol. OS was defined as time from randomization to death from any cause. ORR was the sum of complete response (CR) and partial response (PR), while CBR was the sum of CR, PR and stable disease (SD) with duration ≥6 months. DoR was defined as time from first tumor response (CR or PR) to PD or death, whichever was first. The exploratory endpoints included Trop-2 expression level.

Assessments

Stratification factor information was gathered from an interactive web-based response system. The tumor measurements by computed tomography or magnetic resonance imagery were performed every 6 weeks up to 54 weeks. After 54 weeks, measurements were performed every 12 weeks. Safety was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0, and the events were coded using MedDRA v26.0. QoL was assessed using EORTC

QLQ-C30 v3.0 and the EuroQOL EQ-5D-5L questionnaire. Blood and tumor samples for biomarker analyses were collected before the first dose of SG. The *UGT1A1* genotype was tested through gene sequencing of whole blood, and tumor Trop-2 expression was evaluated using immunohistology staining of fresh or archived specimens. Membrane Trop-2 expression was determined using a validated research IHC assay at a central laboratory. The data were categorized using the H-score, which is the sum of percent staining weighted by staining intensity.

Statistical analysis

Sample size was calculated on the basis of the primary endpoint of PFS per BICR. Assuming an HR of 0.70 (median 5.3 versus 3.7 months), approximately 250 PFS events were needed to detect a statistically significant difference between the two groups at a two-sided 0.05 significance level and 80% power. Based on an estimated 12 month enrollment and 24 month total study duration, it was estimated that approximately 330 patients would need to be randomized.

There was no interim analysis planned for the primary endpoint. The primary analysis of PFS was conducted on the basis of a total of 244 PFS events observed as of the data cutoff date (30 April 2023). At the time of the primary analysis of PFS, all secondary endpoints were analyzed and reported. Only the primary endpoint of PFS was formally tested for the study.

All statistical analyses were performed using SAS (SAS Institute, version 9.4 or later, SAS Institute). Comparisons of PFS and OS between the treatment groups were performed using a stratified log-rank test (with the three stratification factors used during randomization). Median PFS and OS were determined using the Kaplan–Meier method, and their associated 95% CIs were calculated by the Brookmeyer and Crowley method with log–log transformation. The Kaplan–Meier estimates of PFS and OS were plotted over time. HRs were estimated using a Cox proportional-hazards model stratified by the stratification factors used in randomization. ORR and CBR were calculated with exact 95% CIs using the Clopper–Pearson method, and a comparison between treatment groups was performed with a stratified Cochran–Mantel–Haenszel test. Kaplan–Meier analyses were performed for DoR.

Safety was summarized by treatment group using descriptive statistics. TEAEs were defined as any AE that started on or after the first dose date and up to 30 days after the last dose date. EAIR was defined as number of patients who had at least one event divided by total patient-years of exposure from first dose date to first onset of event (for those who had an event) or to data cutoff date (for those who did not have an event and were continuing study drug) or last dose (for those who did not have an event and discontinued study drug).

Results from the EQ-5D-5L questionnaire were descriptively evaluated. TTD was measured using EORTC QLQ-C30 and was defined as time from randomization to first date patient reached ≥10-point deterioration from baseline or death, whichever occurred earlier. TTD was also analyzed considering death as censored. HRs and 95% CIs were calculated for TTD using a stratified Cox proportional-hazards model.

The intent-to-treat population consisted of all patients who were randomized to a treatment group. All patients who received at least one dose of study treatment were included in the safety analysis population. The HRQoL-evaluable and the EQ-5D-5L-evaluable populations were defined as patients in the intent-to-treat population with an evaluable assessment at baseline and at least one evaluable assessment at postbaseline visits.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

To protect the privacy of study participants and proprietary information, Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting nonconflict of interest. The request proposal must also include a statistician. The data provided include demographic, efficacy and safety information. A redacted version of the study protocol and the statistical analysis plan will also be provided upon request to qualified external researchers. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data and the intended use of the data. Data requests should be sent to data-request@gilead.com.

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Author contributions

All authors were involved in the original drafting and revision of the manuscript for publication. D.J., T.V., A.D., Y.Z., Y.Y. and K.M.K. were involved in the conceptualization and design of the study. B.X., S.W., M.Y., J.S., W.L., J.T., X.W., Y.W., S.-A.I., W.-P.C., F.M. and M.-S.D. were involved in data acquisition. D.J., T.V., A.D., Y.Z., Y.Y. and K.M.K. were involved in data analysis, and all authors were involved in data interpretation. All authors had full access to all study data and provided final approval to submit the manuscript for publication.

