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Sacituzumab tirumotecan in previously treated metastatic triple-negative breast cancer: a randomized phase 3 trial

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Chemotherapy remains a standard treatment option for metastatic triple-negative breast cancer (TNBC) but is associated with limited survival. Although some targeted antibody–drug conjugates have demonstrated clinical benefits and are considered standard therapy, persistent unmet medical needs remain due to varying accessibility. The OptiTROP-Breast01 phase 3 trial assessed sacituzumab tirumotecan (sac-TMT) versus chemotherapy in patients with locally recurrent or metastatic TNBC who had received two or more prior therapies, including at least one for metastatic disease. Patients were randomized to sac-TMT ($n = 130$) or chemotherapy ($n = 133$). The primary endpoint of progression-free survival (PFS) by blinded independent central review (BICR) was met based on the protocol-specified interim analysis. At final analysis, the median PFS by BICR was 6.7 (95% confidence interval (CI), 5.5–8.0) months with sac-TMT and 2.5 (95% CI, 1.7–2.7) months with chemotherapy (hazard ratio (HR), 0.32; 95% CI, 0.24–0.44; $P < 0.00001$). Concurrently, at the protocol-specified interim analysis for overall survival (OS), the median OS was not reached (95% CI, 11.2 months to not estimable (NE)) with sac-TMT and 9.4 (95% CI, 8.5–11.7) months with chemotherapy (HR, 0.53; 95% CI, 0.36–0.78; $P = 0.0005$). The percentage of patients with an objective response was 45.4% with sac-TMT and 12.0% with chemotherapy. The median duration of response was 7.1 (95% CI, 5.6–NE) months with sac-TMT and 3.0 (95% CI, 2.5–NE) months with chemotherapy. The most common treatment-related adverse event with sac-TMT was hematologic toxicity. Sac-TMT demonstrated statistically significant and clinically meaningful improvements in PFS compared to chemotherapy, with a manageable safety profile. The study findings support sac-TMT as an additional effective treatment option for pretreated metastatic TNBC. ClinicalTrials.gov identifier: NCT05347134.

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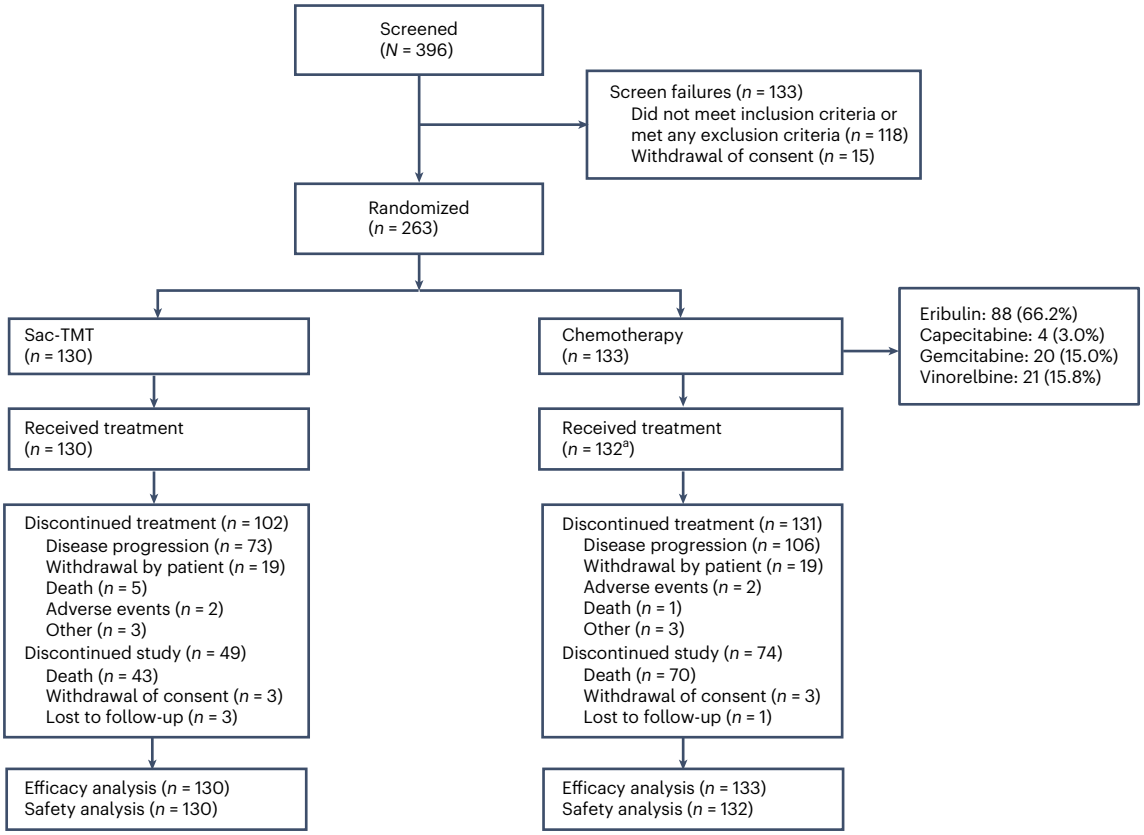

Fig. 1 | Patient flow diagram. Data cutoff: 30 November 2023. [a]Of the patients who underwent randomization, one patient in the chemotherapy group was included in the efficacy analysis but was excluded from the safety analysis.

Triple-negative breast cancer (TNBC) (characterized by the lack of expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2)) is an aggressive subtype of breast cancer accounting for approximately 15% of all cases[1,2] and is known to be associated with poor prognosis[3,4]. For patients with previously treated metastatic TNBC, standard-of-care chemotherapy typically results in a median progression-free survival (PFS) of approximately 2–3 months and a median overall survival (OS) of approximately 5–8 months[5,6]. The current standard of care also incorporates targeted therapies, such as the anti-trophoblast cell-surface antigen 2 (anti-TROP2) antibody–drug conjugate (ADC) sacituzumab govitecan (SG) and the anti-HER2 ADC trastuzumab deruxtecan (also known as DS-8201/T-DXd), the latter of which is indicated for HER2-low metastatic breast cancer based on a small cohort from the DESTINY-Breast04 study[7]. Although these therapies significantly improve patient outcomes compared to traditional chemotherapy, access to these treatments may vary and may not be universally available in all regions.

TROP2 is a tumor-associated calcium signal transducer overexpressed in more than 80% of TNBC cases[8]. Based on the high expression levels of TROP2 in TNBC, anti-TROP2 therapies are being explored in clinical trials[9–13]. SG is the only TROP2-targeted ADC approved for metastatic TNBC in multiple countries to date, and there is a need for novel and optimized TROP2-targeted ADCs to provide more therapeutic options for this patient population. Sacituzumab tirumotecan (sac-TMT; also known as MK-2870/SKB264) is a novel anti-TROP2 ADC developed with a proprietary Kthiol (pyrimidine-thiol) linker to conjugate its payload, a belotecan-derivative topoisomerase I inhibitor, to achieve an average drug-to-antibody ratio of 7.4. The hydrolytic linker permits both extracellular cleavage before internalization and intracellular cleavage to release the membrane-permeable payload after internalization, enabling the 'bystander effect'[14] (Supplementary Fig. 1). Results from our preclinical studies indicated that sac-TMT was associated with high tumor cell growth inhibition[14]. Furthermore, the first-in-human, open-label, multicenter, global, phase 1/2 study (NCT04152499) of sac-TMT in patients with metastatic or locally advanced tumors demonstrated the anti-tumor activity of sac-TMT and a manageable safety profile[11–13,15–17]. In the phase 2 expansion cohort of patients with TNBC in that study, the objective response rate (ORR) was 42.4%, and the disease control rate (DCR) was 76.3%[13]. Given the promising results from the phase 1/2 study, the OptiTROP-Breast01 study was designed to approve the superiority of efficacy and safety of sac-TMT versus chemotherapy in patients with locally recurrent or metastatic TNBC who had received two or more prior therapies, including at least one for metastatic disease. At the start of the OptiTROP-Breast01 study, SG was inaccessible in certain countries or regions, including China, and chemotherapy constituted the standard of care. Therefore, single-agent chemotherapy of the physician's choice was selected as the control arm.

Results

Patients and characteristics

Between 11 August 2022 and 26 April 2023, 396 patients were assessed for eligibility. A total of 263 patients with locally advanced, recurrent or metastatic TNBC were enrolled across 49 sites in China (Supplementary Table 1). Patients were randomly assigned to receive either sac-TMT ($n = 130$) or chemotherapy of the physician's choice ($n = 133$). Among the patients in the chemotherapy group, 88 (66.2%) received eribulin, four (3.0%) received capecitabine, 20 (15.0%) received gemcitabine and 21 (15.8%) received vinorelbine. Only one patient assigned to receive chemotherapy received no study treatment and was included in the efficacy analysis but not in the safety analysis. At the final analysis for PFS corresponding to protocol-specified interim analysis of OS (data

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Table 1 | Baseline patient characteristics

	Sac-TMT (*n*=130)	Chemotherapy (*n*=133)[a]
Female, *n* (%)	130 (100)	133 (100)
Median age (range), years	51.0 (19–70)	51.0 (25–72)
Age <65 years, *n* (%)	119 (91.5)	119 (89.5)
TNBC at initial diagnosis, *n* (%)	92 (70.8)	88 (66.2)
ECOG performance status, *n* (%)		
0	40 (30.8)	39 (29.3)
1	90 (69.2)	94 (70.7)
Location of metastases, *n* (%)		
Visceral sites[b]	115 (88.5)	113 (85.0)
Lymph node	81 (62.3)	75 (56.4)
Lung	62 (47.7)	64 (48.1)
Liver	45 (34.6)	45 (33.8)
Previous chemotherapy lines in advanced setting[c], *n* (%)		
Median (range)	3.0 (2–6)	2.0 (2–6)
2[d]	62 (47.7)	76 (57.1)
3	52 (40.0)	37 (27.8)
>3	16 (12.3)	20 (15.1)
Prior therapy, *n* (%)		
Taxane(s)	130 (100)	133 (100)
Anthracycline(s)	122 (93.8)	122 (91.7)
PD-1 or PD-L1 inhibitor(s)	32 (24.6)	36 (27.1)
(Neo)adjuvant	116 (89.2)	117 (88.0)
TROP2 expression, *n* (%)		
High (H-score >200)	73 (56.1)	74 (55.6)
Low (H-score ≤200)	53 (40.8)	48 (36.1)
Unknown	4 (3.1)	11 (8.3)

