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CLINICAL TRIAL PROTOCOL

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TroFuse-011 study design: sacituzumab tirumotecan with or without pembrolizumab for advanced triple-negative breast cancer with PD-L1 CPS <10

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ABSTRACT

Patients with advanced TNBC with PD-L1 CPS < 10 are typically treated with chemotherapy and experience poor outcomes. Sacituzumab tirumotecan (sac-TMT; MK-2870/SKB264) is a trophoblast cell-surface antigen 2 (TROP2)–directed antibody-drug conjugate with a unique, bifunctional linker that maximizes payload delivery to tumor cells. Combining sac-TMT with immunotherapy may improve outcomes given their complementary respective direct cytotoxic and immune-mediated antitumor effects regardless of tumor PD-L1 expression. The TroFuse-011 study evaluates sac-TMT with/without pembrolizumab versus treatment of physician's choice (TPC; paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin) in previously untreated, centrally confirmed, locally recurrent unresectable or metastatic TNBC with PD-L1 CPS <10. Eligible adults with measurable disease per RECIST version 1.1, ECOG PS 0/1, and tumor tissue sample for central PD-L1 and TROP2 testing will be randomized to receive sac-TMT (arm A), sac-TMT plus pembrolizumab (arm B), or TPC (arm C). Primary endpoints include progression-free survival (PFS; arm A vs C and arm B vs C) and overall survival (OS; arm A vs C). Secondary endpoints include PFS (arm B vs A), OS (arm B vs C and arm B vs A), objective response rate (arm A vs C and arm B vs C), duration of response, patient-reported outcomes, and safety. Enrollment is ongoing.

Clinical trial registration: www.clinicaltrials.gov identifier is NCT06841354.

PLAIN LANGUAGE SUMMARY

Triple-negative breast cancer (TNBC), a type of breast cancer which lacks expression of the estrogen receptor, the progesterone receptor, and the human epidermal growth factor receptor 2, represents approximately 10% to 20% of all breast cancers. Chemotherapy is a current first-line standard-of-care treatment for patients with advanced TNBC that has no or a low amount of a protein called PD-L1. However, many patients experience poor outcomes and additional treatment options are needed. A drug called sacituzumab tirumotecan (sac-TMT) binds to a protein on the surface of cancer cells called trophoblast cell-surface antigen 2 and carries chemotherapy to those cells; this kills the cancer cells while minimizing the killing of healthy cells. This phase III study is investigating sac-TMT, either alone (treatment arm 1) or in combination with pembrolizumab (a drug that helps the immune system fight cancer; treatment arm 2) versus treatment of physician's choice (treatment arm 3) in females or males 18 years of age or older who have advanced TNBC and have PD-L1 protein on less than 10% of cells in their tumors. Participants are randomly assigned to study treatment. Participants will be assessed for how long they live without their disease getting worse, how long they live overall, whether the tumor shrinks or goes away completely, and how long they respond to treatment; safety and quality of life will also be evaluated. This study is currently enrolling participants.

ARTICLE HISTORY

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KEYWORDS

Triple-negative breast cancer; pembrolizumab; antibody-drug conjugate; targeted therapy; sacituzumab tirumotecan; phase III; clinical trial protocol; PD-L1 CPS <10

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Article highlights

Background
- Today, chemotherapy is the standard first-line treatment for patients with metastatic TNBC with PD-L1 CPS <10 who are not candidates for immunotherapy per current standard of care.
- Treatment outcomes for metastatic TNBC are poor, with approximately 50% of patients who receive first-line treatment in the metastatic setting not going on to receive a second line of therapy; real-world evidence indicates that within this population, outcomes are worse for patients with PD-L1–positive tumors compared with those with PD-L1–negative tumors.
- Antibody-drug conjugates (ADCs) represent one approach toward improved treatment of advanced TNBC; combination with immune checkpoint inhibitors has shown promising efficacy in patients with metastatic TNBC regardless of PD-L1 expression, and ADCs have shown promising efficacy compared with chemotherapy as first-line treatment for patients with advanced TNBC.

Rationale
- TROP2, a cell-surface glycoprotein involved in the regulation of cancer growth and invasion, is often expressed in TNBC and may be associated with poor outcomes in this setting.
- Sacituzumab tirumotecan (sac-TMT; MK-2870/SKB264) is an ADC composed of a humanized anti-TROP2 monoclonal antibody, a unique bifunctional linker, and a novel belotecan-derived topoisomerase I inhibitor payload.
- In participants with previously treated metastatic TNBC, sac-TMT monotherapy has shown superior efficacy with a manageable safety profile compared with standard chemotherapy in the phase III OptiTROP-Breast01 study.