Competing interests

B.X. has held consulting or advisory roles with AstraZeneca and Novartis. S.W. has held consulting or advisory roles with Daiichi-Sankyo and AstraZeneca; has held speaker's bureau roles with Pfizer, Roche, AstraZeneca, Novartis and Eli Lilly; and has received research funding from Pfizer and AstraZeneca. J.S. has received research grants from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, GSK, MSD, Novartis, Pfizer, Roche, Sanofi and Seagen. M.-S.D, M.Y., W.L., J.T., X.W., Y.W. and F.M. declare no competing interests. W.-P.C. has received honoraria from Amgen, AstraZeneca, Daiichi-Sankyo, Eli Lilly, Gilead Sciences, Inc., Novartis, Pfizer and Roche; has received support for attending meetings or travel from AstraZeneca, Novartis and Pfizer; and has held data safety monitoring board or advisory board roles with AstraZeneca, Daiichi-Sankyo, Gilead Sciences, Inc., Novartis, Pfizer, Roche and Sanofi. S.-A.I. has held advisory roles with AstraZeneca, Bertis, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Hanmi, Idience, MSD, Novartis, Pfizer and Roche; has received clinical trial support from AstraZeneca, Daiichi-Sankyo, Eisai, Eli Lilly, Hanmi, MDS, Novartis, Pfizer and Roche; and has received research grants from AstraZeneca, Boryung Pharm, Dae Woong, Daiichi-Sankyo, Eisai, Pfizer and Roche. T.V. is an employee of Gilead Sciences, Inc and has stock ownership in Gilead Sciences, Inc and Novavax. A.D., D.J., Y.Y., Y.Z. and K.M.K. are employees of and have stock ownership in Gilead Sciences, Inc.

Additional information

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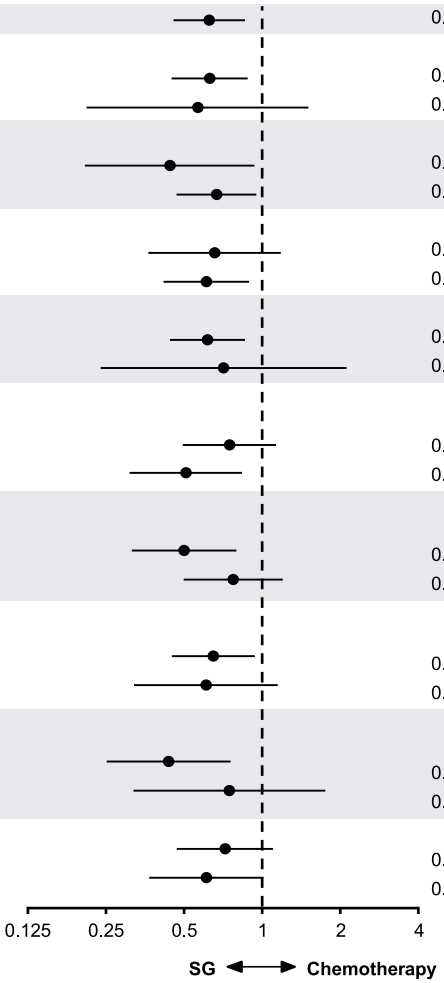
Category	Median OS, months (95% CI)		Unstratified HR (95% CI)
	SG	Chemotherapy	
Overall (*N* = 331)	21.0 (16.5–NE)	15.3 (13.2–18.4)	0.62 (0.45–0.86)
Age, y			
<65 (*n* = 293)	21.1 (16.3–NE)	15.8 (13.2–18.7)	0.63 (0.45–0.88)
≥65 (*n* = 38)	20.0 (12.1–NE)	14.9 (8.6–NE)	0.56 (0.21–1.51)
Baseline ECOG PS			
0 (*n* = 74)	23.8 (21.1–NE)	18.0 (11.1–20.9)	0.44 (0.21–0.93)
1 (*n* = 257)	20.5 (16.2–NE)	15.1 (12.3–18.4)	0.67 (0.47–0.95)
HER2[a]			
IHC0 (*n* = 99)	21.0 (13.5–NE)	14.4 (9.7–NE)	0.65 (0.36–1.18)
Low (*n* = 232)	21.1 (16.3–NE)	15.8 (12.7–19.0)	0.61 (0.42–0.89)
Visceral metastasis			
Yes (*n* = 293)	20.5 (16.3–NE)	15.1 (12.8–18.1)	0.62 (0.44–0.86)
No (*n* = 38)	21.0 (10.6–NE)	NE (9.7–NE)	0.71 (0.24–2.12)
No. of prior chemotherapy regimens in the metastatic setting			
2 (*n* = 186)	20.5 (15.4–23.8)	15.1 (12.7–19.1)	0.75 (0.49–1.13)
3-4 (*n* = 145)	NE (16.2–NE)	15.3 (11.7–18.7)	0.51 (0.31–0.84)
Prior treatment with CDK4/6i in the metastatic setting			
Yes (*n* = 161)	21.1 (14.9–NE)	12.3 (10.8–17.0)	0.50 (0.31–0.80)
No (*n* = 170)	20.5 (16.3–23.8)	18.1 (15.1–20.9)	0.77 (0.50–1.20)
Prior endocrine therapy in the metastatic setting ≥6 months			
Yes (*n* = 257)	21.1 (20.0–NE)	16.9 (13.2–20.9)	0.65 (0.45–0.94)
No (*n* = 74)	18.0 (10.6–NE)	13.5 (8.3–17.7)	0.61 (0.32–1.75)
Prior CDK4/6i treatment duration			
≤12 months (*n* = 109)	21.1 (14.7–NE)	12.3 (10.7–17.0)	0.44 (0.25–0.75)
>12 months (*n* = 52)	NE (9.5–NE)	14.9 (7.5–NE)	0.75 (0.32–1.75)
Trop-2 H-score			
<100 (*n* = 184)	20.0 (14.7–NE)	15.1 (11.9–21.6)	0.72 (0.47–1.10)
≥100 (*n* = 122)	20.5 (16.2–NE)	17.3 (13.0–19.1)	0.61 (0.37–1.01)