[a]The chemotherapy group included patients randomly assigned to receive eribulin (88 patients, 66.2%), capecitabine (four patients, 3.0%), gemcitabine (20 patients, 15.0%) and vinorelbine (21 patients, 15.8%). [b]The results were assessed by the investigator based on baseline imaging findings. Visceral metastases were defined as the presence of metastases from sites other than soft tissue, skin, lymph nodes and chest wall. [c]For (neo) adjuvant chemotherapy, if progression occurred during treatment or within 12 months after treatment discontinuation, it would be considered one regimen for advanced setting. [d]This category includes two patient populations: (1) patients who have received only one previous chemotherapy regimen in advanced setting and experienced progression during (neo) adjuvant treatment or within 12 months after treatment discontinuation (sac-TMT group: 37 patients; chemotherapy group: 43 patients); (2) patients who have received two previous chemotherapy regimens in advanced setting (sac-TMT group: 25 patients; chemotherapy group: 33 patients).

cutoff: 30 November 2023), 28 patients (21.5%) continued to receive sac-TMT, and two patients (1.5%) continued to receive chemotherapy. The most common reason for treatment discontinuation was disease progression (73 patients with sac-TMT and 106 patients with chemotherapy) (Fig. 1).

Across both treatment groups, the median age of the enrolled patients was 51.0 years, and 90.5% of patients were younger than 65 years. More than two-thirds of cases (68.4%) were confirmed as TNBC at initial diagnosis. All patients received taxanes as part of prior therapy. Additionally, most patients (92.8%) received prior anthracyclines; 25.9% of patients received programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors; and 88.6% of patients received prior neoadjuvant or adjuvant therapy. Overall, 86.7% of patients presented with visceral metastases, and 34.2% of patients presented with liver metastases. Almost half of the patients (47.5%) had received three or more previous chemotherapy regimens in advanced setting. The baseline demographics and clinical characteristics were generally balanced between the treatment groups (Table 1).

Efficacy

PFS. The primary endpoint of PFS by blinded independent central review (BICR) was met based on the protocol-specified interim analysis with a median follow-up of 5.1 months (data cutoff: 21 June 2023), and the PFS outcomes by investigator assessment were consistent with those assessed by BICR (Extended Data Figs. 1 and 2). At the final analysis for PFS with a median follow-up of 10.4 months (data cutoff: 30 November 2023), the median PFS as assessed by BICR was 6.7 (95% confidence interval (CI), 5.5–8.0) months with sac-TMT and 2.5 (95% CI, 1.7–2.7) months with chemotherapy (hazard ratio (HR), 0.32; 95% CI, 0.24–0.44; $P < 0.00001$) (Fig. 2a). The PFS rates at 9 months were 34.0% and 5.9%, respectively. The PFS outcomes by investigator assessment were consistent with those by BICR (6.5 months with sac-TMT and 2.6 months with chemotherapy; HR, 0.32; 95% CI, 0.24–0.44) (Extended Data Fig. 3).

Outcomes for PFS were more favorable with sac-TMT versus chemotherapy across all predetermined subgroups (Fig. 3 and Extended Data Fig. 4), including in patients who had received more than three lines of prior therapy, in patients who had received PD-1 or PD-L1 inhibitors as prior therapy, in patients who did not have TNBC at initial diagnosis and in patients whose tumors had low HER2 expression.

OS. At the protocol-specified interim analysis for OS (data cutoff: 30 November 2023), the median OS was not reached (95% CI, 11.2 months to not estimable (NE)) with sac-TMT and was 9.4 (95% CI, 8.5–11.7) months with chemotherapy (HR, 0.53; 95% CI, 0.36–0.78; $P = 0.0005$), which crossed the prespecified efficacy boundary (Fig. 2b). Subgroup analyses of OS demonstrated similar superior benefit with sac-TMT compared to chemotherapy (Extended Data Fig. 5).

At the data cutoff, subsequent anti-cancer therapies were received by 66 patients (50.8%) in the sac-TMT group and by 95 patients (71.4%) in the chemotherapy group. Most patients received chemotherapy during follow-up. Seven patients (5.4%) in the sac-TMT group and 28 patients (21.1%) in the chemotherapy group were treated with subsequent ADCs. A summary of subsequent anti-cancer therapies, including the types of ADCs, is provided (Supplementary Table 2).

Tumor response. The ORR assessed by BICR was 45.4% (95% CI, 36.6–54.3%) with sac-TMT and 12.0% (95% CI, 7.0–18.8%) with chemotherapy ($P < 0.00001$) (Extended Data Table 1 and Extended Data Fig. 6). The DCR also exhibited improvements with sac-TMT compared to chemotherapy and was 78.5% (95% CI, 70.4–85.2%) with sac-TMT and 52.6% (95% CI, 43.8–61.3%) with chemotherapy. The median duration of response (DOR) assessed by BICR was 7.1 (95% CI, 5.6–NE) months with sac-TMT and 3.0 (95% CI, 2.5–NE) months with chemotherapy (HR, 0.50; 95% CI, 0.22–1.13). The median time to response (TTR) assessed by BICR was 1.4 (range, 1.2–5.7) months with sac-TMT and 1.5 (range, 1.2–3.0) months with chemotherapy (Extended Data Table 1). The results for tumor response outcomes by investigator assessment were consistent with those assessed by BICR (Extended Data Table 2).

Safety

All patients who received at least one dose of study treatment were included in the safety analysis (130 patients in the sac-TMT group and 132 patients in the chemotherapy group). The median duration of exposure was 24.9 weeks (range, 2.0–66.1 weeks) with sac-TMT and 8.6 weeks (range, 1.0–65.0 weeks) with chemotherapy. The median relative dose intensity with sac-TMT was 89.5% (Supplementary Table 3).

All patients in the sac-TMT group and 96.2% of patients in the chemotherapy group experienced treatment-related adverse events (TRAEs). The most common TRAEs were anemia (82.3% with sac-TMT and 54.5% with chemotherapy), decreased neutrophil count (78.5%

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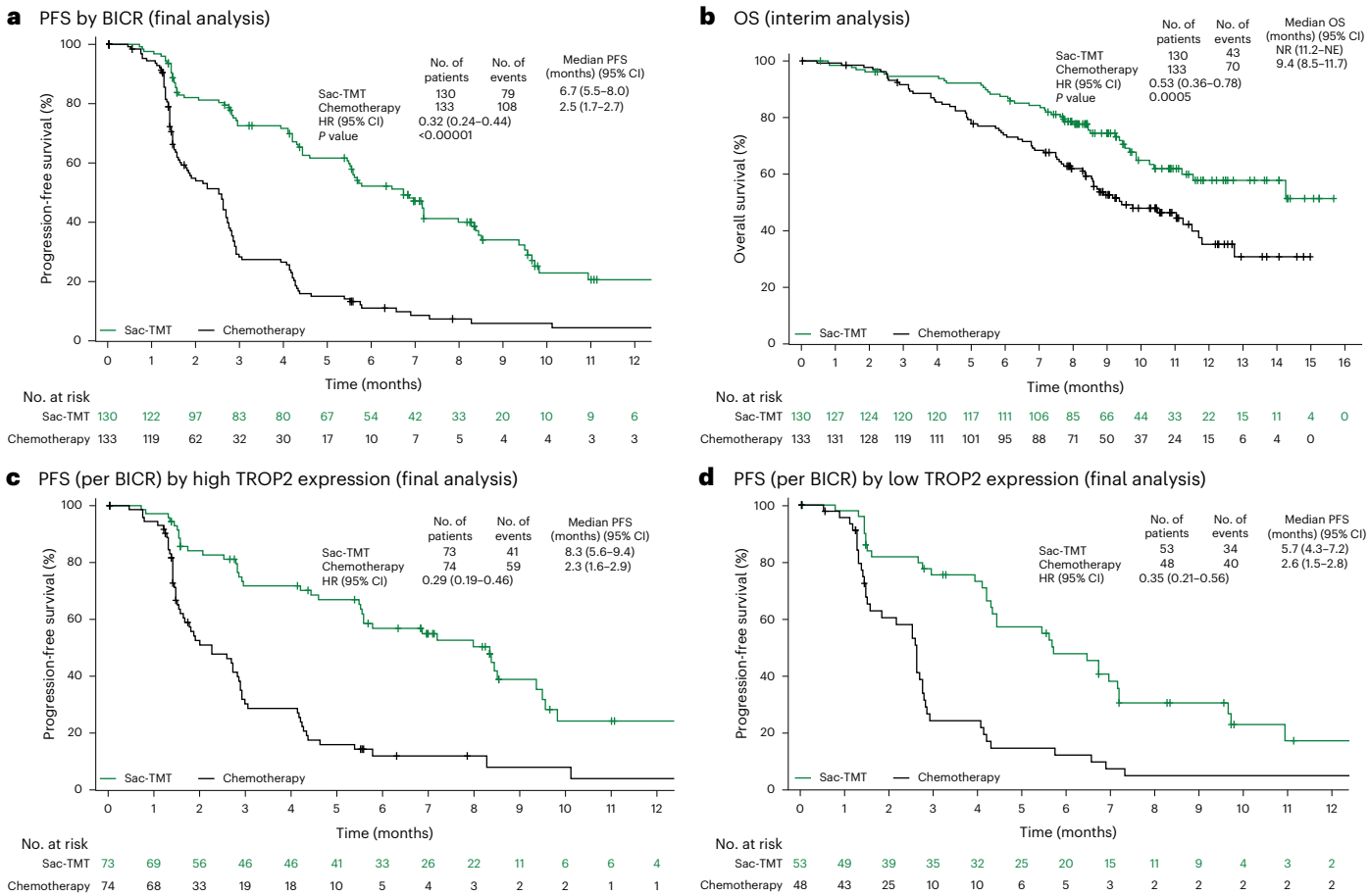