TroFuse-011 trial design and eligibility
- This phase III, randomized, open-label trial is evaluating sac-TMT as monotherapy (arm A) or in combination with pembrolizumab (arm B) versus treatment of physician's choice (TPC; arm C) in participants with previously untreated, locally recurrent unresectable or metastatic TNBC with PD-L1 CPS <10.
- Participants will be randomized 2:1:2 to receive sac-TMT, sac-TMT plus pembrolizumab, or TPC.

Endpoints
- The primary endpoints are PFS (arm A vs C and arm B vs C) and OS (arm A vs C).
- Secondary endpoints include OS (arm B vs C and arm A vs B), PFS (arm A vs B), objective response (arm A vs C and arm B vs C), duration of response, changes in health-related quality of life (arm A vs C and arm B vs C), and safety.

Takeaway
- Enrollment for the phase III, randomized, open-label TroFuse-011 study began in March 2025.
- Recruitment is currently ongoing across 257 sites in 34 countries.
- The estimated study completion date is May 2030.

1. Introduction

Triple-negative breast cancer (TNBC), defined as estrogen receptor–negative, progesterone receptor–negative, and human epidermal growth factor receptor 2–negative (HER2–) breast cancer, represents approximately 10% to 20% of all breast cancers [1–3]. Compared with other breast cancer subtypes, individuals with TNBC are generally younger, have higher tumor grade, have more advanced disease at diagnosis, regularly have distant recurrence occur earlier, often within 3 years of TNBC diagnosis, and have a shorter survival due to limited treatment options with lack of targetable receptors [4–6]. However, significant treatment advancements have been made over the past decade. For patients with metastatic TNBC with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥10, chemotherapy plus immune-checkpoint inhibition is the current recommended first-line therapy [1,7]. In the phase III KEYNOTE-355 study in participants with previously untreated advanced TNBC and PD-L1 CPS ≥10, addition of pembrolizumab, an anti–programmed cell death protein 1 (anti–PD-1) monoclonal antibody, to chemotherapy as first-line treatment significantly prolonged overall survival (OS) compared with chemotherapy alone [8].

For patients with TNBC and PD-L1 CPS <10 (approximately two-thirds of patients with metastatic TNBC [8]), chemotherapy alone remains a standard first-line treatment option [1,7] and the prognosis for these patients is often poor. Patients who begin first-line treatment with chemotherapy for metastatic TNBC have a real-world median progression-free survival (PFS) of 4 to 5 months and median OS of 12 to 13 months [9,10]. Moreover, a real-world study evaluating clinical outcomes in patients receiving first-line treatment for metastatic TNBC observed that patients with PD-L1–positive tumors versus those with PD-L1–negative tumors had a longer median real-world OS (19.0 vs 13.2 months) and longer median time to next treatment or death (5.2 vs 4.3 months) [11]. New therapeutic options with superior efficacy are needed for patients with PD-L1–negative advanced TNBC.

1.1. Background and rationale

Antibody-drug conjugates (ADCs) targeting trophoblast cell-surface antigen 2 (TROP2) represent one approach toward improved treatment of metastatic TNBC. TROP2, a cell-surface glycoprotein involved in the regulation of cancer growth and invasion, is preferentially expressed and upregulated in many breast cancers, including TNBC (observed in up to 93% of cases) [12–14] and is associated with poor outcomes in multiple tumor types, including metastatic TNBC [12,15,16]. Notably, it is important to identify the most effective treatment for patients in this population as approximately 50% of patients who receive first-line therapy for metastatic TNBC do not go on to receive a second-line therapy [11].

Standard of care options for TNBC in the second-line setting and beyond include the TROP2-directed ADCs sacituzumab govitecan, approved in the second-line setting [1], and sacituzumab tirumotecan (sac-TMT; MK-2870/SKB264), which is approved in China in the third-line setting and beyond based on findings from the OptiTROP-Breast01 trial [17,18]. More recently, TROP2-targeting ADCs have begun to be investigated in the first-line setting. In the ASCENT-04/KEYNOTE-D19 trial of patients with TNBC previously untreated in the advanced setting and tumor PD-L1 CPS ≥10, median PFS was 11.2 months with sacituzumab govitecan plus pembrolizumab and 7.8 months with pembrolizumab plus chemotherapy (HR, 0.65; 95% CI, 0.51–0.84; $p < 0.001$) [19]. Additionally, in the phase III ASCENT-03 trial of patients with previously untreated, advanced TNBC who were not candidates for PD-(L)1 inhibitor therapy, median PFS was 9.7 months with sacituzumab govitecan and 6.9 months with chemotherapy (HR, 0.62; 95% CI, 0.50–0.77; $p < 0.001$) [20]. In the phase III TROPION-Breast02 trial in patients with previously untreated locally recurrent inoperable or metastatic TNBC, median PFS was 10.8 months with datopotamab deruxtecan and 5.6 months with