Extended Data Fig. 1 | Subgroup analysis of OS. OS with SG versus chemotherapy was analyzed across multiple subgroups. Median OS was calculated using the Kaplan–Meier method, and HR values were estimated using a Cox proportional-hazards model. [a]HER2-low was defined as IHC score of 1 + , or score of 2+ with negative fluorescence in situ hybridization result; HER2 IHC0 was defined as IHC score of 0.

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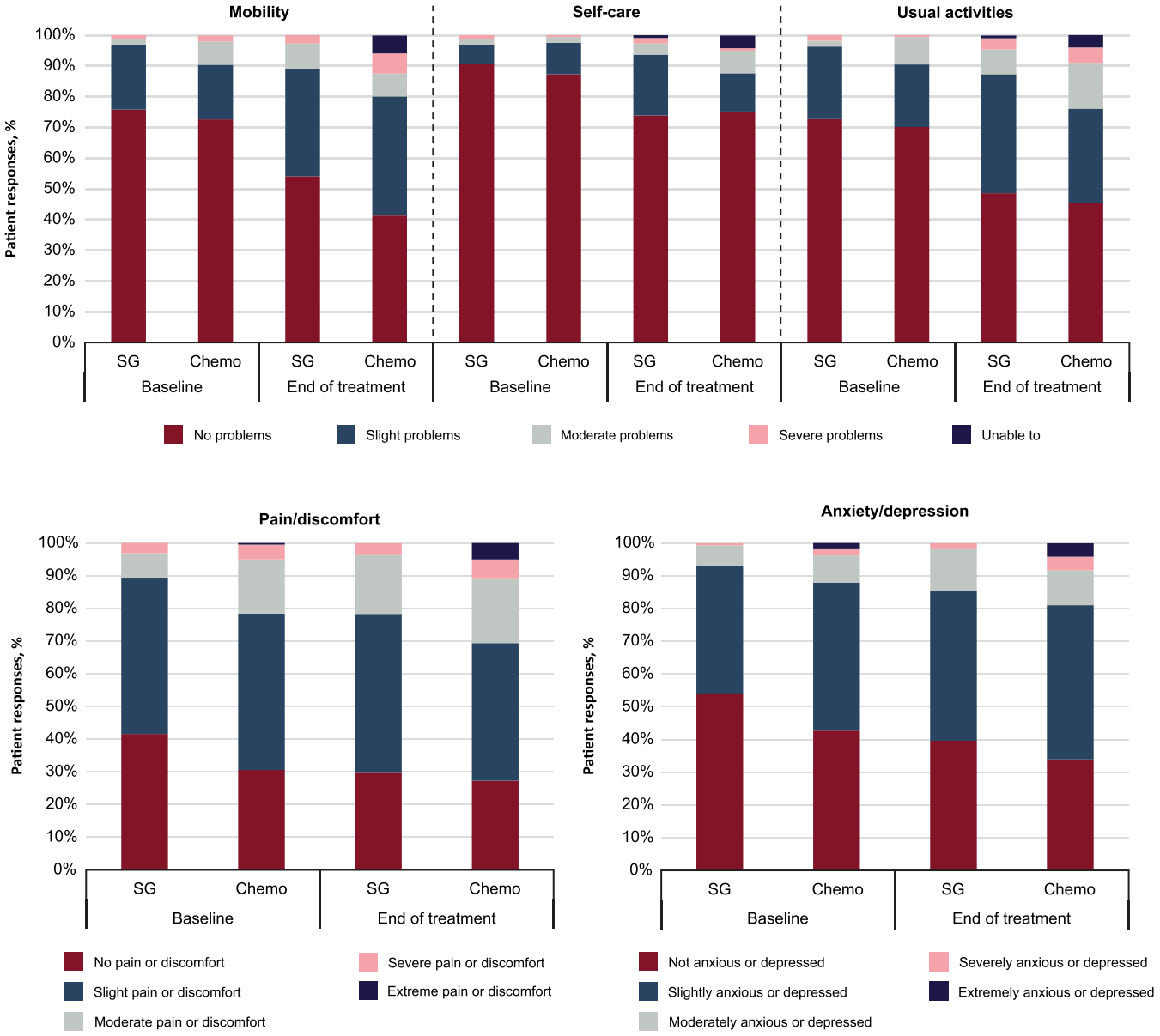