Fig. 2 | Kaplan–Meier curves for PFS and OS. a–**d**, PFS by BICR (final analysis) (**a**), OS (interim analysis) (**b**), PFS (per BICR) by high TROP2 expression (final analysis) (**c**) and PFS (per BICR) by low TROP2 expression (final analysis) (**d**). Data cutoff of final analysis for PFS and interim analysis for OS was 30 November 2023. High TROP2 expression: H-score >200; low TROP2 expression: H-score ≤200. The 95% CIs of median PFS/OS were determined using the Brookmeyer and Crowley method with log–log transformation. HRs along with 95% CIs were estimated using a stratified Cox proportional hazards model. The *P* value was calculated by a stratified log-rank test. The multiplicity-adjusted, one-sided alpha at OS interim analysis (determined using the Lan–DeMets O'Brien–Fleming spending function) was 0.0042. The exact one-sided *P* value for PFS by BICR (final analysis) was 7.7×10^{-14} and for OS (interim analysis) was 0.0005. NR, not reached.

and 74.2%), decreased white blood cell count (76.2% and 76.5%), stomatitis (49.2% and 4.5%), decreased platelet count (40.8% and 25.8%) and increased aspartate aminotransferase (23.1% and 47.7%). Grade 3 or higher TRAEs occurred in 63.1% of patients in the sac-TMT group and in 56.8% of patients in the chemotherapy group. The most frequent grade 3 or higher TRAEs were decreased neutrophil count (34.6% with sac-TMT and 47.0% with chemotherapy), anemia (29.2% and 6.1%) and decreased white blood cell count (27.7% and 36.4%) (Table 2).

In the sac-TMT group, decreased neutrophil count of grade 3 or higher was less common than in the chemotherapy group. Two patients (1.5%) developed febrile neutropenia, and both cases were grade 3. Decreased neutrophil count most commonly occurred within the first two cycles. No patients discontinued sac-TMT treatment due to decreased neutrophil count. Five patients (3.8%) reduced the sac-TMT dose due to decreased neutrophil count. Granulocyte colony-stimulating factor was administered as supportive care, including for prophylactic use, in 25.4% of patients. Common TRAEs with sac-TMT also included anemia, with 29.2% of patients experiencing grade 3 events (no patients had grade 4 or 5 anemia). Overall, sac-TMT dose reduction due to anemia occurred in 15.4% of patients, and no patient experienced sac-TMT treatment discontinuation. Additionally, in the sac-TMT group, three patients (2.3%) reported peripheral neuropathy (all grade 1), and one patient (0.8%) reported grade 2 interstitial lung disease; three patients (2.3%) reported xerophthalmia, with one at grade 1 and two at grade 2; and blurred vision (all grade 1) occurred in two patients (1.5%).

Serious TRAEs occurred in 20.8% of patients who received sac-TMT compared to 13.6% of patients who received chemotherapy. Across both treatment groups, only one fatal TRAE was reported—multiple organ dysfunction syndrome in one patient in the sac-TMT group. This patient received only one dose of sac-TMT, and the death occurred 24 d after administration. The reasons for this death assessed by the investigator were possibly due to confounding factors, including coronavirus disease 2019 (COVID-19) infection presented before sac-TMT dosing, rapid tumor progression and liver failure due to acute cholecystitis. Dose reductions due to TRAEs were reported in 30.8% of patients who received sac-TMT and in 15.9% of patients who received chemotherapy. TRAEs leading to treatment discontinuation occurred with a low incidence rate of 1.5% in both treatment groups (Table 2).

Analysis of TROP2 expression

Of the 248 patients available for analysis of TROP2 expression levels, 147 patients had high TROP2 expression, defined as H-score >200 (73 patients in the sac-TMT group and 74 patients in the chemotherapy group), and 101 had low TROP2 expression, defined as H-score ≤200 (53 and 48, respectively) (Table 1). The median PFS assessed by BICR was 8.3 months with sac-TMT and 2.3 months with chemotherapy in patients with high TROP2 expression (HR, 0.29; 95% CI, 0.19–0.46) and was 5.7 months with sac-TMT and 2.6 months with chemotherapy

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Subgroup	No. of patients	Median PFS (95% CI) Sac-TMT	Median PFS (95% CI) Chemotherapy	HR for PFS (95% CI)
All patients	263	6.7 (5.5–8.0)	2.5 (1.7–2.7)	0.32 (0.24–0.44)
Age				
<65 years	238	7.0 (5.6–8.3)	2.6 (1.8–2.8)	0.30 (0.22–0.42)
ECOG performance status				
0	79	5.7 (4.2–8.4)	2.6 (1.5–4.1)	0.39 (0.23–0.67)
1	184	6.9 (5.5–8.3)	2.3 (1.6–2.8)	0.31 (0.22–0.45)
Prior line of therapy				
2	138	7.2 (5.8–9.4)	2.7 (1.9–2.9)	0.37 (0.24–0.57)
3	89	5.5 (3.9–8.4)	1.6 (1.4–2.7)	0.24 (0.14–0.41)
>3	36	5.7 (2.7–NE)	1.5 (1.4–2.9)	0.24 (0.10–0.57)
Liver metastases				
Yes	90	4.3 (1.6–5.6)	1.8 (1.4–2.6)	0.36 (0.22–0.60)
No	173	8.4 (6.9–9.7)	2.7 (1.8–2.9)	0.29 (0.19–0.43)
Initial diagnosis of TNBC				
Yes	180	5.8 (4.6–8.0)	2.0 (1.5–2.8)	0.37 (0.26–0.53)
No	83	7.2 (4.2–10.9)	2.6 (1.7–2.8)	0.25 (0.14–0.45)
Prior treatment with PD-1 or PD-L1 inhibitors				
Yes	68	5.6 (4.4–7.2)	2.7 (1.5–3.9)	0.31 (0.17–0.54)
No	195	7.2 (5.6–9.4)	2.3 (1.6–2.7)	0.34 (0.23–0.48)
Lymph node metastases				
Yes	156	6.7 (4.4–8.3)	2.5 (1.7–2.7)	0.33 (0.23–0.49)
No	107	7.2 (5.5–9.5)	2.6 (1.5–2.9)	0.31 (0.19–0.51)
Visceral metastases				
Yes	228	5.8 (4.4–7.2)	2.5 (1.6–2.7)	0.27 (0.19–0.38)
No	35	8.3 (4.6–NE)	4.2 (1.5–8.3)	0.30 (0.10–0.94)
HER2 expression				
Low expression	112	5.6 (3.0–8.4)	2.3 (1.5–2.7)	0.30 (0.18–0.49)
0	151	7.2 (5.6–8.5)	2.6 (1.6–2.8)	0.33 (0.22–0.49)
Course of disease (months)				
≤24	92	5.8 (4.1–8.4)	2.5 (1.6–2.8)	0.35 (0.21–0.58)
>24	171	7.2 (5.5–8.4)	2.5 (1.6–2.8)	0.31 (0.21–0.46)

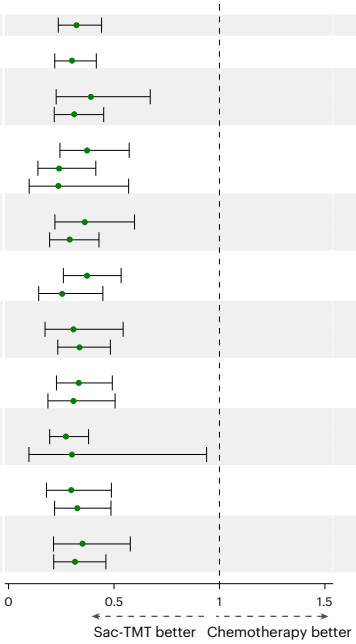

Fig. 3 | Forest plot of PFS (per BICR) in key patient subgroups. Data cutoff: 30 November 2023. Statistical analysis was not performed when the number of patients in the subgroup was less than 10% of the total patients. HRs along with 95% CIs were estimated using an unstratified Cox proportional hazards model in each subgroup.

in patients with low TROP2 expression (HR, 0.35; 95% CI, 0.21–0.56) (Fig. 2c,d). Irrespective of TROP2 expression level, a favorable ORR with sac-TMT compared to chemotherapy was also demonstrated (Extended Data Fig. 7).

Additional analysis dividing the low TROP2 expression group into two subgroups (H-score: 0 to <100 and 100 to ≤200) was performed. In the subgroup with very low TROP2 expression (H-score <100), patients in the sac-TMT group also achieved favorable PFS and ORR compared to chemotherapy (Extended Data Table 3 and Extended Data Fig. 7).

Discussion

In the phase 3 OptiTROP-Breast01 study in patients with previously treated locally recurrent or metastatic TNBC, sac-TMT demonstrated statistically significant and clinically meaningful improvements in PFS compared to chemotherapy (median PFS: 6.7 months versus 2.5 months; HR, 0.32; $P < 0.00001$). The benefit was also observed in all predetermined subgroups, suggesting that sac-TMT maintained its benefits in survival outcomes irrespective of the relevant clinical factors outlined in the trial. Notably, with the emergence of immunotherapy, the combination of pembrolizumab with chemotherapy has become the standard first-line treatment for metastatic TNBC with PD-L1 Combined Positive Score ≥10. This study included patients who had previously received treatment with PD-1 or PD-L1 inhibitors, which accounted for 25.9% of the total. Subgroup analysis results revealed that sac-TMT showed superior PFS benefits over chemotherapy, irrespective of prior therapy with or without PD-1 or PD-L1 inhibitors (HR: 0.31 and HR: 0.34, respectively).