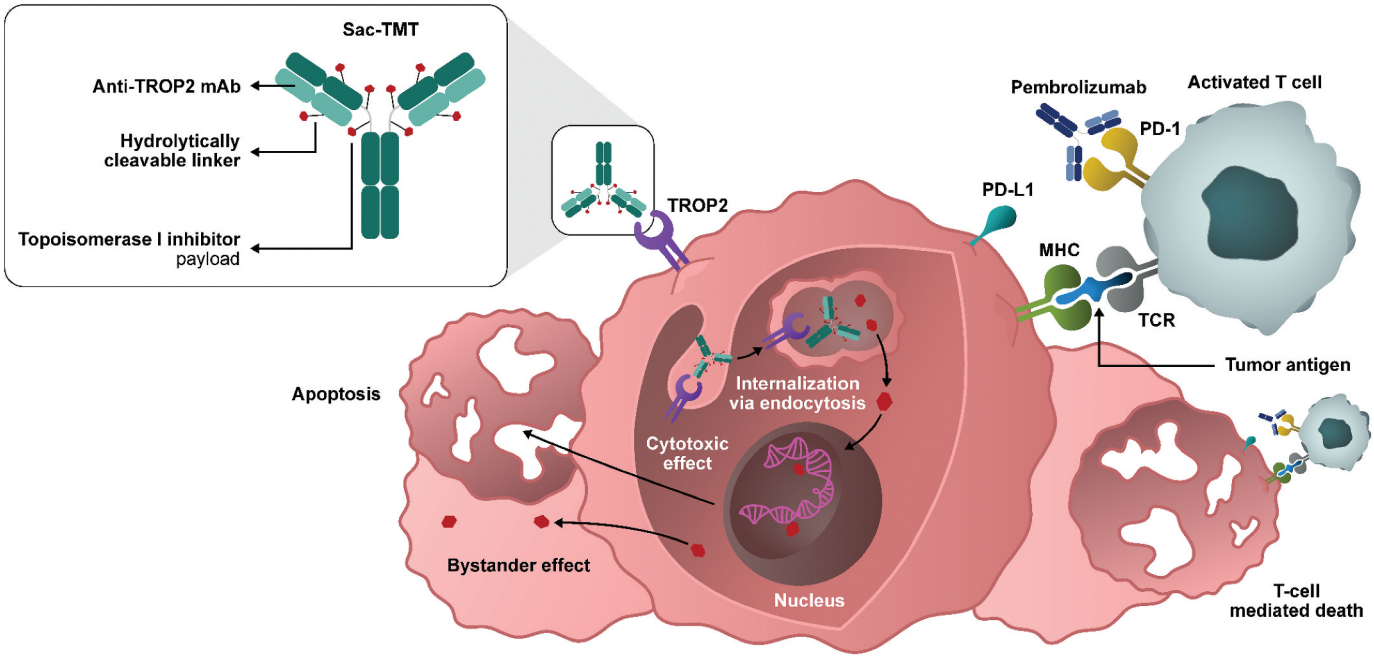

Figure 1. Complementary mechanisms of action of sac-TMT and pembrolizumab.

Abbreviations: mAb, monoclonal antibody; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; sac-TMT, sacituzumab tirumotecan; TCR, T-cell receptor; TROP2, trophoblast cell-surface antigen 2.

chemotherapy (HR, 0.57; 95% CI, 0.47–0.69; $p < 0.0001$) and the median OS was 23.7 months versus 18.7 months, respectively (HR, 0.79; 95% CI, 0.64–0.98; $p = 0.0291$) [21]. In addition to utilization of TROP2-directed ADC monotherapy in the later-line settings in TNBC, these studies have demonstrated activity of TROP2-directed ADCs in the first-line setting as monotherapy in patients ineligible for immunotherapy or in combination with pembrolizumab in patients with PD-L1 CPS ≥10.