Extended Data Fig. 2 | EQ-5D-5L questionnaire responses. Patient responses to the EuroQoL EQ-5D-5L questionnaire were descriptively evaluated for patients randomized to SG ($n = 161, 111$) or chemotherapy ($n = 157, 121$) at baseline and end of treatment in the EQ-5D-5L-evaluable population.

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Extended Data Table 1 | Prior therapies

	SG (*n* = 166)	Chemotherapy (*n* = 165)
Setting of prior anticancer regimens, *n* (%)		
Neoadjuvant	33 (20)	27 (16)
Adjuvant	124 (75)	119 (72)
Most common prior anticancer therapy in the metastatic setting,[a] by class, n (%)		
Endocrine therapy[b]	153 (92)	149 (90)
CDK4/6i	81 (49)	81 (49)
Targeted agent[c]	62 (37)	68 (41)
Immunotherapy	9 (5)	11 (7)
Chemotherapy	166 (100)	165 (100)
Capecitabine[d]	124 (75)	128 (78)
Paclitaxel[d]	62 (37)	59 (36)
Docetaxel[d]	48 (29)	59 (36)

[a]Includes any treatment used either as single agent or in combination. [b]Patients not treated with endocrine therapy in the metastatic setting were treated with these agents in early-stage disease. [c]Targeted agents include mTOR, HDAC, VEGF, PI3K inhibitors, HER2-targeted agents, and other targeted agents. [d]Most common chemotherapy agents. SG, govitecan.

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Extended Data Table 2 | Patient treatment exposure

	SG (*N* = 165)	Chemotherapy (*N* = 164)	Eribulin (*n* = 131)	Capecitabine (*n* = 11)	Gemcitabine (*n* = 8)	Vinorelbine (*n* = 14)
Median treatment duration, months (range)	5.1 (0.03–24.9)	3.3 (0.03–28.1)	3.9 (0.03–28.1)	4.9 (1.2–15.2)	2.3 (1.0–8.3)	1.4 (0.03–5.3)
Median treatment cycles received, *n* (range)	7.0 (1–34)	5.0 (1–40)	6.0 (1–40)	7.0 (2–22)	3.0 (2–10)	2.5 (1–8)
Median relative dose intensity, %	100	–	98	92	98	84
Patients with dose delays, *n* (%)	125 (76)	–	64 (49)	4 (36)	1 (13)	3 (21)
Patients with dose reductions, *n* (%)	42 (25)	57 (35)	43 (33)	4 (36)	4 (50)	6 (43)

SG, sacituzumab govitecan.

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Extended Data Table 3 | Safety by EAIR

EAIR of TEAEs	SG (*n* = 165)	Chemotherapy (*n* = 164)
Any grade TEAE		
PYE	2.5	2.8
EAIR (95% CI)	67.04 (57.20 to 78.08)	59.49 (50.73 to 69.32)
EAIR difference vs chemotherapy (95% CI)	7.55 (-6.36 to 21.65)	
TEAEs Grade ≥3		
PYE	27.1	23.4
EAIR (95% CI)	4.99 (4.18 to 5.90)	4.87 (4.02 to 5.85)
EAIR difference vs chemotherapy (95% CI)	0.12 (-1.15 to 1.37)	
TEAEs leading to treatment discontinuation		
PYE	88.7	58.7
EAIR (95% CI)	0.06 (0.02 to 0.13)	0.10 (0.04 to 0.22)
EAIR difference vs chemotherapy (95% CI)	-0.05 (-0.17 to 0.05)	
TEAEs leading to dose interruption		
PYE	39.8	40.3
EAIR (95% CI)	2.81 (2.32 to 3.38)	1.64 (1.27 to 2.08)
EAIR difference vs chemotherapy (95% CI)	1.18 (0.51 to 1.86)	
TEAEs leading to dose reduction		
PYE	65.9	43.4
EAIR (95% CI)	0.64 (0.46 to 0.86)	1.22 (0.91 to 1.60)
EAIR difference vs chemotherapy (95% CI)	-0.58 (-1.00 to -0.20)	
TE SAEs		
PYE	76.8	56.3
EAIR (95% CI)	0.50 (0.35 to 0.68)	0.57 (0.39 to 0.80)
EAIR difference vs chemotherapy (95% CI)	-0.074 (-0.35 to 0.18)	
TEAEs leading to death		
PYE	88.5	58.6
EAIR (95% CI)	0.011 (0.00 to 0.06)	0.02 (0.00 to 0.10)
EAIR difference vs chemotherapy (95% CI)	-0.01 (-0.09 to 0.05)	