Our findings regarding the efficacy advantages of a TROP2-targeted ADC over chemotherapy presented in the OptiTROP-Breast01 study are aligned with the results reported for SG in the phase 3 ASCENT study[9,10]. The OS outcome with chemotherapy in our study is consistent with historical data[18–20], albeit longer than the ASCENT study (median, 9.4 months versus 6.7 months). One potential explanation is that the OptiTROP-Breast01 study included a higher proportion of patients who had received three or fewer prior lines of therapy (more than three prior lines of therapy: 15% in OptiTROP-Breast01 and 30% in ASCENT)[9]. Another possibility is that a higher proportion of patients in the OptiTROP-Breast01 study received eribulin at the physician's discretion than in the ASCENT study (66% versus 54%)[9]. Additionally, T-DXd (HER2-targeted ADC) was not approved for patients with HER2-low breast cancer at the time of the ASCENT study. With multiple ADCs approved during the course of our trial, subsequent treatment after patients' disease progression or treatment discontinuation is likely to have affected survival results. With the aim of providing patients an effective treatment option, the results of the OptiTROP-Breast01 study confirmed again the role of TROP2-targeted ADC in metastatic TNBC. In addition, research for the application of combination therapies and frontline treatments also warrants further exploration. With the promising results from the BEGONIA or MORPHEUS-pan BC study[21,22], ongoing global phase 3 study of sac-TMT in combination with pembrolizumab in TNBC (NCT06393374) and sac-TMT with or without pembrolizumab in hormone receptor–positive/HER2-negative metastatic breast cancer (NCT06312176) will further expand its application in breast cancer.

Efficacy was also demonstrated across different TROP2 expression levels in an exploratory analysis, suggesting that patients benefit irrespective of TROP2 expression levels. Patients with high TROP2 expression experienced numerically better PFS and ORR as compared to those with low TROP2 expression. Furthermore, the improvement observed with sac-TMT over chemotherapy for patients with low TROP2 expression may be due to the drug design, which allows both extracellular cleavage before internalization and intracellular cleavage to release the membrane-permeable payload after internalization. These post hoc analyses were exploratory in nature and not powered to perform formal statistical tests to evaluate the impact of TROP2 expression on the benefit of sac-TMT versus chemotherapy. The trend of efficacy benefit by different TROP2 expression levels observed in this study is also consistent with the biomarker analysis findings in the ASCENT study[23].

In the phase 3 DESTINY-Breast04 trial, T-DXd demonstrated significant improvements in PFS and OS outcomes compared to chemotherapy in patients with metastatic breast cancer with confirmed HER2-low status, including in a small cohort of patients with TNBC

Table 2 | Summary of TRAEs in the safety population

	Sac-TMT (*n*=130)		Chemotherapy (*n*=132)	
	Any grade *n* (%)	Grade 3 or 4 *n* (%)	Any grade *n* (%)	Grade 3 or 4 *n* (%)
TRAEs	130 (100)	82 (63.1)	127 (96.2)	75 (56.8)
Serious TRAEs	27 (20.8)	22 (16.9)	18 (13.6)	11 (8.3)
TRAEs leading to treatment discontinuation	2 (1.5)	2 (1.5)	2 (1.5)	1 (0.8)
TRAEs leading to dose reduction	40 (30.8)	38 (29.2)	21 (15.9)	14 (10.6)
TRAEs leading to treatment interruption	73 (56.2)	49 (37.7)	54 (40.9)	35 (26.5)
TRAEs leading to death	1 (0.8)	0	0	0
Investigations				
Decreased neutrophil count	102 (78.5)	45 (34.6)	98 (74.2)	62 (47.0)
Decreased white blood cell count	99 (76.2)	36 (27.7)	101 (76.5)	48 (36.4)
Decreased platelet count	53 (40.8)	17 (13.1)	34 (25.8)	5 (3.8)
Increased alanine aminotransferase	34 (26.2)	1 (0.8)	47 (35.6)	0
Increased aspartate aminotransferase	30 (23.1)	3 (2.3)	63 (47.7)	1 (0.8)
Blood and lymphatic system disorders				
Anemia	107 (82.3)	38 (29.2)	72 (54.5)	8 (6.1)
Gastrointestinal disorders				
Stomatitis	64 (49.2)	13 (10.0)	6 (4.5)	1 (0.8)
Nausea	52 (40.0)	0	26 (19.7)	0
Vomiting	45 (34.6)	0	18 (13.6)	0
Skin and subcutaneous tissue disorders				
Rash	42 (32.3)	5 (3.8)	1 (0.8)	0

Data cutoff: 30 November 2023. Shown are TRAEs of any grade that occurred in at least 30% of the patients in either treatment group and grade 3 or 4 TRAEs that occurred in at least 10% of the patients in either treatment group. The safety population included all patients who received at least one dose of study treatment. Alopecia: any grade, 28.5% with sac-TMT and 10.6% with chemotherapy; no grade 3 or 4 alopecia; diarrhea: any grade, 13.1% and 3.0%; grade 3 or 4, 0.8% and 0.

(T-DXd, $n = 40$; chemotherapy, $n = 18$) who received one or two previous lines of chemotherapy for metastatic breast cancer[7]. A consistent benefit was observed in our OptiTROP-Breast01 study with a larger sample size in a similar patient population. Sac-TMT had PFS improvement compared to chemotherapy regardless of HER2-low or HER2-zero status. Future research may be required to explore the sequence of applications for these treatment options.

Adverse events reported with sac-TMT were generally consistent with those reported previously, and no unexpected safety signals were observed in this study[11–13,15–17]. The incidence of grade 3 or higher TRAEs was similar between the two treatment groups despite almost three times longer median duration of exposure to sac-TMT compared to chemotherapy. TRAEs resulting in treatment discontinuation were reported in only 1.5% of patients who received sac-TMT. Sac-TMT demonstrated a different safety profile from chemotherapy. The most common grade 3 or higher TRAEs with sac-TMT were decreased neutrophil count and anemia, which could be managed with dose modifications and appropriate supportive care.

T-DXd, a HER2-directed ADC with deruxtecan (an exatecan derivative) as its payload, demonstrated an incidence rate of 10.4–15.8% for interstitial lung disease or pneumonitis[7,24–26]. Enfortumab vedotin-ejfv, a nectin-4–directed ADC with a monomethyl auristatin E as the payload, has been frequently associated with peripheral neuropathy (46.3%) and ocular disorders (18.6%)[27]. As the first approved TROP2-targeted ADC, the most common TRAEs in the Chinese TNBC patient population for SG were hematologic toxicity, including decreased neutrophil count (any grade: 85.0%; grade 3 or higher: 62.5%), anemia (82.5%; 21.3%) and decreased white blood cell count (81.3%; 48.8%), along with gastrointestinal toxicity, with vomiting (55.0%; 0), nausea (50.0%; 0) and diarrhea (36.3%; 2.5%)[28]. Such a safety profile is typically expected with an SN-38 payload, the active metabolite of irinotecan. Sac-TMT is a TROP2-directed ADC developed with a more stable linker conjugated to a belotecan-derivative topoisomerase I inhibitor as the payload[14]. As such, sac-TMT showed a different safety profile compared to other ADCs. This study showed that the most common TRAEs in the Chinese TNBC patient population for sac-TMT were anemia (any grade: 82.3%; grade 3 or higher: 29.2%), decreased neutrophil count (78.5%; 34.6%), decreased white blood cell count (76.2%; 27.7%) and decreased platelet count (40.8%; 13.1%), followed by stomatitis (49.2%; 10.0%). Moreover, peripheral neuropathy and interstitial lung disease with sac-TMT occurred at low frequency (2.3% and 0.8%, respectively); xerophthalmia with sac-TMT occurred in three patients (2.3%); and blurred vision with sac-TMT occurred in two patients (1.5%).

Our study had several limitations, including that it is a clinical study conducted only in China. Nevertheless, the prevailing therapy landscape for metastatic TNBC is analogous in China and globally, and the global studies of other ADCs, such as SG, demonstrated consistent efficacy and safety results across Chinese and global patient populations[9,10,28]. Multiple global multicenter clinical studies of sac-TMT (NCT06393374, NCT06074588 and NCT06132958) are ongoing to further confirm its extensive applicability. Another limitation of the present study is the impact of the COVID-19 pandemic on treatment administration in both groups. Of the patients who received study treatment, 14.6% in the sac-TMT group and 7.8% in the chemotherapy group experienced delays in receiving their assigned treatments due to COVID-19 infections, which could have impacted the study outcomes. Excluding the effect of COVID-19 on administration, the median relative dose intensity with sac-TMT would be increased to 94.6%.

In conclusion, the OptiTROP-Breast01 study demonstrated that sac-TMT significantly improved PFS compared to chemotherapy in patients with previously treated metastatic TNBC with a manageable safety profile. Because the population was drawn from a broad range of patients with previously treated metastatic TNBC, the study findings support sac-TMT as an effective treatment option for this patient population that has limited treatment options.

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/s41591-025-03630-w.

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Methods

Inclusion and ethics

This trial was approved by the research ethics committee of each participating institution. All participating patients read and signed an informed consent form. This trial was performed in accordance with Good Clinical Practice standards, the Declaration of Helsinki and relevant laws and regulations.

An unblinded independent data and monitoring committee (IDMC), consisting of qualified scientists not affiliated with the investigators or sponsor, was established to provide trial oversight. The IDMC was responsible for the following: review of safety data at planned intervals, identification of any safety concerns that arose during the course of the study and review of the efficacy and safety data during prespecified interim analyses for efficacy.

Patients

Patients were eligible for enrollment if they met the following criteria: histologically confirmed diagnosis of TNBC according to standard American Society of Clinical Oncology–College of American Pathologists criteria based on local laboratory assessment and previous treatment with two or more systemic therapies (with at least one for metastatic disease and previous taxane therapy) for unresectable, locally advanced or metastatic disease. For (neo)adjuvant chemotherapy, if progression occurred during treatment or within 12 months after treatment discontinuation, it would be considered one regimen for advanced setting. A full list of inclusion and exclusion criteria is available in the protocol and the Supplementary Information (Supplementary Table 4).

Study design and treatment

This study was a phase 3, multicenter, open-label, randomized, controlled trial (OptiTROP-Breast01, NCT05347134). Patients were randomly assigned in a 1:1 ratio to receive sac-TMT or single-agent chemotherapy. Patients in the sac-TMT group received 5 mg kg^{-1} sac-TMT intravenously once every 2 weeks over a 28-d cycle. Patients in the chemotherapy group received one of the following four options at the physician's discretion: eribulin, given intravenously at 1.4 mg m^{-2} on days 1 and 8 of a 21-d cycle; capecitabine, given as oral tablets at 1,000–1,250 mg m^{-2} twice daily on days 1 through 14 of a 21-d cycle; gemcitabine, given intravenously at 1,000 mg m^{-2} on days 1 and 8 of a 21-d cycle; or vinorelbine, given intravenously at 25 mg m^{-2} on days 1 and 8 of a 21-d cycle. All treatments were administered to patients until disease progression, unacceptable toxicity or any other reason for discontinuation.

