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# Sacituzumab Govitecan in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer

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abstract

**PURPOSE** Hormone receptor–positive (HR+) human epidermal growth factor receptor 2–negative (HER2–) endocrine-resistant metastatic breast cancer is treated with sequential single-agent chemotherapy with poor outcomes. Sacituzumab govitecan (SG) is a first-in-class antibody-drug conjugate with an SN-38 payload targeting trophoblast cell-surface antigen 2, an epithelial antigen expressed in breast cancer.

**METHODS** In this global, randomized, phase III study, SG was compared with physician's choice chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine) in endocrine-resistant, chemotherapy-treated HR+/HER2– locally recurrent inoperable or metastatic breast cancer. The primary end point was progression-free survival (PFS) by blinded independent central review.

**RESULTS** Patients were randomly assigned to receive SG (n = 272) or chemotherapy (n = 271). The median age was 56 years, 95% had visceral metastases, and 99% had a prior cyclin-dependent kinase 4/6 inhibitor, with three median lines of chemotherapy for advanced disease. Primary end point was met with a 34% reduction in risk of progression or death (hazard ratio, 0.66 [95% CI, 0.53 to 0.83; $P$ = .0003]). The median PFS was 5.5 months (95% CI, 4.2 to 7.0) with SG and 4.0 months (95% CI, 3.1 to 4.4) with chemotherapy; the PFS at 6 and 12 months was 46% (95% CI, 39 to 53) *v* 30% (95% CI, 24 to 37) and 21% (95% CI, 15 to 28) *v* 7% (95% CI, 3 to 14), respectively. Median overall survival (first planned interim analysis) was not yet mature (hazard ratio, 0.84; $P$ = .14). Key grade ≥ 3 treatment-related adverse events (SG *v* chemotherapy) were neutropenia (51% *v* 38%) and diarrhea (9% *v* 1%).

**CONCLUSION** SG demonstrated statistically significant PFS benefit over chemotherapy, with a manageable safety profile in patients with heavily pretreated, endocrine-resistant HR+/HER2– advanced breast cancer and limited treatment options.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

Although endocrine therapy combined with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) has extended overall survival (OS) for metastatic hormone receptor–positive (HR+) human epidermal growth factor receptor 2–negative (HER2–) breast cancer to over 5 years in the first-line setting[1-5] and combinations with phosphoinositide 3-kinase or mammalian target of rapamycin inhibitors offer benefit in subsequent treatment lines,[6] endocrine resistance eventually develops. Sequential single-agent chemotherapy is the next therapeutic option but is associated with declining response rates and disease control and increased toxicity.[6-10]

Sacituzumab govitecan (SG) is a first-in-class trophoblast cell-surface antigen 2 (Trop-2)–directed antibody-drug conjugate (ADC), consisting of a humanized anti–Trop-2 monoclonal antibody conjugated to the active metabolite of irinotecan, SN-38,[11] via a hydrolyzable CL2A linker.[12] Trop-2 is a transmembrane calcium signal transducer highly expressed in solid tumors, especially HR+/HER2– and triple-negative breast cancers (with a prevalence of > 90%), and linked to tumor progression and poor prognosis.[13-15] Internalization of Trop-2–bound SG delivers SN-38 into the tumor cell through hydrolysis of the linker.[16] Because SN-38 is a membrane-permeable free molecule released in the tumor microenvironment, it

## CONTEXT

### Key Objective

Hormone receptor–positive (HR+) human epidermal growth factor receptor 2–negative (HER2–) breast cancer is treated with sequential endocrine therapy combined with targeted agents, followed by sequential single-agent chemotherapy, with declining response rates and increased toxicity. This randomized, global phase III study evaluates sacituzumab govitecan (SG), a trophoblast cell-surface antigen 2–directed antibody-drug conjugate, versus single-agent chemotherapy in HR+/HER2– advanced breast cancer.

### Knowledge Generated

SG demonstrated a significant improvement in progression-free survival over chemotherapy (median, 5.5 months *v* 4.0 months; hazard ratio, 0.66; $P = .0003$) in patients who have received prior endocrine-based therapy, including cyclin-dependent kinase 4/6 inhibitors and ≥ 2 prior chemotherapy regimens in the metastatic setting. The SG safety profile was manageable and consistent with previous studies, with neutropenia and diarrhea as the most common treatment-related adverse events.

### Relevance *(K.D. Miller)*

SG is a treatment option for patients with heavily pretreated, endocrine-resistant HR+/HER2– advanced breast cancer.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

may elicit antitumor effects in adjacent non–Trop-2-expressing tumor cells (bystander effect).[16]

SG received full authorization from the Food and Drug Administration and European Medicines Agency for patients with metastatic triple-negative breast cancer who had received at least two prior chemotherapies (at least one for metastatic disease) and has accelerated approval for locally advanced or metastatic urothelial cancer.[17-19] In the phase I/II IMMU-132-01 basket study, SG showed encouraging activity and safety in 54 patients with HR+/HER2– metastatic breast cancer (MBC) who progressed on at least one line of endocrine therapy and at least one prior chemotherapy in the metastatic setting.[20] The objective response rate was 31.5%, and the median progression-free survival (PFS) and OS were 5.5 and 12 months, respectively (CDK4/6i-pretreated group, 25%, 3.8 and 11 months).