Most common TEAEs[a]	SG (*n* = 165)	Chemotherapy (*n* = 164)
Neutropenia		
PYE	16.7	17.4
EAIR (95% CI)	8.69 (7.33 to 10.22)	7.38 (6.15 to 8.77)
EAIR difference vs chemotherapy (95% CI)	1.31 (-0.63 to 3.26)	
Anemia		
PYE	37.0	37.1
EAIR (95% CI)	3.16 (2.62 to 3.79)	2.46 (1.98 to 3.01)
EAIR difference vs chemotherapy (95% CI)	0.71 (-0.07 to 1.50)	
Leukopenia		
PYE	33.3	27.6
EAIR (95% CI)	3.40 (2.80 to 4.09)	3.76 (3.08 to 4.56)
EAIR difference vs chemotherapy (95% CI)	-0.37 (-1.36 to 0.61)	
Alopecia		
PYE	32.6	33.1
EAIR (95% CI)	3.16 (2.58 to 3.83)	1.99 (1.54 to 2.53)
EAIR difference vs chemotherapy (95% CI)	1.16 (0.37 to 1.97)	
Nausea		
PYE	44.8	44.7
EAIR (95% CI)	2.12 (1.71 to 2.59)	1.16 (0.87 to 1.53)
EAIR difference vs chemotherapy (95% CI)	0.95 (0.41 to 1.51)	
Thrombocytopenia		
PYE	74.7	46.4
EAIR (95% CI)	0.44 (0.30 to 0.62)	1.25 (0.95 to 1.62)
EAIR difference vs chemotherapy (95% CI)	-0.81 (-1.20 to -0.46)	
Aspartate aminotransferase increased		
PYE	72.5	42.0
EAIR (95% CI)	0.74 (0.56 to 0.97)	1.38 (1.05 to 1.78)
EAIR difference vs chemotherapy (95% CI)	-0.64 (-1.08 to -0.23)	

Most common TEAEs includes the 5 most common any-grade TEAEs from both treatment groups. EAIRs that are similar between treatment groups are reflected by an EAIR difference that includes 0 in the 95% CI. A positive EAIR difference and 95% CI indicates higher EAIR in the SG group, while a negative EAIR difference and 95% CI indicates higher EAIR in the chemotherapy group. [a]The 5 most common TEAEs from each treatment group were included. EAIR, exposure-adjusted incidence rate; PYE, patient years of exposure.

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Extended Data Table 4 | Safety by *UGT1A1* genotype