Randomization and blinding

Patients were stratified at randomization according to lines of prior therapy (2 or 3 versus >3) and presence of liver metastases (yes versus no). The records of the random allocation sequences were maintained by an independent, third-party and unblinded statistician. The randomization of patients was carried out through an interactive response technology system. An IDMC was established to review the interim analysis results provided by an independent statistical team. After interim analysis, blinding was still maintained until the final analysis. A rigorous 'firewall' was implemented between the independent submission team and the continuation study team, which includes local investigators.

Endpoints and assessments

The primary endpoint was PFS as assessed by BICR using Response Evaluation Criteria in Solid Tumors version 1.1. The secondary endpoints included PFS by investigator assessment, OS, ORR, DCR, DOR, TTR and safety.

The baseline characteristics were collected from a combination of medical files, interviews and medical examinations. Tumor response was assessed by radiographic imaging every 6 weeks for the first year and every 12 weeks thereafter, until disease progression (confirmed by BICR). Other assessments, such as laboratory tests, Eastern Cooperative Oncology Group (ECOG) performance status evaluation and physical examinations, were conducted throughout the treatment period to assess the condition of patients. Adverse events were graded per Common Terminology Criteria for Adverse Events version 5.0 and were summarized using Medical Dictionary for Regulatory Activities preferred terms version 25.0. Protein-level expression of TROP2 was assessed by immunohistochemistry using anti-TROP2 antibody (EPR20043 by Abcam) at a dilution of 1:3,000 (MEDx Translational Medicine Co., Ltd.). TROP2 expression was scored semiquantitatively using the H-score method. Based on previous study data, the cutoff point for high versus low TROP2 expression was prespecified to 200 (ref. 13): H-score >200 (high TROP2 expression) and H-score ≤200 (low TROP2 expression).

Statistical analysis

The planned sample size was 254 patients. Under the assumption of an HR for PFS (sac-TMT versus chemotherapy) of 0.60 and the expected median PFS of 2 months for the chemotherapy group, 183 events of progression or death would provide approximately 93% power to detect a significant between-group difference in PFS. To control the family-wise type I error at a one-sided alpha level of 0.025, a hierarchical testing procedure was implemented with a prespecified order of PFS, OS and ORR (Supplementary Fig. 2). An interim analysis and a final analysis of PFS were planned to be conducted for this study. The timing of the interim analysis of OS coincided with the timing of the protocol-specified final analysis of PFS. The Lan–DeMets alpha-spending function approximating the O'Brien–Fleming stopping boundary was used to allocate alpha. At the data cutoff for the protocol-specified interim analysis of PFS (21 June 2023), a total of 140 BICR-assessed PFS events had occurred. The multiplicity-adjusted, one-sided alpha at this interim analysis (determined using the Lan–DeMets O'Brien–Fleming spending function) was 0.0104. Similarly, at the data cutoff for the protocol-specified interim analysis of OS (30 November 2023), a total of 113 OS events had occurred, and the one-sided alpha at this interim analysis was 0.0042.

Efficacy analysis was performed in the intention-to-treat population, which included all patients who underwent randomization. PFS and OS were analyzed using the Kaplan–Meier method, with medians and corresponding 95% CIs determined according to the Brookmeyer and Crowley method with log–log transformation. The treatment effect was compared by a stratified log-rank test. HRs and their 95% CIs were estimated by a stratified Cox proportional hazards model. The percentage of patients with an objective response was compared between the treatment groups using the Cochran–Mantel–Haenszel method. More detailed descriptions of the statistical analysis are provided in the statistical analysis plan. All calculations and analyses were performed using SAS software (version 9.4).

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, the sponsor shares anonymized individual patient data upon reasonable request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The data provided include demographic, efficacy and safety information. Approval of such requests is at the sponsor's discretion and depends 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 mict@kelun.com. In response to the inquiry, the timeframe for responding

to requests is approximately 2 weeks. The redacted version of the trial protocol and statistical analysis plan is in the supplementary documents.

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Author contributions
Conception and design: B.X., X.J. and Y.D. Provision of study materials or patients: B.X., Y.Y., Y.F., Q.O., L.S., X.W., W.L., M.L., X.Y., S.W., T.S., Y.T., X.T., Z.T. and Z.S. Collection and assembly of data: B.X., Y.Y., Y.F., Q.O., L.S., X.W., W.L., M.L., X.Y., S.W., T.S., Y.T., X.T., Z.T. and Z.S. Data analysis and interpretation: B.X., Y.Y., J.G., X.J., Y.D. and G.L. Writing, review and editing of the paper: all authors. Final approval of the paper: all authors. Accountable for all aspects of the work: all authors.

Competing interests
B.X. has served as advisor or consultant for Novartis and AstraZeneca. J.G., X.J., Y.D. and G.L. are employees of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. The other authors declare no competing interests.

Additional information
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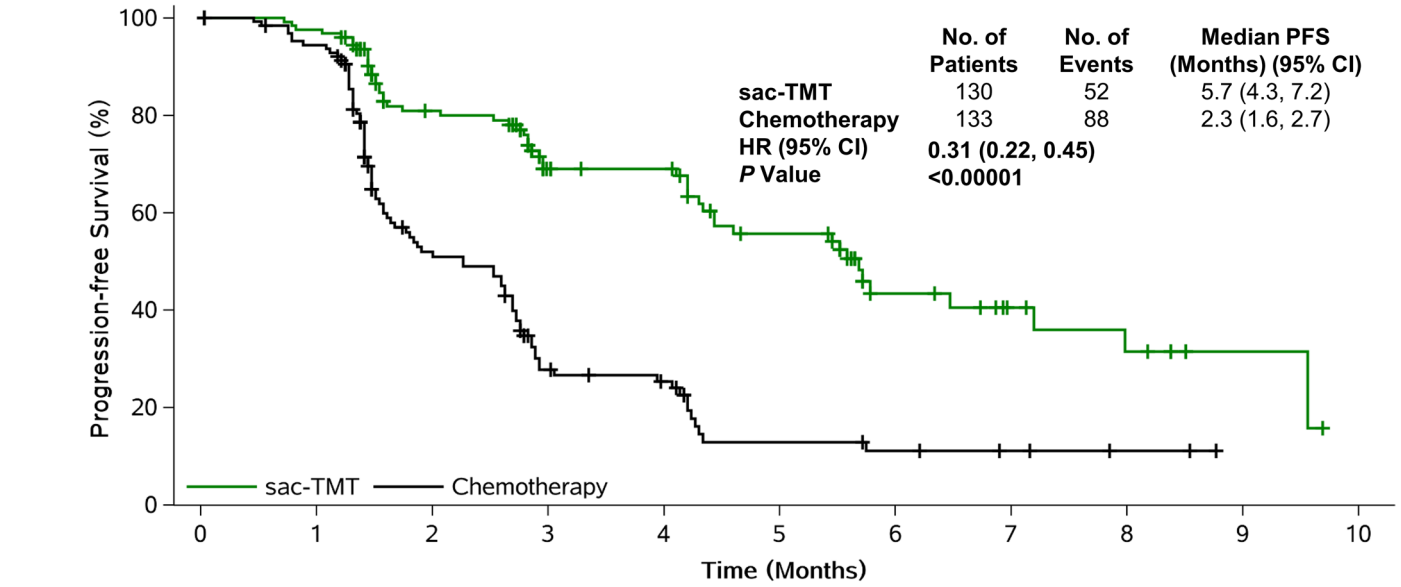

No. at Risk

sac-TMT	130	122	84	53	50	35	16	10	7	2	0
Chemotherapy	133	119	52	24	19	8	6	4	2	0	

Extended Data Fig. 1 | Kaplan-Meier Curves for PFS by BICR Assessment (Interim Analysis). Data cutoff: June 21, 2023; the protocol-specified interim analysis of PFS. The 95% CI of median PFS was determined using the Brookmeyer and Crowley method with log-log transformation. HR along with 95% CI was estimated by a stratified Cox proportional hazards model. The *P* value was calculated by a stratified log-rank test. The multiplicity-adjusted, one-sided alpha at this interim analysis (determined using the Lan-DeMets O'Brien-Fleming spending function) was 0.0104. The exact one-sided *P* value was 2.0×10^{-11}. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; sac-TMT, sacituzumab tirumotecan.

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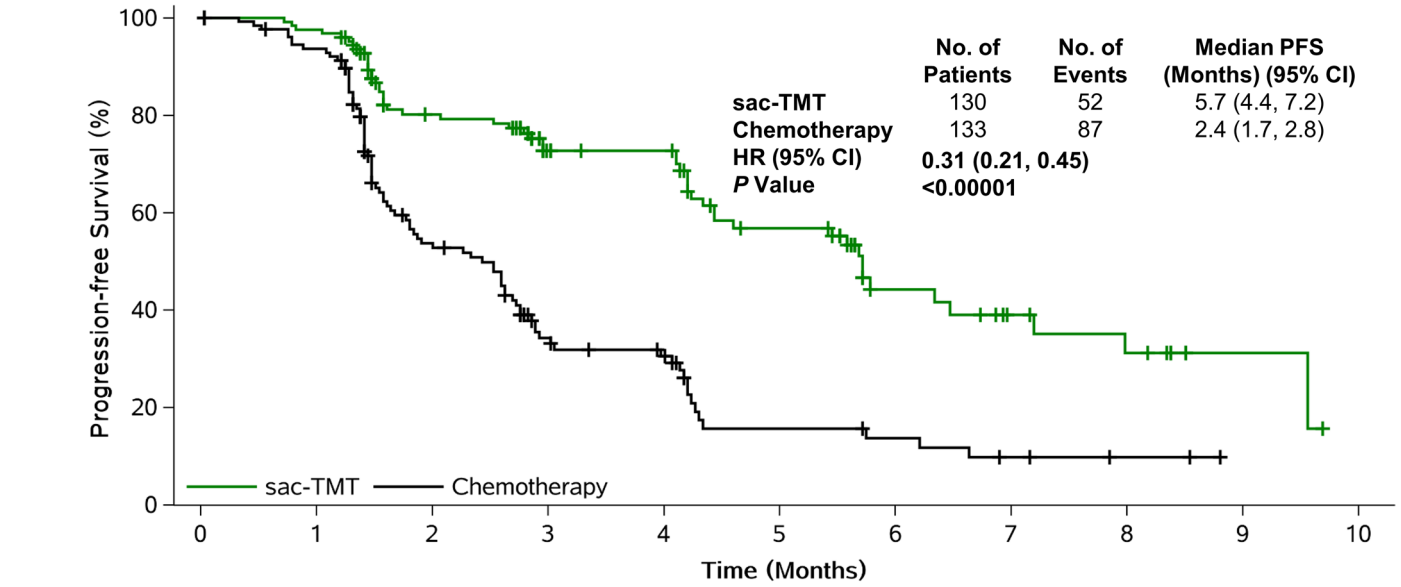