Antibody-drug conjugates trigger immunogenic cell death, cytotoxicity, and dendritic cell activation [22]. They also induce tumor-specific adaptive immunity by increasing T-cell infiltration into the tumor microenvironment, which may offer a potential avenue for more potent antitumor activity when combined with immune checkpoint inhibitors [23]. The complementary mechanisms of the direct cytotoxic effects of sac-TMT and the immune-mediated antitumor effects (including enhanced T-cell activation) of pembrolizumab provide a strong biologic rationale for combining sac-TMT with pembrolizumab (Figure 1) [22,24]. Additionally, combination of sac-TMT and pembrolizumab may demonstrate additive benefit as topoisomerase I inhibitor payload can trigger dendritic cell activation and maturation in the tumor microenvironment, leading to increased T-cell infiltration and PD-L1 expression and thereby sensitizing tumor cells to pembrolizumab [23]. In a phase Ib/II study in participants with unresectable locally advanced or metastatic TNBC (BEGONIA), including those with low tumor PD-L1 expression, the ADC datopotamab deruxtecan combined with the anti–PD-L1 monoclonal antibody durvalumab demonstrated high response rates (79.0%) and durable responses (17.6 months) [25]. A phase Ib/II study (MORPHEUS-panBC) reported an encouraging overall response rate (76.7% vs 66.7%) and median PFS (12.2 vs 5.9 months) with a durable response (14.0 vs 7.1 months) following treatment with atezolizumab plus sacituzumab govitecan versus atezolizumab plus chemotherapy in participants with inoperable, PD-L1–positive (≥1% by immunohistochemistry [IHC]), locally advanced/metastatic TNBC with no prior systemic therapy [26]. The combination of TROP2 ADCs with immunotherapy has shown activity in a number of different types of cancer, regardless of PD-L1 expression, including advanced non–small-cell lung cancer [27], unresectable locally advanced or metastatic TNBC [25], and metastatic castration-resistant prostate cancer [28].

Sacituzumab tirumotecan is an ADC composed of a humanized anti-TROP2 monoclonal antibody, a unique bifunctional linker, and a novel belotecan-derived topoisomerase I inhibitor payload with a drug-to-antibody ratio of 7.4 [29]. Recently, the phase II OptiTROP-Lung01 study showed promising results with the combination of sac-TMT plus the anti–PD-L1 monoclonal antibody tagitanlimab as first-line treatment for participants with nonsquamous advanced non–small-cell lung cancer, regardless of PD-L1 status [30]. Sac-TMT monotherapy has shown promising efficacy with a manageable safety profile in the phase III OptiTROP-Breast01 study in participants with previously treated metastatic TNBC [31]. The most common treatment-related AEs with sac-TMT in the OptiTROP-Breast01 study were hematologic in nature, the most frequent of which were decreased neutrophil count, decreased white blood cell count, and decreased platelet count [31]. More recently, the phase II OptiTROP-Breast05 study demonstrated promising antitumor activity as a first-line treatment for advanced or metastatic TNBC, with no new safety signals observed [32]. Additionally, in the phase III OptiTROP-Breast02 trial of patients with previously treated locally advanced or metastatic hormone receptor–positive and HER2– breast cancer, median PFS was 8.3 months with sac-TMT and 4.1 months with

chemotherapy (HR, 0.35; 95% CI, 0.26–0.48; $p < 0.0001$) [33]. Based on these preliminary efficacy and safety outcomes, sac-TMT is currently being studied in combination with pembrolizumab and other immune checkpoint inhibitors in several ongoing trials. One such trial is the 2870-002/TroFuse-020/Gog-3101/ENGOTcx20 trial investigating clinical efficacy and safety of sac-TMT monotherapy versus treatment of physician's choice (TPC) in participants with recurrent or metastatic cervical cancer (ClinicalTrials.gov, NCT06459180).

Building on previous research, TroFuse-011 is a phase III trial investigating sac-TMT in the first-line setting as either monotherapy (arm A) or in combination with pembrolizumab (arm B) versus TPC (arm C) in participants with metastatic TNBC that is PD-L1 CPS <10 (i.e., not eligible for immunotherapy). This unique 3-arm design will allow the evaluation of sac-TMT as monotherapy versus TPC and sac-TMT plus pembrolizumab versus TPC.

1.2. Objectives

The TroFuse-011 study (NCT06841354) is evaluating sac-TMT as monotherapy or in combination with pembrolizumab versus TPC in participants with previously untreated, locally recurrent unresectable or metastatic TNBC with PD-L1 CPS <10. The primary objectives are to evaluate (a) the effects of sac-TMT versus TPC (arm A vs C) on PFS as assessed per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by blinded independent central review (BICR), (b) the effects of sac-TMT plus pembrolizumab versus TPC (arm B vs C) on PFS as assessed per RECIST version 1.1 by BICR, and (c) the effects of sac-TMT versus TPC (arm A vs C) on OS.