	SG (*N* = 165)[a]					
TEAEs	***1/*1 (*n* = 77)**		***1/*6 (*n* = 40)**		***1/*28 (*n* = 18)**	
Any grade	77 (100)		40 (100)		18 (100)	
Grade ≥3	57 (74)		35 (88)		16 (89)	
TEAEs leading to treatment discontinuation	3 (4)		1 (3)		1 (6)	
TEAEs leading to dose interruption	45 (58)		29 (73)		14 (78)	
TEAEs leading to dose reduction	12 (16)		16 (40)		5 (28)	
TE SAEs	9 (12)		7 (18)		4 (22)	
TEAEs leading to death	1 (1)		0		0	
Treatment-related	0		0		0	
Most common TEAEs[b]	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Hematological TEAEs						
Neutropenia[c]	64 (83)	51 (66)	36 (90)	28 (70)	18 (100)	14 (78)
Anemia[d]	52 (68)	12 (16)	34 (85)	10 (25)	14 (78)	4 (22)
Leukopenia[e]	42 (55)	24 (31)	32 (80)	24 (60)	16 (89)	9 (50)
Lymphopenia[f]	15 (19)	4 (5)	6 (15)	1 (3)	5 (28)	2 (11)
Thrombocytopenia[g]	9 (12)	3 (4)	13 (33)	0	2 (11)	2 (11)
Non-hematological TEAEs						
Alopecia	51 (66)	0	21 (53)	0	14 (78)	0
Nausea	47 (61)	1 (1)	22 (55)	1 (3)	11 (61)	0
Diarrhea	34 (44)	2 (3)	22 (55)	5 (13)	12 (67)	2 (11)
Constipation	31 (40)	0	10 (25)	0	7 (39)	0
Decreased appetite	29 (38)	0	20 (50)	2 (5)	7 (39)	1 (6)
Alanine aminotransferase increased	26 (34)	0	19 (48)	0	7 (39)	0
Vomiting	24 (31)	1 (1)	18 (45)	2 (5)	7 (39)	0
Aspartate aminotransferase increased	23 (30)	1 (1)	17 (43)	0	8 (44)	0
Fatigue	19 (25)	4 (5)	18 (45)	7 (18)	9 (50)	1 (6)
Hypoalbuminemia	16 (21)	1 (1)	12 (30)	0	5 (28)	0
Hypokalemia	15 (19)	8 (10)	12 (30)	3 (8)	6 (33)	3 (17)
Abdominal pain	14 (18)	1 (1)	10 (25)	0	6 (33)	0
Hyperglycemia	14 (18)	0	9 (23)	0	3 (17)	0
Gamma-glutamyltransferase increased	14 (18)	0	5 (13)	1 (3)	5 (28)	0
Hyponatremia	13 (17)	2 (3)	8 (20)	1 (3)	2 (11)	1 (6)
Hypocalcemia	13 (17)	1 (1)	8 (20)	0	5 (28)	1 (6)
Upper respiratory infection	12 (16)	2 (3)	5 (13)	1 (3)	4 (22)	0
Blood alkaline phosphatase increased	11 (14)	0	8 (20)	0	7 (39)	0
Blood lactate dehydrogenase increased	11 (14)	0	8 (20)	0	3 (17)	0
Dizziness	10 (13)	0	1 (3)	0	4 (22)	0
Urinary tract infection	6 (8)	1 (1)	8 (20)	0	2 (11)	0
Stomatitis	5 (6)	0	3 (8)	0	2 (11)	2 (11)
Rash	4 (5)	0	3 (8)	0	5 (28)	0

Data are presented as *n* (%). [a]Other *UGT1A1* genotypes included *6/*6 (*n*=5), *28/*28 (*n*=3), *6/*28 (*n*=3), *27/*28 (*n*=2), and *6/*27/*28 (*n*=1). *UGT1A1* status missing/not done, n=16. [b]Includes any-grade TEAEs observed in at least 20% of patients or grade ≥3 TEAEs observed in at least 10% of patients in any of the SG-treated *1/*1, *1/*6, and *1/*28 subgroups. [c]Combined preferred terms of neutropenia and neutrophil count decreased. [d]Combined preferred terms of anemia, red blood cell count decreased, and hemoglobin decreased. [e]Combined preferred terms of leukopenia and white blood cell count decreased. [f]Combined preferred terms of lymphopenia and lymphocyte count decreased. [g]Combined preferred terms of thrombocytopenia and platelet count decreased. SAE, serious adverse event; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event; *UGT1A1*, uridine diphosphate glucuronosyltransferase 1A1.

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Extended Data Table 5 | Quality of life: EORTC QLQ-C30 TTD from baseline

EORTC QLQ-C30 TTD from baseline[a]	Death as event		Death as censored	
Global health status/QoL	**SG (*n* = 160)**	**Chemotherapy (*n* = 155)**	**SG (*n* = 160)**	**Chemotherapy (*n* = 155)**
Median (95% CI), months	3.9 (3.0–5.5)	3.3 (2.2–4.2)	3.9 (2.9–5.1)	2.8 (2.1–4.1)
HR (95% CI); *P*-value	0.91 (0.70–1.18); *P* = 0.500		0.86 (0.64–1.16); *P* = 0.300	
Pain	**SG (*n* = 160)**	**Chemotherapy (*n* = 153)**	**SG (*n* = 160)**	**Chemotherapy (*n* = 153)**
Median (95% CI), months	5.3 (3.3–7.0)	3.2 (2.7– to 4.8)	5.3 (3.3–7.7)	2.9 (2.3–4.1)
HR (95% CI); *P*-value	0.81 (0.62–1.05); *P* = 0.100		0.69 (0.51–0.94); *P* = 0.020	
Fatigue	**SG (*n* = 161)**	**Chemotherapy (*n* = 155)**	**SG (*n* = 161)**	**Chemotherapy (*n* = 155)**
Median (95% CI), months	2.1 (1.5–3.2)	1.8 (1.5–2.7)	1.9 (1.5–3.0)	1.7 (1.5–2.7)
HR (95% CI); *P*-value	0.93 (0.72–1.19); *P* = 0.500		0.92 (0.69–1.21); *P* = 0.500	
Physical functioning	**SG (*n* = 160)**	**Chemotherapy (*n* = 157)**	**SG (*n* = 160)**	**Chemotherapy (*n* = 157)**
Median (95% CI), months	4.5 (2.9–7.5)	3.4 (2.7–4.2)	4.3 (2.9–9.9)	2.8 (2.1–4.2)
HR (95% CI); *P*-value	0.73 (0.56–0.95); *P* = 0.020		0.68 (0.50–0.93); *P* < 0.001	