No. at Risk											
sac-TMT	130	122	84	57	54	36	17	11	8	2	0
Chemotherapy	133	118	56	29	23	9	7	4	2	0	

Extended Data Fig. 2 | Kaplan-Meier Curves for PFS by Investigator Assessment (Interim Analysis). Data cutoff: June 21, 2023; the protocol-specified interim analysis of PFS. The 95% CI of median PFS was determined using the Brookmeyer and Crowley method with log-log transformation. HR along with 95% CI was estimated by a stratified Cox proportional hazards model. The *P* value was calculated by a stratified log-rank test. The exact one-sided *P* value was 4.0×10^{-11}. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; sac-TMT, sacituzumab tirumotecan.

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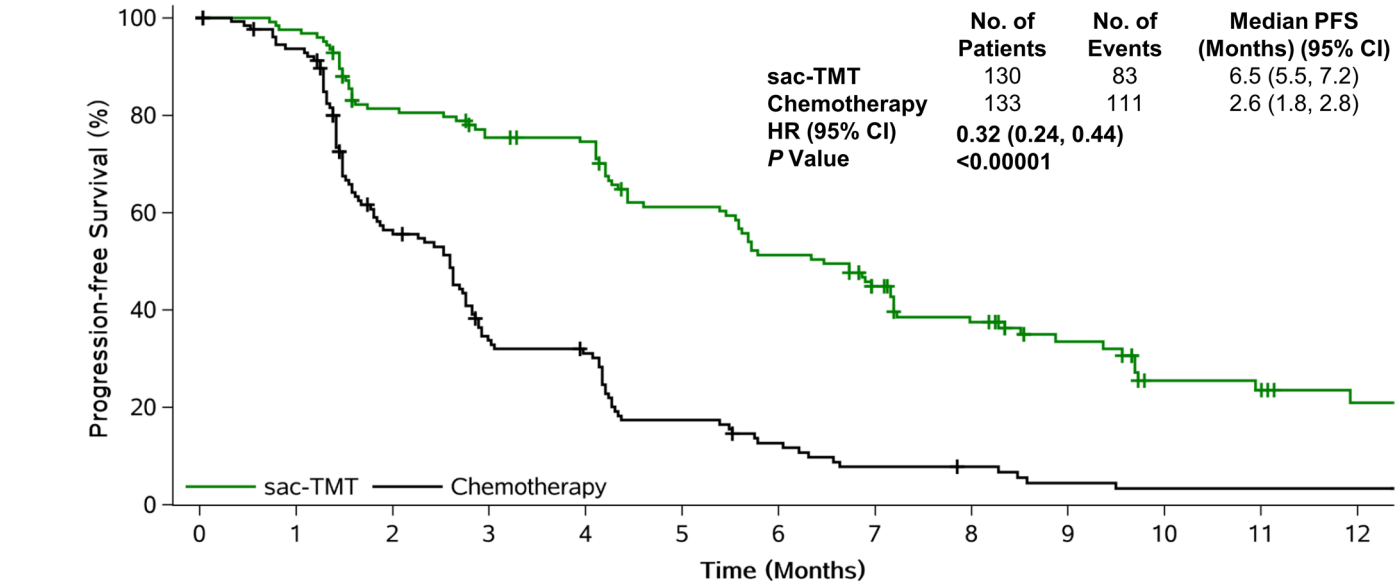

No. at Risk

sac-TMT	130	122	97	88	85	68	57	45	35	23	13	12	8
Chemotherapy	133	118	66	38	34	19	13	8	7	4	3	3	3

Extended Data Fig. 3 | Kaplan-Meier Curves for PFS by Investigator Assessment (Final Analysis). Data cutoff: November 30, 2023; the protocol-specified final analysis of PFS. The 95% CI of median PFS was determined using the Brookmeyer and Crowley method with log-log transformation. HR along with 95% CI was estimated by a stratified Cox proportional hazards model. The *P* value was calculated by a stratified log-rank test. The exact one-sided *P* value was 2.9×10^{-14}. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; sac-TMT, sacituzumab tirumotecan.

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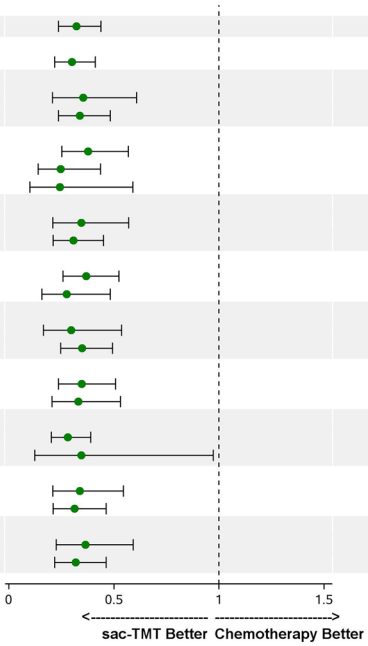
Subgroup	No. of Patients	Median PFS (95% CI) sac-TMT	Median PFS (95% CI) Chemotherapy	HR for PFS (95% CI)
All patients	263	6.5 (5.5-7.2)	2.6 (1.8-2.8)	0.32 (0.24-0.44)
Age				
<65 yr	238	6.9 (5.6-8.0)	2.6 (1.8-2.8)	0.30 (0.22-0.41)
ECOG Performance Status				
0	79	6.7 (4.2-8.9)	2.6 (1.5-4.1)	0.35 (0.21-0.61)
1	184	6.3 (4.4-7.2)	2.6 (1.8-2.8)	0.34 (0.24-0.48)
Prior Line of Therapy				
2	138	7.2 (5.7-8.3)	2.6 (1.9-2.9)	0.38 (0.25-0.57)
3	89	4.6 (4.1-10.9)	1.8 (1.4-2.9)	0.25 (0.14-0.44)
>3	36	5.7 (2.7-8.9)	2.6 (1.4-4.1)	0.24 (0.10-0.59)
Liver Metastases				
Yes	90	4.2 (1.6-5.8)	1.9 (1.4-2.5)	0.35 (0.21-0.57)
No	173	7.2 (5.7-9.7)	2.8 (1.9-4.0)	0.31 (0.21-0.45)
Initial Diagnosis of TNBC				
Yes	180	5.7 (4.6-7.2)	2.3 (1.6-2.9)	0.37 (0.26-0.52)
No	83	7.2 (4.2-9.7)	2.6 (1.7-2.9)	0.28 (0.16-0.48)
Prior Treatment with PD-1 or PD-L1 Inhibitors				
Yes	68	5.7 (4.4-9.7)	2.8 (2.3-4.2)	0.30 (0.16-0.54)
No	195	6.7 (4.4-8.0)	2.3 (1.6-2.8)	0.35 (0.25-0.49)
Lymph Node Metastases				
Yes	156	5.7 (4.4-7.2)	2.5 (1.7-2.7)	0.35 (0.24-0.51)
No	107	6.7 (5.5-9.7)	2.8 (1.6-3.1)	0.33 (0.21-0.53)
Visceral Metastases				
Yes	228	5.7 (4.4-7.2)	2.6 (1.8-2.8)	0.28 (0.20-0.39)
No	35	8.3 (4.6-NE)	4.2 (1.5-6.6)	0.35 (0.12-0.97)
HER2 Expression				
Low Expression	112	5.6 (4.1-8.9)	2.6 (1.8-2.9)	0.34 (0.21-0.55)
0	151	6.5 (5.6-8.0)	2.3 (1.6-2.8)	0.31 (0.21-0.46)
Course of Disease (Months)				
≤ 24	92	5.8 (4.2-8.0)	2.3 (1.6-2.8)	0.36 (0.22-0.59)
>24	171	7.0 (4.6-8.3)	2.6 (1.7-2.9)	0.32 (0.22-0.46)



Extended Data Fig. 4 | Forest Plot of PFS (per Investigator Assessment) in Key Patient Subgroups. Data cutoff: November 30, 2023; the protocol-specified final analysis of PFS. Statistical analysis was not performed when the number of patients in the subgroup was less than 10% of the total patients. HRs along with 95% CIs were estimated using an unstratified Cox proportional hazards model in each subgroup. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NE, not estimable; PD-1: programmed death-1; PD-L1: programmed death-ligand 1; PFS, progression-free survival; sac-TMT, sacituzumab tirumotecan; TNBC, triple-negative breast cancer.