2. Study design

TroFuse-011 is a phase III, randomized, open-label trial of sac-TMT administered as monotherapy or in combination with pembrolizumab versus TPC in participants with previously untreated, locally recurrent unresectable or metastatic TNBC. The study design is presented in Figure 2.

3. Methods

3.1. Eligibility criteria

The study is enrolling participants (aged ≥ 18 years) with centrally confirmed, locally recurrent unresectable or metastatic TNBC, measurable disease per RECIST version 1.1, an Eastern Cooperative Oncology Group performance status of 0 or 1, and a tumor tissue sample evaluable for central PD-L1 and TROP2 testing. Participants with prior treatment in the early-stage setting must have completed all prior therapy at least 6 months

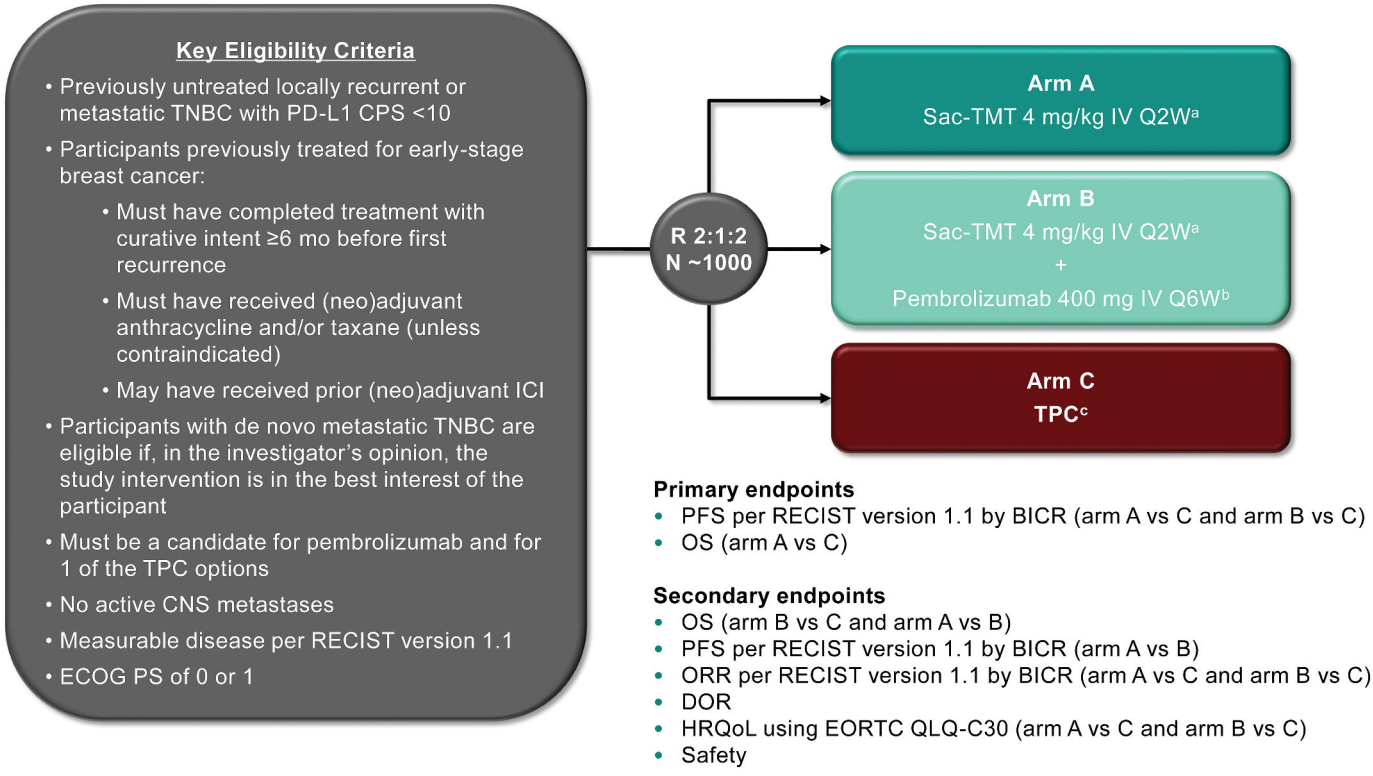

Figure 2. TroFuse-011 study design.