Here, we provide the primary results of TROPiCS-02, a global, randomized, open-label, multicenter phase III study of SG versus single-agent chemotherapy in patients with locally recurrent inoperable or metastatic HR+/HER2– breast cancer (Data Supplement, online only).

## METHODS

### Patients

Eligible patients had histologically locally confirmed measurable HR+/HER2– MBC and 2-4 prior systemic chemotherapy regimens for metastatic disease. (Neo)adjuvant therapy for early-stage disease qualified as one of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within 12 months of therapy (early relapse). Patients must have previously received at least one taxane, at least one anticancer hormonal treatment, and at least one CDK4/6i, reflecting standard clinical practice. Additional details are provided in the Data Supplement.

### Trial Design and Treatment

Patients were randomly assigned 1:1 to receive 10 mg/kg of SG (Trodelvy; Gilead Sciences Inc, Foster City, CA) intravenously once weekly on day 1 and day 8 every 21 days or chemotherapy of physician's choice determined before random assignment (eribulin, capecitabine, gemcitabine, or vinorelbine). The chemotherapy agents included in this trial, and their recommended doses, were in accordance with locally approved prescribing information or according to National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (National Comprehensive Cancer Network Guidelines) for Breast Cancer.[21] Recommended doses are summarized below: eribulin, 1.4 mg/m$^2$ (North America) or 1.23 mg/m$^2$ (Europe) intravenously once weekly on days 1 and 8 every 21 days; vinorelbine, 25 mg/m$^2$ intravenously once weekly; gemcitabine, 800-1, 200 mg/m$^2$ intravenously once weekly on days 1, 8, and 15 every 28 days; and capecitabine, 1,000-1,250 mg/m$^2$ orally twice daily for 2 weeks followed by a 1 week rest period, every 21 days.

Random assignment was stratified by number of prior chemotherapy regimens for metastatic disease, visceral metastases, and prior endocrine treatment in the metastatic setting for at least 6 months. Patients were treated until disease progression, unacceptable toxicity, withdrawal of consent, or per investigator's decision that it was in the patient's best interest to discontinue. Treatment beyond progression was permitted if deemed clinically beneficial by the investigator. Additional details are provided in the Data Supplement.

### Trial Oversight

The study was approved by national regulatory authorities and each investigational site's institutional review/ethics committee before implementation and was compliant with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent.

### End Points

The primary end point was PFS as determined by blinded independent central review (BICR) per the RECIST v1.1.[22] Secondary end points included OS, objective response, clinical benefit rate, duration of response, patient-reported outcomes, and safety (Data Supplement).

### Assessments

The primary and secondary end points were measured by computed tomography or magnetic resonance imaging, conducted every 6 weeks for the first 54 weeks and every 12 weeks thereafter. Additional details are provided in the Data Supplement.

Safety and tolerability were assessed in all treated patients throughout the study, with severity of adverse events (AEs) graded using National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Patients were allowed premedications (eg, antipyretics and H1 blockers) for prevention of infusion reactions and supportive medications for the prevention and treatment of chemotherapy-induced nausea, vomiting, and diarrhea.

### Statistical Analysis

Anticipated recruitment was 520 patients; sample size calculation was based on treatment group comparisons, with PFS as the primary end point and OS as the key secondary end point. For PFS, assuming a hazard ratio (HR) of 0.70, 350 events of progression or death were needed to detect a statistically significant PFS difference between treatment groups at a two-sided $\alpha$ of .05 with 92% power. For OS, assuming a HR of 0.73, 438 events were needed to detect a statistically significant difference with 87% power at a two-sided $\alpha$ of .05. OS would be formally tested sequentially if PFS is statistically significant, and then objective response and quality of life (QoL) if the prior end point in the hierarchy is significant. The study was planned to have two interim analyses and a final analysis of OS, with 272 events targeted for the first interim and .036 $\alpha$ to be spent on the basis of Lan DeMets $\alpha$ spending function that approximated a Pocock approach. Analysis of OS was combined with the primary PFS analysis since the required OS events for the first interim analysis were reached earlier than PFS events (329 events occurred).

AEs summarized were treatment-emergent unless otherwise specified (defined as any AEs that began or worsened on or after study drug administration through 30 days after the last dose of study drug).

The intent-to-treat population includes all randomly assigned patients (efficacy population). Stratification factors used in random assignment were applied to all stratified analyses. All patients who received at least one dose of study drug were included in safety analyses. Additional details are provided in the Data Supplement.

## RESULTS

### Patient Characteristics

From May 2019 to April 2021, 543 patients with HR+/HER2– locally inoperable or MBC were enrolled in 91 centers across North America (United States and Canada) and Europe (the United Kingdom, France, Spain, Italy, Germany, Belgium, and the Netherlands). Patients were randomly assigned to the SG group (272 patients) or chemotherapy group (271 patients; 48% eribulin, 23% vinorelbine, 21% gemcitabine, and 8% capecitabine; Data Supplement). In total, 268 patients (99%) in the SG group and 249 patients (92%) in the chemotherapy group received study treatment. Of the 26 patients randomly assigned but not treated, 16 withdrew consent (one for SG and 15 for chemotherapy).

The median age was 56 years (range, 27-86; Table 1). Most had visceral metastases (95%) and received endocrine therapy in the metastatic setting for at least 6 months (86%); 40% of patients received CDK4/6i therapy for more than 12 months. Patients received a median of 3 (range, 0-8) prior lines of chemotherapy in the metastatic setting (57% at least three lines). At the data cutoff date (January 3, 2022), 18 patients (7%) in the SG group and four (1.5%) in the chemotherapy group remained on study treatment. Patients discontinued study treatment primarily because of progressive disease (SG group, 77%; chemotherapy group, 73%; Fig 1).