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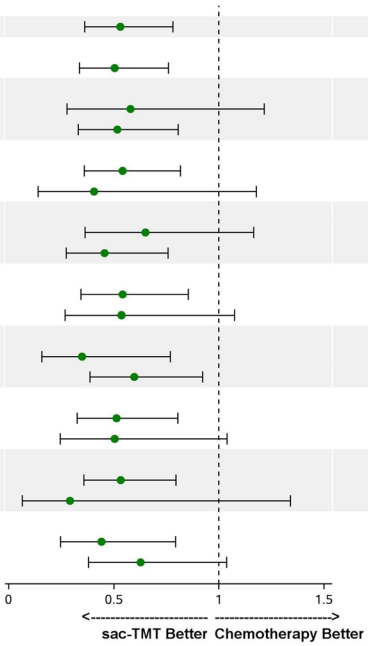
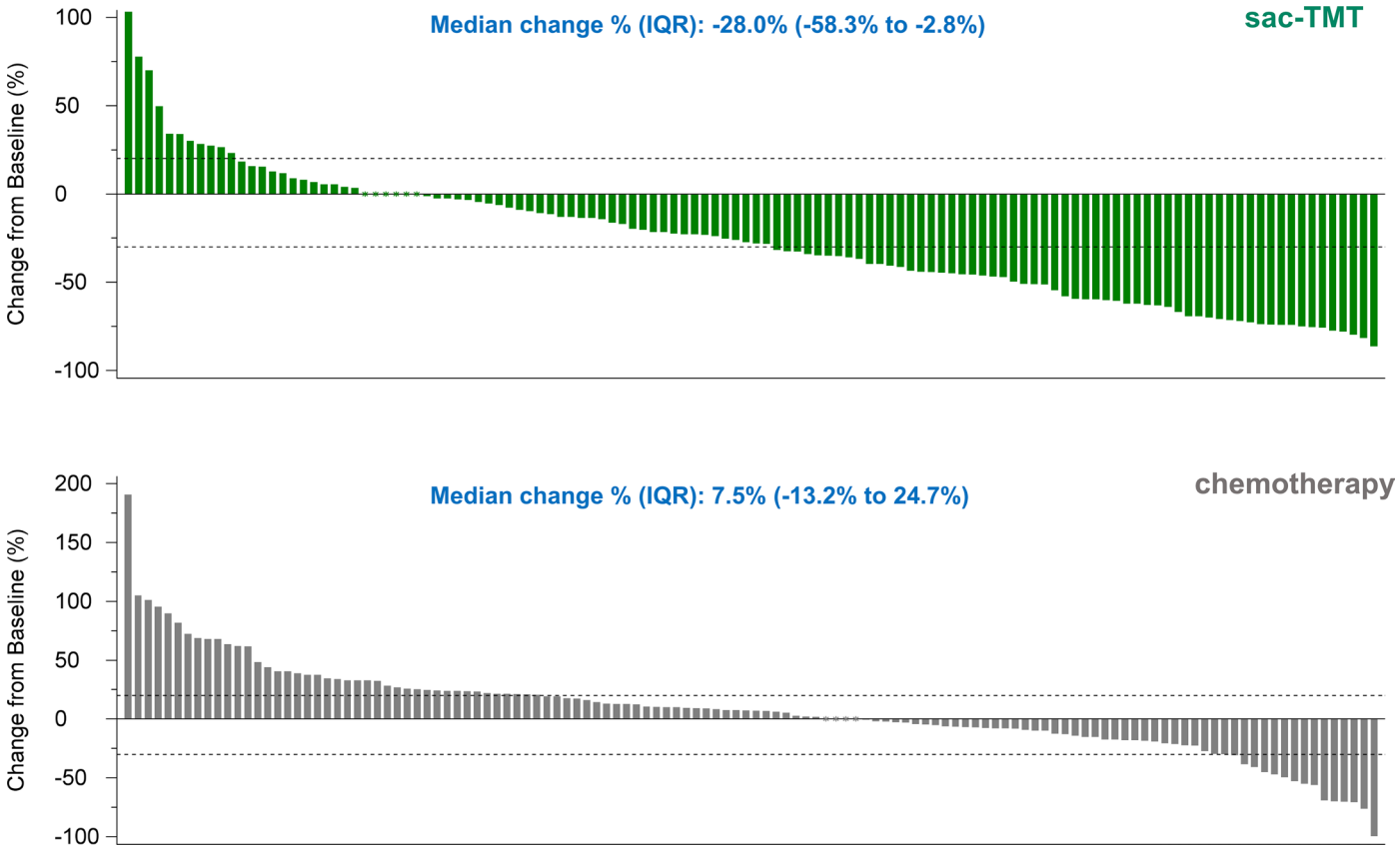
Subgroup	No. of Patients	Median OS (95% CI) sac-TMT	Chemotherapy	HR for OS (95% CI)
All patients	263	NR (11.2-NE)	9.4 (8.5-11.7)	0.53 (0.36-0.78)
Age				
<65 yr	238	NR (11.2-NE)	9.4 (8.5-11.7)	0.50 (0.34-0.76)
ECOG Performance Status				
0	79	NR (9.9-NE)	11.2 (7.7-NE)	0.58 (0.28-1.22)
1	184	14.3 (10.4-NE)	8.9 (7.6-11.5)	0.52 (0.33-0.81)
Prior Line of Therapy				
2 or 3	227	14.3 (11.2-NE)	9.8 (8.4-11.8)	0.54 (0.36-0.82)
>3	36	NR (8.5-NE)	9.2 (5.0-NE)	0.41 (0.14-1.18)
Liver Metastases				
Yes	90	9.9 (7.7-NE)	8.7 (6.0-9.4)	0.65 (0.36-1.17)
No	173	NR (NE-NE)	11.0 (8.5-NE)	0.46 (0.27-0.76)
Initial Diagnosis of TNBC				
Yes	180	NR (9.9-NE)	9.4 (8.5-11.8)	0.54 (0.34-0.85)
No	83	14.3 (10.3-NE)	11.0 (7.5-12.7)	0.54 (0.27-1.07)
Prior Treatment with PD-1 or PD-L1 Inhibitors				
Yes	68	NR (9.9-NE)	11.2 (8.3-11.8)	0.35 (0.16-0.77)
No	195	14.3 (10.3-NE)	9.4 (7.7-12.7)	0.60 (0.39-0.92)
Lymph Node Metastases				
Yes	156	11.5 (9.9-NE)	8.4 (6.4-11.2)	0.51 (0.33-0.81)
No	107	NR (NE-NE)	11.5 (9.4-NE)	0.50 (0.25-1.04)
Visceral Metastases				
Yes	228	14.3 (10.4-NE)	9.4 (8.3-11.5)	0.53 (0.36-0.80)
No	35	NR (8.4-NE)	11.8 (5.7-NE)	0.29 (0.06-1.34)
HER2 Expression				
Low Expression	112	NR (11.5-NE)	8.6 (6.4-NE)	0.44 (0.25-0.79)
0	151	14.3 (9.9-NE)	9.8 (8.6-12.7)	0.63 (0.38-1.04)



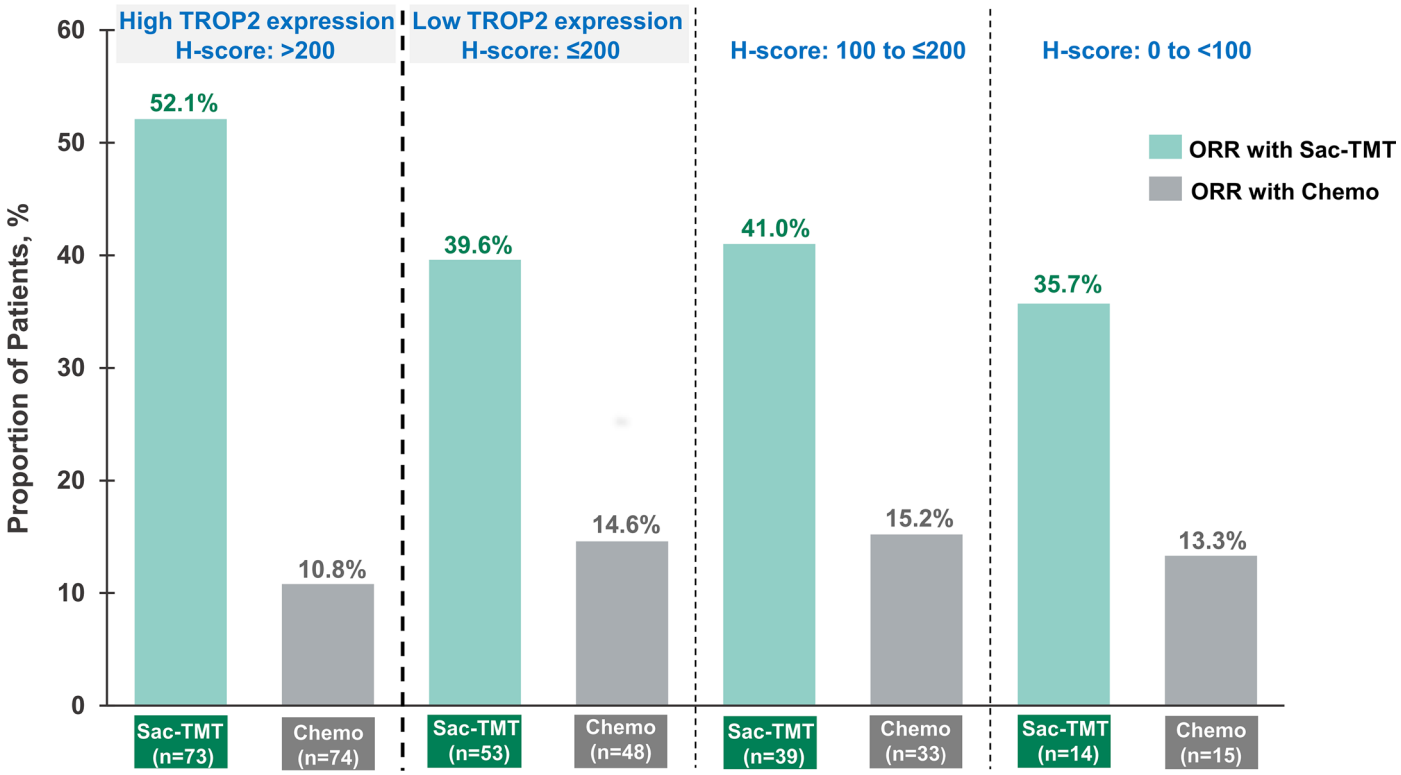
Extended Data Fig. 5 | Forest Plot of OS in Key Patient Subgroups. Data cutoff: November 30, 2023; the protocol-specified interim analysis of OS. Statistical analysis was not performed when the number of patients in the subgroup was less than 10% of the total patients. HRs along with 95% CIs were estimated using an unstratified Cox proportional hazards model in each subgroup. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival; PD-1: programmed death-1; PD-L1: programmed death-ligand 1; sac-TMT, sacituzumab tirumotecan; TNBC, triple-negative breast cancer.