Median TTD was derived as a Kaplan-Meier estimate. 95% CI associated with median was computed using the Brookmeyer-Crowley method. HR (95% CI) and *P*-value were estimated using a stratified Cox proportional hazards regression analysis and stratified log-rank test, respectively, with treatment arm (SG vs. chemotherapy) as covariate and the prior chemotherapy regimens for treatment of metastatic disease (two vs. three/four lines), visceral metastasis (yes/no), and prior treatment with CDK4/6 inhibitors in the metastatic setting (yes/no) as stratification factors. A two-tailed *P*-value < 0.05 was deemed statistically significant. No adjustments were made for multiple comparisons. [a]Patients with baseline scores so poor that it was impossible for the change score to exceed or equal the threshold measure for worsening were excluded. EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoL, quality of life; SG, sacituzumab govitecan; TTD, time to deterioration.

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☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used.
Data analysis	All statistical analyses were performed using SAS® (SAS Institute, Version 9.2 or later, Cary, North Carolina).

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Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	The majority of the patients in this study were women (99%)
Population characteristics	Patients from mainland China, Republic of Korea, and Taiwan (n=331) diagnosed with HR+/HER2– metastatic or locally recurrent inoperable breast cancer were enrolled. The median age was 52 years. Most patients had visceral metastases at baseline (SG, 88%; chemotherapy, 89%). Approximately half of patients had received prior CDK4/6i therapy in the metastatic setting (SG, 49%; chemotherapy, 48%). In both treatment groups, 56% of patients had received two prior chemotherapy regimens for treatment of metastatic disease, and 44% had received 3–4 prior regimens.
Recruitment	Patients with HR+/HER2- mBC were recruited from 41 sites in China, Republic of Korea, and Taiwan using eligibility criteria specified in the study protocol. Patients were required to have received two to four prior systemic chemotherapy regimens for mBC and to be eligible for one of the options for chemotherapy of investigator's choice. Adjuvant or neoadjuvant chemotherapy was counted as one of the required prior regimens if development of unresectable, locally advanced or mBC occurred within a 12-month period after completion of chemotherapy. Previous treatment included at least one taxane and at least one anticancer endocrine therapy in any setting; prior use of CDK4/6i was not mandatory. Documented measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (by computed tomography (CT) or magnetic resonance imagery (MRI)) following the most recent anticancer therapy was required. Patients were required to be aged ≥18 years and to provide written informed consent, Eastern Cooperative Oncology Group performance status of 0 or 1, and to be recovered from all prior treatment-related toxicities to grade ≤1 per CTCAE v5.0 (except alopecia or stable sensory neuropathy, which could be grade ≤2). Exclusion criteria included previous treatment with topoisomerase 1 inhibitors, known brain metastases, second active malignancy within 3 years prior to providing informed consent (non-melanoma skin cancer and histologically confirmed completed excision of carcinoma in situ excepted), human immunodeficiency virus positivity, active hepatitis B or C virus infection, known history of unstable angina/myocardial infarction/congestive heart disease within 6 months before first dose, clinically significant cardiac arrythmia requiring anti-arrythmia therapy or left ventricular ejection fraction <50%, known history of clinically significant active chronic obstructive pulmonary disease or other moderate-to-severe chronic respiratory illness within 6 months before first dose, active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease)/clinically significant gastrointestinal bleeding/intestinal obstruction/gastrointestinal perforation within 6 months before first dose, active serious infection requiring systemic antibiotic use within 7 days before first dose, high-dose systemic corticosteroid use within 2 weeks before first dose, scheduled surgery that would delay study treatment during study, receipt of live vaccine within 30 days before first dose, other concurrent medical or psychiatric conditions that may confound study interpretation or prevent completion of study procedures or follow-up examinations, known hypersensitivity or intolerance to study treatments or any of the excipients, anticancer treatment with chemotherapy/radiation/small molecule targeted therapy/endocrine therapy within 2 weeks before first dose, biological therapy within 4 weeks before first dose, current treatment in another clinical study or use of any investigational drug or device within five half-lives or 4 weeks before first dose (whichever is longer), pregnancy or lactation, and women of childbearing potential/fertile men unwilling to use highly effective contraception during the study and up to 6 months after treatment discontinuation for women of childbearing potential and 3 months for fertile men.