### Efficacy

As of the data cutoff date, the median duration of follow-up was 10.2 months (11.3 months with SG and 9.8 months with chemotherapy). The primary end point of PFS was met with a 34% reduction in risk of progression or death (HR, 0.66; 95% CI, 0.53 to 0.83; $P = .0003$; 329 events); the median PFS determined by BICR was 5.5 months (95% CI, 4.2 to 7.0) for SG and 4.0 months (95% CI, 3.1 to 4.4) for chemotherapy (Fig 2A and Table 2). The reduction in risk of progression or death was consistent with local investigator assessment (HR, 0.73; 95% CI, 0.60 to 0.88; $P = .001$; Data Supplement).

In landmark analyses, the PFS rates at 6 and 12 months (SG *v* chemotherapy) were 46% versus 30% and 21% versus 7%, respectively (Fig 2A and Table 2). The PFS benefit for SG over chemotherapy was maintained in most predefined subgroups, including patients with three or more prior chemotherapy regimens in the metastatic setting, visceral metastases, and age 65 years or older (Fig 3).

Because PFS results were statistically significant, OS was sequentially tested. The median OS (first planned interim

**TABLE 1.** Baseline Characteristics and Treatment History of Patients

| Characteristic | SG (n = 272) | Chemotherapy (n = 271) | All (N = 543) |
|---|---|---|---|
| Female, No. (%) | 270 (99) | 268 (99) | 538 (99) |
| Median age, years (range) | 57 (29-86) | 55 (27-78) | 56 (27-86) |
| Race or ethnic group, No. (%) | | | |
| White | 184 (68) | 178 (66) | 362 (67) |
| Black | 8 (3) | 13 (5) | 21 (4) |
| Asian | 11 (4) | 5 (2) | 16 (3) |
| Others[a] | 0 | 5 (2) | 5 (1) |
| Not specified[b] | 69 (25) | 70 (26) | 139 (26) |
| ECOG PS, No. (%) | | | |
| 0 | 116 (43) | 126 (46) | 242 (45) |
| 1 | 156 (57) | 145 (54) | 301 (55) |
| Visceral metastases at baseline, No. (%) | 259 (95) | 258 (95) | 517 (95) |
| Liver metastases,[c] No. (%) | 229 (84) | 237 (87) | 466 (86) |
| De novo MBC, No. (%) | 78 (29) | 60 (22) | 138 (25) |
| Median time from initial metastatic diagnosis to random assignment, months (range) | 48.5 (1.2-243.8) | 46.6 (3.0-248.8) | 47.8 (1.2-248.8) |
| Prior chemotherapy in the (neo)adjuvant setting, No. (%) | 173 (64) | 184 (68) | 357 (66) |
| Prior endocrine therapy in the metastatic setting > 6 months, No. (%) | | | |
| Yes | 235 (86) | 234 (86) | 469 (86) |
| No | 37 (14) | 37 (14) | 74 (14) |
| Prior CDK4/6i use, months, No. (%) | | | |
| ≤ 12 | 161 (59) | 166 (61) | 327 (60) |
| > 12 | 106 (39) | 102 (38) | 208 (38) |
| Unknown | 5 (2) | 3 (1) | 8 (1) |
| Median prior chemotherapy regimens in the metastatic setting, No. (%)[d] | 3 (0-8)[d] | 3 (1-5)[d] | 3 (0-8)[d] |
| 0 | 1 (< 1) | 0 | 1 (< 1) |
| 1 | 8 (3) | 2 (1) | 10 (2) |
| 2 | 104 (38) | 118 (43) | 222 (41) |
| ≥ 3 | 159 (58) | 151 (56) | 310 (57) |
| Median prior chemotherapy regimens, No. (range) | 4 (1-9) | 4 (2-7) | 4 (1-9) |
| Median prior anticancer regimens,[e] No. (range) | 7 (3-17) | 7 (3-16) | 7 (3-17) |
| Setting of prior anticancer regimens,[e] No. (%) | | | |
| Neoadjuvant | 67 (25) | 62 (23) | 129 (24) |
| Adjuvant | 186 (68) | 206 (76) | 392 (72) |
| Advanced/metastatic | 272 (100) | 271 (100) | 543 (100) |
| Others/unknown | 12 (4) | 9 (3) | 21 (4) |
| Most common prior anticancer therapy,[e] No. (%) | | | |
| Palbociclib | 238 (88) | 228 (84) | 466 (86) |
| Capecitabine | 226 (83) | 234 (86) | 460 (85) |
| Fulvestrant | 235 (86) | 223 (82) | 458 (84) |
| Cyclophosphamide | 204 (75) | 209 (77) | 413 (76) |
| Paclitaxel | 210 (77) | 196 (72) | 406 (75) |
| Letrozole | 185 (68) | 210 (77) | 395 (73) |
| Tamoxifen | 160 (59) | 165 (61) | 325 (60) |

(continued on following page)