https://doi.org/10.1038/s41591-025-03630-w



Extended Data Fig. 6 | Best Change in Target Lesions by BICR. Data cutoff: November 30, 2023. BICR, blinded independent central review; IQR, interquartile range; sac-TMT, sacituzumab tirumotecan.

https://doi.org/10.1038/s41591-025-03630-w



Extended Data Fig. 7 | Overall Response (per BICR) by TROP2 Expression. Data cutoff: November 30, 2023. BICR, blinded independent central review; Chemo, chemotherapy; ORR, objective response rate; sac-TMT, sacituzumab tirumotecan; TROP2, trophoblast cell surface antigen 2.

https://doi.org/10.1038/s41591-025-03630-w

Extended Data Table 1 | Tumor response by BICR

	Sac-TMT (N = 130)	Chemotherapy (N = 133)
ORR, n (%)	59 (45.4)	16 (12.0)
95% CI	36.6, 54.3	7.0, 18.8
P value	<0.00001	
DCR, n (%)	102 (78.5)	70 (52.6)
95% CI	70.4, 85.2	43.8, 61.3
Median DOR (95% CI), months	7.1 (5.6, NE)	3.0 (2.5, NE)
HR (95% CI) †	0.50 (0.22, 1.13)	
Median TTR (range), months	1.4 (1.2, 5.7)	1.5 (1.2, 3.0)

Data cutoff: 30 November 2023. †HR along with 95% CI was estimated using a stratified Cox proportional hazards model. The *P* value was calculated using the Cochran–Mantel–Haenszel method stratified by lines of prior therapy (2 or 3 versus >3) and presence of liver metastases (yes versus no). The exact one-sided *P* value was 2.2×10^{-9}.

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Extended Data Table 2 | Tumor response by investigator assessment

	Sac-TMT (N = 130)	Chemotherapy (N = 133)
ORR, no. (%)	53 (40.8)	15 (11.3)
95% CI	32.2, 49.7	6.5, 17.9
P value	<0.00001	
DCR, no. (%)	101 (77.7)	71 (53.4)
95% CI	69.6, 84.5	44.5, 62.1
Median DOR (95% CI)-months	7.1 (4.5, 8.2)	3.7 (1.4, 7.2)
HR (95% CI) [†]	0.41 (0.19, 0.88)	
Median TTR (range)-months	1.6 (1.2, 6.9)	1.4 (1.2, 2.9)

Data cutoff: 30 November 2023. [†]HR along with 95% CI was estimated using a stratified Cox proportional hazards model. The *P* value was calculated using the Cochran–Mantel–Haenszel method stratified by lines of prior therapy (2 or 3 versus >3) and presence of liver metastases (yes versus no). The exact one-sided *P* value was 5.4×10^{-8}.

https://doi.org/10.1038/s41591-025-03630-w

Extended Data Table 3 | Exploratory efficacy analysis by TROP2 expression

	TROP2 expression					
	H-score: 0 to <100		H-score: 100 to ≤200		H-score: >200	
	Sac-TMT (N = 14)	Chemo (N = 15)	Sac-TMT (N = 39)	Chemo (N = 33)	Sac-TMT (N= 73)	Chemo (N= 74)
Median PFS (95%CI), mo	4.1 (1.5 – 7.2)	2.5 (1.2 – 2.8)	6.7 (4.4 – 9.7)	2.6 (1.4 – 2.8)	8.3 (5.6 – 9.4)	2.3 (1.6 – 2.9)
HR (95% CI)†	0.58 (0.22 – 1.54)		0.30 (0.17 – 0.54)		0.29 (0.19 – 0.46)	
ORR, no. (%)	35.7	13.3	41.0	15.2	52.1	10.8
95%CI	12.8, 64.9	1.7, 40.5	25.6, 57.9	5.1, 31.9	40.0, 63.9	4.8, 20.2

Data cutoff: 30 November 2023. †HRs along with 95% CIs were estimated using a stratified Cox proportional hazards model.

nature portfolio

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Last updated by author(s): Feb 8, 2025

Reporting Summary

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
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☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

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	Data were collected via an internet-based, controlled electronic data capture (EDC) system for further analysis.
Data analysis	All statistical analyses were performed using SAS (version 9.4).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

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To protect the privacy of study participants and proprietary information, the sponsor 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 non-conflict of interest. The data provided include demographic, efficacy, and safety information. Approval of such requests is at the sponsor's discretion and depends 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 mict@kelun.com. In response to the inquiry,

please be informed that the timeframe for responding to requests is approximately 2 weeks. The redacted version of the trial protocol and statistical analysis plan is in the supplementary documents.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The sex of patients in the trial was self-reported. All 263 patients enrolled were female.
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	Patients were randomly assigned to receive either sac-TMT (n = 130) or chemotherapy of the physician's choice (n = 133). Across both treatment groups, the median age of the enrolled patients was 51.0 years, and 90.5% of patients were aged less than 65 years. More than two-thirds of cases (68.4%) were confirmed as TNBC at initial diagnosis. All patients received taxanes as part of prior therapy. Additionally, most patients (92.8%) received prior anthracyclines, 25.9% of patients received programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors, and 88.6% of patients received prior neoadjuvant or adjuvant therapy. Overall, 86.7% of patients presented with visceral metastases and 34.2% of patients presented with liver metastases. Almost half of the patients (47.5%) had received three or more previous chemotherapy regimens in metastatic setting. The baseline demographics and clinical characteristics were generally balanced between the treatment groups (Table 1).
Recruitment	Between 11 August 2022 and 26 April 2023, 396 patients were assessed for eligibility. A total of 263 patients with locally advanced, recurrent, or metastatic TNBC were enrolled across 49 sites in China. Patients were eligible for enrollment if they met the following criteria: histologically confirmed diagnosis of TNBC according to standard American Society of Clinical Oncology–College of American Pathologists criteria based on local lab assessment, and previous treatment with two or more systemic therapies (with at least one for metastatic disease and previous taxane therapy) for unresectable, locally advanced, or metastatic disease. For (neo)adjuvant chemotherapy, if progression occurred during treatment or within 12 months after treatment discontinuation, it would be considered one regimen for advanced setting. A full list of inclusion and exclusion criteria is available in the protocol and Supplementary Information (Supplementary Table S4). A potential bias may exist in the possible difficulty of recruiting patients from some remote areas of China, but this is unlikely to have a major impact on the results. Participants did not receive compensation for study participation; however, they were reimbursed for certain expenses (e.g., hotel rooms, transportation, tumor tissue biopsies).
Ethics oversight	The trial was approved by the research ethics committee of each participating institution. All participating patients read and signed an informed consent form. This trial was performed in accordance with Good Clinical Practice standards, the Declaration of Helsinki, and relevant laws and regulations.

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

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

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

Sample size	The planned sample size was 254 patients. Sample size was calculated based on the primary endpoint of PFS per BICR. Under the assumption of a HR for PFS (sac-TMT versus chemotherapy) of 0.60 and the expected median PFS of 2 months for the chemotherapy group, 183 events of progression or death would provide approximately 93% power to detect a significant between-group difference in PFS, with a one-sided alpha of 0.025. Patients were enrolled in a 1:1 ratio over an anticipated 15-month recruitment period, considering a cumulative dropout rate of 10%.
Data exclusions	Efficacy analysis was performed in the intention-to-treat population, which included all patients who underwent randomization. All patients who received at least one dose of study treatment were included in the safety analysis. Only one patient assigned to receive chemotherapy received no study treatment and was included in the efficacy analysis but not in the safety analysis.
Replication	Not applicable as this was a clinical trial.
Randomization	Patients were stratified at randomization according to lines of prior therapy (2 or 3 vs >3) and presence of liver metastases (yes vs no). The records of the random allocation sequences were maintained by an independent, third-party, and unblinded statistician. The randomization of patients was carried out through an interactive response technology system. Patients were randomly assigned in a 1:1 ratio to receive sac-TMT or single-agent chemotherapy. Patients in the sac-TMT group received 5 mg/kg sac-TMT intravenously once every two weeks over a 28-day cycle. Patients in the chemotherapy group received one of the following four options at the physician's discretion: eribulin, given intravenously at 1.4 mg/m2 on days 1 and 8 of a 21-day cycle; capecitabine, given as oral tablets at 1000–1250 mg/m2 twice daily on days 1

	through 14 of a 21-day cycle; gemcitabine, given intravenously at 1000 mg/m2 on days 1 and 8 of a 21-day cycle; or vinorelbine, given intravenously at 25 mg/m2 on days 1 and 8 of a 21-day cycle.
Blinding	This study was an open-label design.

Reporting for specific materials, systems and methods

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.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Antibodies

Antibodies used	Protein-level expression of TROP2 was assessed by immunohistochemistry using anti-TROP2 antibody (EPR20043 by Abcam) at a dilution of 1:3000.
Validation	Antibodies used in this study are all commercially available. Validation of each antibody for the species, application, relevant citations and antibody profiles are available online from the manufacturer's website.

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	NCT05347134
Study protocol	Study protocol is provided and submitted with the manuscript as the supplementary documents.
Data collection	Between 11 August 2022 and 26 April 2023, 396 patients were assessed for eligibility. A total of 263 patients with locally advanced, recurrent, or metastatic TNBC were enrolled across 49 sites in China.
Outcomes	The primary endpoint was PFS as assessed by BICR using Response Evaluation Criteria in Solid Tumors version 1.1. PFS was defined as the time from randomization to disease progression or death, whichever occurred first. The secondary endpoints included PFS by investigator assessment, OS, ORR, DCR, DOR, TTR, and safety. OS was defined as the time from randomization to death due to any cause. ORR was defined as the proportion of patients with complete response (CR) or partial response (PR) as the best overall response. DCR was defined as the proportion of patients with CR, PR, or stable disease (SD) as the best overall response. DOR was defined as the time from the date of the first response to progression or death, whichever occurred first. TTR was defined as the time from randomization to the first response (CR/PR).

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*