[a]Treatment with sac-TMT continues until disease progression, unacceptably toxicity, participant withdrawal, or any other criterion for discontinuation is met. [b]The maximum number of doses of pembrolizumab is 18. [c]Paclitaxel 80 mg/m^2 QW; paclitaxel 90 mg/m^2 on days 1, 8, and 15 Q4W; nab-paclitaxel 100 mg/m^2 on days 1, 8, and 15 Q4W; or gemcitabine 1000 mg/m^2 + carboplatin AUC 2 mg/mL/min on days 1 and 8 Q3W.

Abbreviations: AUC, area under the concentration-time curve; BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HRQoL, health-related quality of life; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; IV, intravenous; OS, overall survival; PFS, progression-free survival; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; sac-TMT, sacituzumab tirumotecan; TPC, treatment of physician's choice.

Table 1. Key eligibility criteria.

Inclusion criteria	Exclusion criteria
Aged ≥18 y	Breast cancer amenable to treatment with curative intent
Locally recurrent unresectable or metastatic TNBC not previously treated with systemic therapy	Evaluable tumor PD-L1 expression at CPS ≥10 as determined by central testing
Biopsy of tumor lesion for central confirmation of TNBC,[a] PD-L1, and TROP2 expression	Prior treatment with a TROP2-targeted ADC
Participants previously treated with systemic therapy for early-stage breast cancer must have received anthracycline and/or taxane in the (neo)adjuvant setting (unless contraindicated). Prior treatment with ICIs is permitted	Prior treatment with an ADC with a topoisomerase I inhibitor payload
Prior therapy for early-stage breast cancer with curative intent must have been completed ≥6 mo before the first disease recurrence, except endocrine therapy and adjuvant bisphosphonate (if given)	Prior systemic anticancer therapy, including investigational agents, within 4 wk before randomization
Participants who previously had early-stage breast cancer that was not treated with curative intent and who subsequently developed metastatic disease are eligible	Radiotherapy for non-CNS disease, or required corticosteroids for radiation-related toxicities, within 14 d of first dose of study treatment
Participants with de novo metastatic TNBC are eligible if, in the opinion of the investigator, the study intervention is in the best interest of the participant	Participants with PD-L1 expression on tumor-infiltrating immune cells ≥1% of tumor area by SP142 assay who are candidates for atezolizumab treatment per local standard of care[c]
Candidate for treatment with pembrolizumab and 1 of the TPC options: paclitaxel, nab-paclitaxel, or gemcitabine + carboplatin[b]	Known or suspected deleterious germline *BRCA* mutation, receiving care where PARP inhibitors are a local standard of care for metastatic TNBC associated with germline *BRCA* mutations (where approved and available), and is a candidate for first-line treatment with a PARP inhibitor in the opinion of the investigator[d]
Measurable disease per RECIST version 1.1	Skin-only metastatic disease
ECOG PS of 0 or 1	Advanced/metastatic, symptomatic visceral spread at risk of rapidly evolving into life-threatening complications
Adequate organ function	Known active CNS metastases and/or carcinomatous meningitis[e]

Abbreviations: ADC, antibody-drug conjugate; CPS, combined positive score; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; ISH, in situ hybridization; HER2, human epidermal growth factor receptor 2; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice; TROP2, trophoblast cell-surface antigen 2.

[a]Defined as estrogen receptor <1%, progesterone receptor <1%, and HER2 negative (IHC 0, IHC 1+, or IHC 2+/ISH negative). Participants previously diagnosed with early-stage HER2-positive or hormone receptor–positive/HER2-negative breast cancer are eligible if the most recent tumor specimen from a locally recurrent or metastatic region shows centrally confirmed TNBC.

[b]Participants who received taxane and/or platinum agents in the (neo)adjuvant setting can be treated with the same class of chemotherapy (taxane or gemcitabine + carboplatin) if ≥6 months have elapsed between the completion of treatment with curative intent and first recurrence.

[c]PD-L1 testing by SP142 is not required.

[d]Testing for germline *BRCA* mutations is not required unless mandated by local regulations and should be performed as clinically indicated per standard of care.

[e]Participants with previously treated brain metastases are eligible if they are radiographically stable (ie, without evidence of progression) for ≥4 weeks as confirmed by repeat imaging during study screening, are clinically stable, and have not required steroid treatment for ≥14 days before first dose of study treatment.

before disease recurrence (with the exception of endocrine therapy in participants whose initial disease was hormone receptor positive and adjuvant bisphosphonate, if administered). Participants with prior neoadjuvant/adjuvant immune-checkpoint inhibitor therapy are eligible. Tumor samples must have PD-L1 CPS <10. Eligibility criteria are provided in Table 1.