**TABLE 1.** Baseline Characteristics and Treatment History of Patients (continued)

| Characteristic | SG (n = 272) | Chemotherapy (n = 271) | All (N = 543) |
|---|---|---|---|
| Doxorubicin[e] | 149 (55) | 134 (49) | 283 (52) |
| Exemestane | 142 (52) | 134 (49) | 276 (51) |
| Everolimus | 117 (43) | 115 (42) | 232 (43) |
| Docetaxel | 106 (39) | 120 (44) | 226 (42) |
| Eribulin[e] | 97 (36) | 97 (36) | 194 (36) |
| Anastrozole | 87 (32) | 69 (25) | 156 (29) |
| Epirubicin | 78 (29) | 94 (35) | 172 (32) |
| Fluorouracil | 66 (24) | 77 (28) | 143 (26) |
| Most common prior anticancer therapy class in the metastatic setting,[e] No. (%) | | | |
| Endocrine therapy | 268 (99) | 269 (99) | 537 (99) |
| CDK4/6i | 267 (98) | 270 (> 99) | 537 (99) |
| Targeted agent | 181 (67) | 172 (63) | 353 (65) |
| Immunotherapy | 21 (8) | 15 (6) | 36 (7) |
| Chemotherapy | 271 (> 99) | 271(100) | 542 (> 99) |
| Most common prior chemotherapy agent in the metastatic setting,[e] No. (%) | | | |
| Capecitabine | 221 (81) | 232 (86) | 453 (83) |
| Paclitaxel | 174 (64) | 147 (54) | 321 (59) |
| Eribulin[e] | 95 (35) | 88 (33) | 183 (34) |
| ER expression, No. (%)[f] | | | |
| < 1% | 2 (1) | 5 (2) | 7 (1) |
| 1%-10% | 12 (4) | 15 (6) | 27 (5) |
| > 10% | 258 (95) | 246 (91) | 504 (93) |
| Unknown | 0 | 5 (2) | 5 (1) |
| PR expression, No. (%)[f] | | | |
| < 1% | 103 (38) | 101 (37) | 204 (38) |
| 1%-10% | 45 (17) | 44 (16) | 89 (16) |
| > 10% | 124 (46) | 120 (44) | 244 (45) |
| Unknown | 0 | 6 (2) | 6 (1) |

Abbreviations: CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; MBC, metastatic breast cancer; PR, progesterone receptor; SG, sacituzumab govitecan.

[a]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander.

[b]Not reported indicates local regulators who did not allow collection of race or ethnicity information.

[c]Presence of baseline target/nontarget liver lesion per RECIST1.1 by local investigator review.

[d]The reported number of prior therapies was miscounted at screening for some patients. Nine patients had fewer or more prior chemotherapy regimens in the metastatic setting than the specified inclusion criteria and were included in the intention-to-treat population.

[e]Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting and includes endocrine therapy and everolimus. Eribulin includes the preferred drug name eribulin and eribulin mesylate. Doxorubicin includes the preferred drug name doxorubicin, pegylated liposomal doxorubicin hydrochloride, liposomal doxorubicin, doxorubicin hydrochloride, liposomal doxorubicin hydrochloride, and pegylated liposomal doxorubicin.

[f]Per protocol, hormone receptor status was to be documented from locally recurrent or metastatic sites and the few cases that did not have protocol deviations.

analysis) was 13.9 months (95% CI, 12.7 to 15.4) for SG and 12.3 months (95% CI, 10.8 to 14.2) for chemotherapy (HR for death, 0.84; 95% CI, 0.67 to 1.06; $P = .14$; Fig 2B). These results are not yet mature; further follow-up is ongoing. Because OS was not significant, objective response and QoL end points—which fell after OS in the hierarchy—were not formally tested.

The percentage of patients with objective response by BICR was 21% with SG and 14% with chemotherapy (Table 2), of which two patients (1%) and no patients achieved a complete response, respectively. Clinical benefit rate was higher with SG than with chemotherapy (34% *v* 22%). The median time to response was 2.9 (range, 1.2-11.3) months with SG and 2.7 (range, 1.2-10.5) months with