Ethics oversight	EVER-132-002 was compliant with Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines, and was approved by national regulatory authorities, as well as each investigational sites' ethics committee or review board. The investigational sites that approved the study protocol were Cancer Hospital Chinese Academy of Medical Science; Chinese PLA General Hospital; Peking University People's Hospital; Jilin Cancer Hospital; The First Hospital of Jilin University; Chongqing University Cancer Hospital; West China Hospital, Sichuan University; Fujian Medical University Union Hospital; Guangdong Provincial People's Hospital; Sun Yat Sen Memorial Hospital of Sun Yat Sen University; Sun Yat Sen University Cancer Center; Sir Run Run Shaw Hospital Zhejiang University School of Medicine; Zhejiang Cancer Hospital; Anhui Provincial Hospital; The Second Hospital of Anhui Medical University; Shandong Cancer Hospital; Yunnan Cancer Hospital; Linyi Cancer Hospital; Jiangsu Province Hospital; Nanjing Drum Tower Hospital; Shanghai General Hospital; Tianjin Medical University Cancer Institute & Hospital; Hubei Cancer Hospital; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; The First Affiliated Hospital of Xi'an Jiaotong University; Henan Cancer Hospital; Cancer Hospital of Xinjiang Medical University; Dong-A University Hospital; Seoul National University Bundang Hospital; Asan Medical Center; Korea University Anam Hospital; Samsung Medical Center; Seoul National University Hospital; Severance Hospital of Yonsei University Health System; Ajou University Hospital; Changhua Christian Medical Foundation Changhua Christian Hospital; Kaohsiung Medical University Chung-Ho Memorial Hospital; China Medical University Hospital; National Cheng Kung University Hospital; National Taiwan University Hospital; Taipei Veterans General Hospital; Tri-Service General Hospital; Chang Gung Memorial Hospital, Linkou. All patients gave written informed consent.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was calculated based on the primary endpoint of PFS per BICR. Assuming an HR of 0.70 (median 5.3 versus 3.7 months), approximately 250 PFS events were needed to detect a statistically significant difference between the two groups at a two-sided 0.05 significance level and 80% power. Based on an estimated 12-month enrollment and 24-month total study duration, it was estimated that approximately 330 patients would need to be randomized.
Data exclusions	Data were not excluded.
Replication	To ensure reproducibility, we have provided a detailed protocol and statistical analysis plan. The protocol was approved by the ethics committees and/or institutional review boards at each investigational site. The investigational sites are detailed in the manuscript.
Randomization	Patients were randomly assigned at 1:1 to receive SG (10 mg/kg intravenously days 1 and 8 of every 3-week cycle) or chemotherapy TPC (eribulin, capecitabine, gemcitabine, or vinorelbine, with dosing and schedule per package insert depending on region). Randomization was stratified according to presence of visceral metastases (yes versus no), number of prior chemotherapy regimens for the treatment of metastatic disease (two versus three/four), and prior CDK4/6i treatment in the metastatic setting (yes versus no). Patients were randomized via an Interactive Web-based Response System. The randomization list was generated by a designated vendor using stratified blocked randomization with a block size of four.
Blinding	The study was open-label. The primary endpoint of PFS was evaluated per blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1). Secondary endpoints of ORR, DoR, and CBR were also evaluated per BICR.

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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04639986
Study protocol	A study protocol is available with this publication.
Data collection	Enrollment dates were from 9 December 2020 and 2 December 2022 at 41 sites in 3 countries. Data was collected in hospitals and clinics with academic affiliations. Data collection locations are detailed in the primary analysis. The data cutoff date was 30 April 2023.
Outcomes	The primary endpoint was PFS per BICR using RECIST v1.1. PFS was defined as time from randomization to progressive disease (PD) or death, whichever occurred earlier. Secondary endpoints included OS, ORR per BICR, DoR per BICR, CBR per BICR, safety, and QoL. Efficacy by investigator assessment was not a prespecified endpoint but was a planned supportive analysis per the protocol. OS was defined as time from randomization to death from any cause. ORR was the sum of complete response (CR) and partial response (PR), while CBR was the sum of CR, PR, and stable disease (SD) with duration ≥6 months. DoR was defined as time from first tumor response (CR or PR) to PD or death, whichever was first. Exploratory endpoints included Trop-2 expression level.