3.2. Interventions

Participants will be randomized 2:1:2 to receive sac-TMT (arm A), sac-TMT plus pembrolizumab (arm B), or TPC (arm C). Sac-TMT will be administered intravenously at a dose of 4 mg/kg every 2 weeks and pembrolizumab at a dose of 400 mg every 6 weeks. TPC (arm C) can include paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin. Paclitaxel will be administered at a dose of 80 mg/m^2 once weekly or 90 mg/m^2 on days 1, 8, and 15 every 4 weeks. Nab-paclitaxel will be administered at a dose of 100 mg/m^2 on days 1, 8, and 15 every 4 weeks. Gemcitabine will be administered at a dose of 1000 mg/m^2 on days 1 and 8 every 3 weeks, with carboplatin administered at a dose of area under the concentration-time curve 2 mg/mL/min on days 1 and 8 every 3 weeks. The study permits multiple chemotherapy regimens as there are no single standard first-line chemotherapy regimens recommended for previously untreated advanced TNBC with PD-L1 CPS <10. These agents are recognized by major oncology guidelines, widely available, frequently used, and known to be effective. Prior to randomization, investigators will select and record the TPC option and the rationale for selecting that option in the event that the participant will be assigned to the TPC arm. Crossover between treatment arms is not permitted. Treatment will continue until 1 of the following occurs: radiographic disease progression, prolonged dose interruption, requirement of a prohibited medication, consent withdrawal, or (for pembrolizumab only) up to 18 administrations or about 2 years. Participants who complete pembrolizumab treatment or discontinue pembrolizumab treatment can continue to receive sac-TMT until discontinuation criteria are met. Participants who discontinue sac-TMT treatment may continue to receive pembrolizumab if the investigator assesses (in consultation with the sponsor) that it is in the participant's best interests to do so, until they have received 18 administrations of pembrolizumab.

Randomization will be performed centrally using an interactive response technology system.

3.3. Endpoints

The primary endpoints are PFS per RECIST version 1.1 by BICR and OS for sac-TMT monotherapy versus TPC and PFS per

RECIST version 1.1 by BICR for sac-TMT plus pembrolizumab versus TPC. Secondary endpoints include OS for sac-TMT plus pembrolizumab versus TPC and versus sac-TMT; PFS for sac-TMT plus pembrolizumab versus sac-TMT; objective response (i.e., the proportion of participants with an objective response) for each investigational arm versus TPC; duration of response for each treatment arm; changes from baseline in health-related quality of life (HRQoL) for each investigational arm versus TPC, assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30); and safety, assessed via the occurrence of adverse events (AEs) and AEs leading to discontinuation of study treatment. Biomarker assessments are also planned as an exploratory endpoint to identify potential molecular biomarkers that may be indicative of clinical response or resistance to study treatments. PFS is defined as the time from randomization to first documented disease progression or any-cause death, assessed per RECIST version 1.1 by BICR. OS is defined as the time from randomization to any-cause death. Objective response comprises complete and partial responses per RECIST version 1.1 by BICR. Duration of response is defined as the time from first documented complete or partial response to disease progression or any-cause death.

3.4. Assessments

A tissue biopsy (new or archival) will be collected during screening to determine hormone receptor, HER2, PD-L1, and TROP2 status. PD-L1 will be assessed by a central laboratory using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA). TROP2 will be centrally assessed by IHC. Hormone receptor status will be centrally assessed by IHC, and HER2 will be centrally assessed by IHC (and in situ hybridization, if indicated). Results must be available for randomization. Tumor imaging will be performed at screening, every 8 weeks from the date of randomization through week 48, and every 12 weeks thereafter throughout the study. Brain and bone scans for participants with known or suspected brain metastases or bone metastases, respectively, will be performed at screening and at all study-related tumor assessments. HRQoL will be assessed via the patient-reported outcome (PRO) measures of the EORTC QLQ-C30, EORTC breast cancer-specific module (QLQ-BR42), and EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L). Participants in arms A and B and participants in arm C receiving paclitaxel/nab-paclitaxel will complete HRQoL assessments on days 1, 29, and 57 of treatment cycles 1 and 2; days 1 and 57 of cycle 3; day 29 of cycle 4; and day 1 of every subsequent cycle until centrally verified disease progression. Participants in arm C receiving gemcitabine plus carboplatin will complete HRQoL assessments on days 1, 22, and 64 of treatment cycles 1 and 2; days 1 and 64 of cycle 3; day 22 of cycle 4; and day 1 of every subsequent cycle until centrally verified disease progression. AEs are monitored from randomization until 30 days after the last dose of study treatment (90 days for serious AEs) and are graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