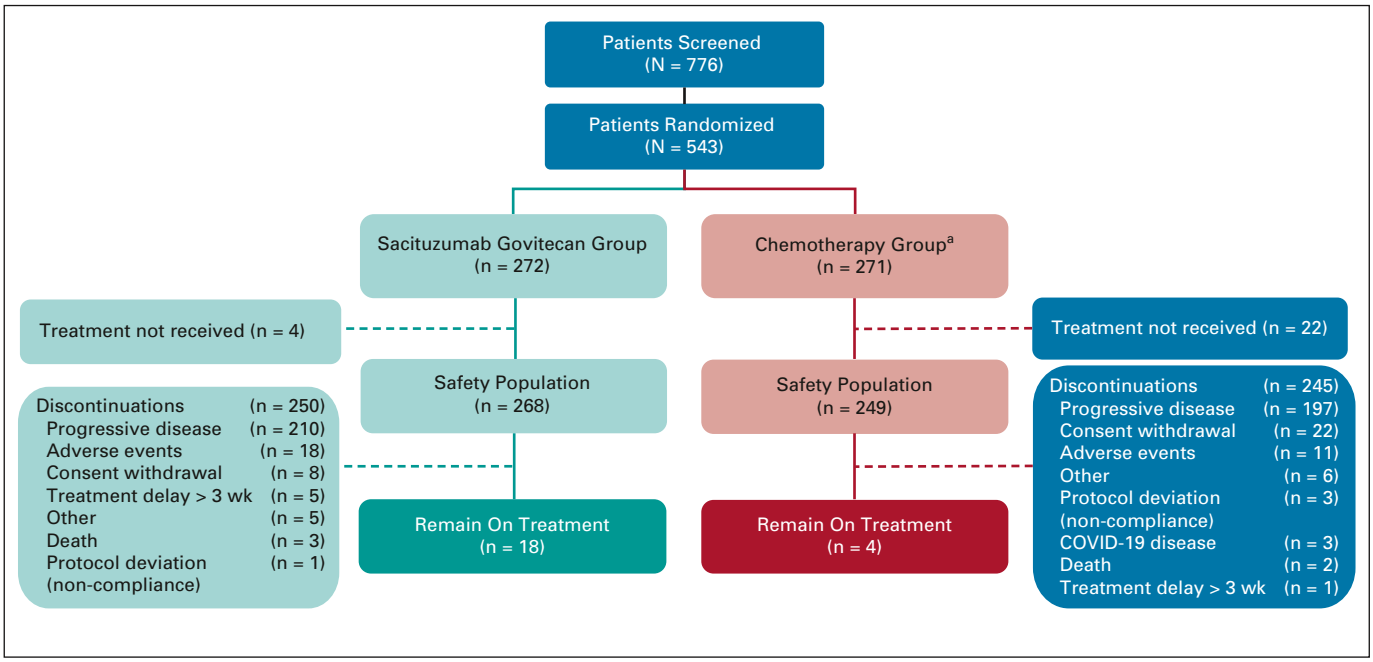


**FIG 1.** CONSORT diagram. [a]Patients in the chemotherapy group were randomly assigned to eribulin (n = 130), vinorelbine (n = 63), gemcitabine (n = 56), or capecitabine (n = 22). AE, adverse event; SG, sacituzumab govitecan.

chemotherapy. The median duration of response was 7.4 months (95% CI, 6.5 to 8.6) with SG and 5.6 months (95% CI, 3.8 to 7.9) with chemotherapy.

For patient-reported outcomes, the European Organization for Research and Treatment of Cancer QoL questionnaire completion rate was at least 85% through cycle 13 day 1 for both SG and chemotherapy and was generally comparable across assessments between treatment groups. Median time to deterioration was longer for SG versus chemotherapy for global health status/QoL (4.0 *v* 2.9 months; HR, 0.74; 95% CI, 0.59 to 0.91) and fatigue (2.1 *v* 1.4 months; HR, 0.76; 95% CI, 0.62 to 0.93). Median time to deterioration for pain was similar (3.7 *v* 3.4 months; HR, 0.92; 95% CI, 0.74 to 1.14).

### Safety

In the safety population, the median duration of treatment was 4.1 (range, 0.03-24.2) months and 2.3 (range, 0.03-22.3) months with SG and chemotherapy, respectively. Patients in the SG group received a mean of 8.2 treatment cycles (range, 1.0-35.0), with a median relative dose intensity of 99%.

An AE summary is found in the Data Supplement. The most common treatment-related AEs of any grade (> 25% incidence) with SG versus chemotherapy were neutropenia (70% *v* 54%), diarrhea (57% *v* 16%), nausea (55% *v* 31%), alopecia (46% *v* 16%), fatigue (37% *v* 29%), and anemia (34% *v* 25%). The most common grade 3 or higher treatment-related AEs (> 5% incidence) were neutropenia (51% *v* 38%), leukopenia (9% *v* 5%), diarrhea (9% *v* 1%), anemia (6% *v* 3%), and fatigue (6% *v* 2%; Table 3). There was a low incidence of treatment-related febrile neutropenia (5% *v* 4%), interstitial lung disease (0% *v* 1%), and neuropathy (9% *v* 15%). For additional results about growth factor use, see the Data Supplement.

Given the difference in treatment durations in the SG and chemotherapy groups, a summary of exposure-adjusted incidence rates (EAIRs) for AEs is provided in the Data Supplement. Although the EAIRs for common AEs of any grade, such as diarrhea, alopecia, and nausea, were higher with SG versus chemotherapy, the EAIRs for other common AEs of any grade, including neutropenia, anemia, and fatigue, were similar between treatment groups (EAIR difference [95% CI]: diarrhea: 2.29 per patient-years of exposure [PYE; 1.72 to 2.87], alopecia: 1.23 per PYE [0.80 to 1.68]; nausea: 0.85 per PYE [0.30 to 1.39]; neutropenia: 0.75 per PYE [–0.16 to 1.66]; anemia: 0 per PYE [–0.37 to 0.35]; fatigue: –0.36 per PYE [–0.82 to 0.07]).

Serious treatment-related AEs were reported in 37 patients (14%) in the SG group and 25 patients (10%) in the chemotherapy group. The most common (≥ 2% incidence) serious treatment-related AEs for SG were diarrhea (5%), febrile neutropenia (4%), neutropenia (3%), and neutropenic colitis (2%); for chemotherapy, they were febrile neutropenia (4%), pneumonia (2%), nausea (2%), and dyspnea (2%). AEs leading to study treatment discontinuations occurred in 17 patients (6%) in the SG group and 11 patients (4%) in the chemotherapy group. Dose delays and reductions can be found in the Data Supplement. Although six patients experienced AEs leading to death in the SG group, only one had a treatment-related AE leading

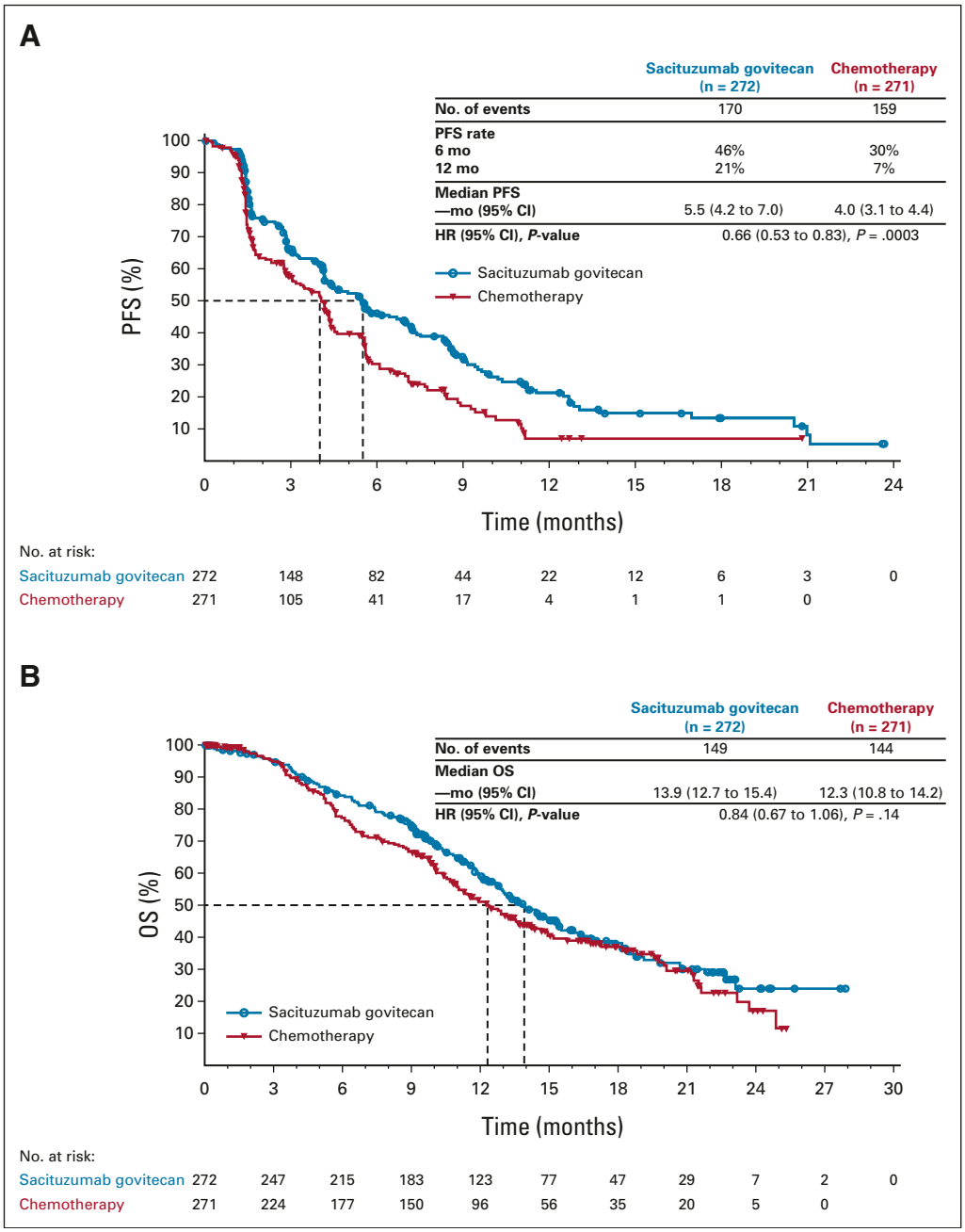


**FIG 2.** Efficacy outcomes in the intent-to-treat population. (A and B) PFS (final analysis) and OS (first planned interim analysis), respectively, in the intent-to-treat population (all randomly assigned patients). PFS was determined by blinded independent central review according to RECIST, version 1.1. HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

to death (septic shock because of neutropenic colitis). The AEs leading to death in the remaining five patients included (n = 1 each) arrhythmia, COVID-19 pneumonia, pulmonary embolism, pneumonia, and nervous system disorder. The patients with fatal infections of COVID-19 pneumonia and pneumonia were not neutropenic at the time of event onset. No mechanistic or etiologic pattern was identified for these AEs (Data Supplement). No AEs leading to death were reported in the chemotherapy group.

## DISCUSSION

Patients with metastatic HR+/HER2– breast cancer ultimately develop endocrine resistance, and treatment options are limited to sequential single-agent chemotherapy. In this phase III trial of patients with heavily pretreated, locally recurrent inoperable, or metastatic HR+/HER2– breast cancer, SG, a Trop-2–directed ADC, demonstrated significant improvement in PFS versus chemotherapy with a 34% reduction in risk of disease