3.5. Statistical analysis

The study is planned to randomize approximately 1000 participants. Efficacy endpoints will be assessed in the intention-to-treat population, comprising all randomized participants. Safety will be assessed in all participants who receive ≥1 dose of study treatment and analyzed according to the treatment received (all-participants-as-treated population). PROs will be assessed in all randomized participants who have ≥1 PRO assessment for the specific endpoint and have received ≥1 dose of study treatment. PFS and OS will be evaluated using a stratified log-rank test, and HRs will be estimated using a stratified Cox proportional hazard model with the Efron method of tie handling. The nonparametric Kaplan-Meier method will be used to estimate the survival curve for each treatment arm. The objective response rate will be compared between treatment groups using the Miettinen and Nurminen method with strata weighting by sample size. Objective response rate point estimates and 95% CIs will be provided for each treatment group using the Clopper and Pearson exact binomial method. Duration of response will be summarized using Kaplan-Meier medians and quartiles. AEs will be analyzed using descriptive statistics for each treatment arm; between-group differences in specific AEs that meet predefined threshold rules will be analyzed using the Miettinen and Nurminen method with point estimates and 95% CIs. Changes from baseline in PRO measures will be analyzed using a constrained longitudinal data analysis model to estimate least-squares mean and 95% CI treatment differences.

Multiplicity will be controlled using the graphical method of Maurer and Bretz. The overall type I error rate will be controlled for between-arm comparisons at 0.025 (1-sided). With a planned enrollment of approximately 1000 participants, the study is powered to detect a treatment difference for sac-TMT monotherapy versus TPC in PFS and OS, and sac-TMT plus pembrolizumab versus TPC in PFS as primary endpoints, and for sac-TMT plus pembrolizumab versus TPC in OS as a secondary endpoint. Interim analyses are planned in addition to the final analysis of the study.

4. Ethics and dissemination

The study is being conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization consolidated Guideline E6 for Good Clinical Practice. The study protocols and amendments are approved by the appropriate institutional review board or independent ethics committee at each study site. All participants will provide written informed consent before entering the trial. Data from the study will be presented at upcoming scientific meetings, submitted to a peer-reviewed journal for publication, and posted on trial registries.

5. Conclusion

TROP2-targeting ADCs have been evaluated across tumor types, and there is clinical evidence showing enhanced anti-

tumor activity when combined with immune checkpoint inhibitors in the TNBC setting irrespective of PD-L1 expression [25,27,30]. Although other TROP2 ADCs with topoisomerase I inhibitors are available for the treatment of metastatic TNBC, sac-TMT may offer favorable antitumor activity with a differential toxicity profile due to maximized delivery of payload to tumor cells, localized bystander effect with diffusion of free payload to neighboring tumor cells, and minimal release of linker and payload in the circulation. Moreover, the combination of TROP2 ADCs with immunotherapy in patients with PD-L1–negative advanced TNBC is of great interest based on preclinical data supporting activation of the immune system with this approach [22,23]. This phase III, randomized, open-label TroFuse-011 study will investigate sac-TMT in the first-line setting as either monotherapy or in combination with pembrolizumab versus TPC in participants with metastatic TNBC with PD-L1 CPS <10. Given the mechanism of action of sac-TMT and the strong biologic rationale for combining ADCs with immune checkpoint inhibitors, sac-TMT monotherapy or in combination with pembrolizumab has the potential to show improved clinical outcomes compared with TPC in this population with high unmet treatment need. If sac-TMT is shown to provide benefit in the TroFuse-011 study, it would likely represent a new standard of care therapy in this setting. Enrollment of TroFuse-011 began in March 2025, and recruitment is currently ongoing across 257 sites in 34 countries. Approximately 1000 participants will be randomized. The estimated study completion date is May 2030.

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Author contributions

CRediT: **Hope S. Rugo:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Peter Schmid:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Javier Cortes:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Toshimi Takano:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Peter A. Fasching:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Yeon Hee Park:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Giampaolo Bianchini:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Sandra Ximena Franco:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Cynthia Villarreal-Garza:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Olivier Tredan:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Yongmei Yin:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Romualdo Barroso-Sousa:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Xuan Peng:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Usha Malhotra:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Karen Lisa Smith:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Aditya Bardia:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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Ethical declaration

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Data availability statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: *https://externaldatasharing-msd.com/*) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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