**TABLE 2.** Summary of Treatment Efficacy (per blinded independent central review)

| Efficacy Outcome | SG (n = 272) | Chemotherapy (n = 271) |
|---|---|---|
| Median PFS, months (95% CI), | 5.5 (4.2 to 7.0) | 4.0 (3.1 to 4.4) |
| HR; *P* (95% CI) | 0.66 (0.53 to 0.83); *P* = .0003 | |
| PFS rate, %, months (95% CI) | | |
| 6 | 46 (39 to 53) | 30 (24 to 37) |
| 12 | 21 (15 to 28) | 7 (3 to 14) |
| Median OS, months (95% CI) | 13.9 (12.7 to 15.4) | 12.3 (10.8 to 14.2) |
| HR; *P* (95% CI) | 0.84 (0.67 to 1.06); *P* = .14 | |
| Objective response rate, No. (%) | 57 (21) | 38 (14) |
| Best overall response, No. (%) | | |
| Complete response | 2 (1) | 0 |
| Partial response | 55 (20) | 38 (14) |
| Stable disease | 142 (52) | 106 (39) |
| Stable disease ≥ 6 months | 35 (13) | 21 (8) |
| Progressive disease | 58 (21) | 76 (28) |
| Not evaluable | 15 (6) | 51 (19) |
| CBR,[a] No. (%) | 92 (34) | 59 (22) |
| Median DOR, months (95% CI) | 7.4 (6.5 to 8.6) | 5.6 (3.8 to 7.9) |

Abbreviations: CBR, clinical benefit rate; DOR, duration of response; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

[a]CBR is defined as the percentage of patients with a confirmed best overall response of complete response, partial response, and stable disease ≥ 6 months.

progression or death (HR, 0.66; *P* = .0003) and a higher proportion of patients who are alive and progression-free at all landmark time points with nonoverlapping confidence intervals compared with chemotherapy.

The population in this study had progressive disease and extensive prior chemotherapy treatment in the advanced setting (median prior lines of chemotherapy = 3), and uniquely, all patients had received prior CDK4/6i, reflecting standard of care and allowing assessment of efficacy post-CDK4/6i treatment.

Benefit with SG was seen across most of the prespecified subgroups, including patients who received at least three prior chemotherapies for metastatic disease, had visceral metastases, and were age 65 years or older. The OS results (16% reduction in risk of death; *P* = .14) are not yet mature in the first planned interim analysis. Overall, results are consistent with those from the HR+/HER2– cohort of the phase I/II IMMU-132-01 basket study,[20] and performance of the control group is as previously reported.[6-10] Additional preplanned follow-up will provide more clarity into the survival benefit of SG in this patient population.

With limited advancements for treatments in this later-line setting, the most recent phase III trials in a similar patient population were EMBRACE,[8] which led to the approval of eribulin in 2010,[23] and Study 301.[24] A pooled analysis demonstrated a significant PFS improvement (4.1 *v* 3.4 months; HR, 0.84; *P* = .03) with eribulin, but no significant OS benefit (15.7 *v* 13.5 months; HR, 0.87; *P* = .06) versus other chemotherapies in patients with HR+ MBC.[25] Comparison with this pooled analysis is complicated by the fact that these two studies involved different patient populations with regard to the extent of prior chemotherapy for advanced disease (eligibility, EMBRACE: 2-5; Study 301: up to 2), HER2 status, and lack of prior use of CDK 4/6i.

Recently, the phase III DESTINY-Breast04 trial compared the ADC trastuzumab deruxtecan with chemotherapy of physician's choice in a patient population that partially overlaps with those enrolled in TROPiCS-02. Trastuzumab deruxtecan significantly improved both PFS and OS in patients with HR+/HER2-low MBC;[26] however, there are important differences in the study populations that limit comparisons with this trial. DESTINY-Breast04 only included patients with HER2-low (immunohistochemistry 1+ or immunohistochemistry 2+/in situ hybridization-negative) less heavily pretreated disease (median number of prior chemotherapies in the metastatic setting = 1), along with other differences. It is clear that the standard of care now includes treatment with ADCs for a number of breast cancer subtypes; sequential efficacy is yet to be evaluated.

SG demonstrated a manageable safety profile, with a low incidence of treatment discontinuation because of AEs

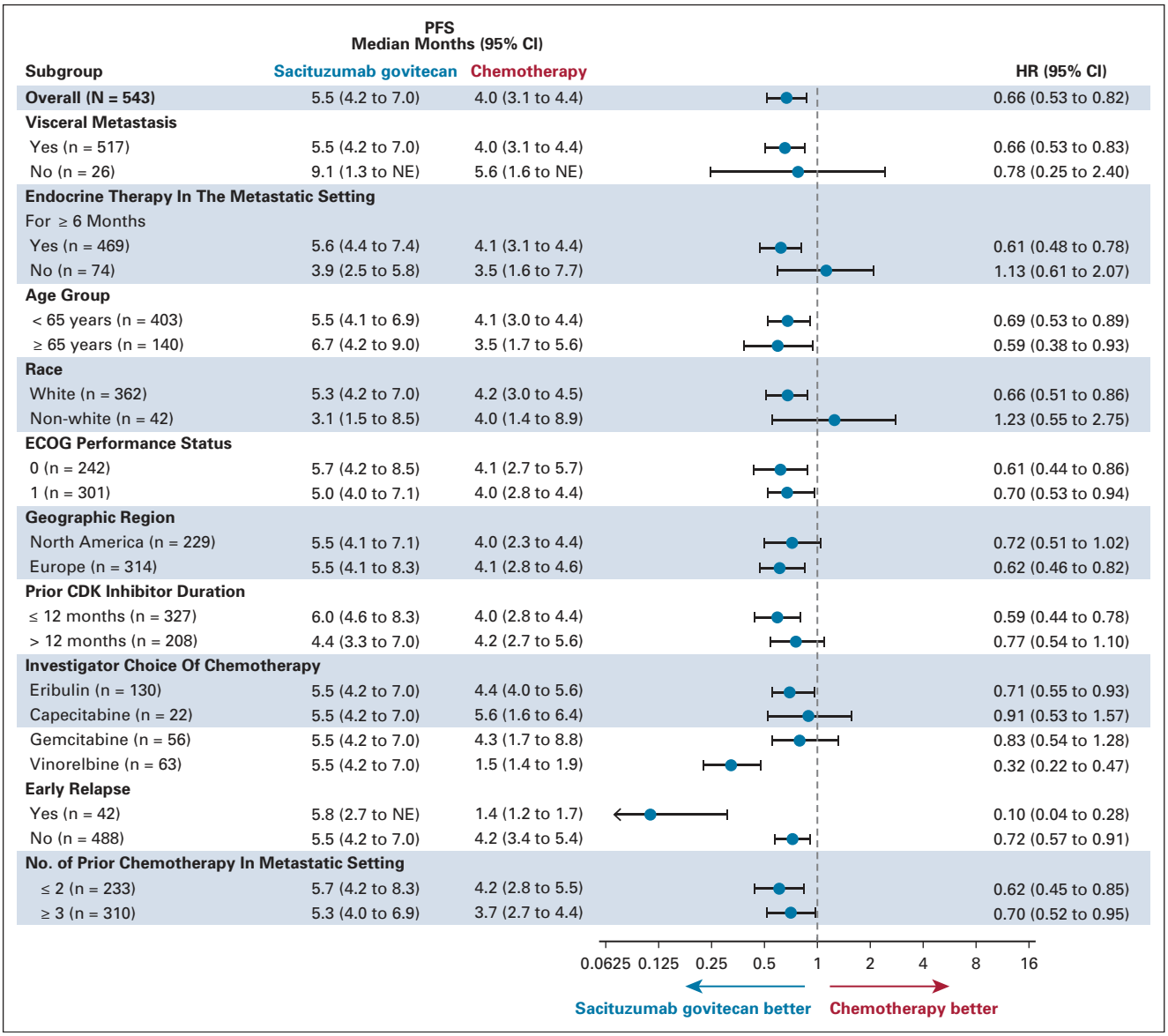


**FIG 3.** Subgroup analysis of PFS. Early relapse is defined as relapse to metastatic disease within 1 year of the end of (neo)adjuvant chemotherapy. Patients without chemotherapy in the (neo)adjuvant setting are not considered as early relapse. CDK, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NE, not evaluable; PFS, progression-free survival; SG, sacituzumab govitecan.

(6%). The most clinically relevant grade 3 or 4 AEs with SG were neutropenia and diarrhea, adequately managed with established supportive care measures, as previously reported.[27] The incidence of treatment-related febrile neutropenia and neuropathy was low with SG; no interstitial lung disease was reported in the SG arm of this trial.

This study has some potential limitations. A number of patients randomly assigned to the chemotherapy group were not treated (n = 22; 8%), likely because of patient preference not to receive standard chemotherapy. Most patients had visceral metastases (95%), consistent with aggressive disease, and had received multiple lines of chemotherapy, which are the factors associated with shorter PFS and higher neutropenia risk. The heterogeneity of prior treatments and chemotherapy of physician's choice options might have affected efficacy findings. Hormone receptor status was determined locally at any stage of disease, which has historically presented challenges for accurate assessment. The study did not require real-time BICR assessment of progressive disease, potentially increasing censoring.

SG is a Trop-2–directed ADC that demonstrated significant clinical benefit and manageable safety compared with standard chemotherapy in a phase III trial of patients with unresectable locally advanced or metastatic heavily pretreated, endocrine-resistant HR+/HER2– breast cancer, a population with limited treatment options. The magnitude of PFS benefit should be considered in the

**TABLE 3.** Summary of Treatment-Related AEs of Any Grade (≥ 10%) and Worst Grade 2 or Grade ≥ 3 (≥ 5%) in the Safety Population (all patients who received ≥ 1 dose of study treatment)

| | SG (n = 268) | | | Chemotherapy (n = 249) | | |
|---|---|---|---|---|---|---|
| **Treatment-Related AE[a]** | **All Grade** | **Grade 2** | **Grade ≥ 3** | **All Grade** | **Grade 2** | **Grade ≥ 3** |
| Hematologic, No. (%) | | | | | | |
| Neutropenia[b] | 188 (70) | 45 (17) | 136 (51) | 134 (54) | 29 (12) | 94 (38) |
| Anemia[c] | 91 (34) | 44 (16) | 17 (6) | 62 (25) | 31 (12) | 8 (3) |
| Leukopenia[d] | 37 (14) | 7 (3) | 23 (9) | 23 (9) | 8 (3) | 13 (5) |
| Lymphopenia[e] | 31 (12) | 11 (4) | 10 (4) | 25 (10) | 7 (3) | 8 (3) |
| Febrile neutropenia | 14 (5) | 0 | 14 (5) | 11 (4) | 0 | 11 (4) |
| GI, No. (%) | | | | | | |
| Diarrhea | 152 (57) | 56 (21) | 25 (9) | 41 (16) | 12 (5) | 3 (1) |
| Nausea | 148 (55) | 56 (21) | 3 (1) | 77 (31) | 23 (9) | 7 (3) |
| Vomiting | 50 (19) | 12 (4) | 1 (< 1) | 30 (12) | 8 (3) | 4 (2) |
| Constipation | 49 (18) | 8 (3) | 0 | 36 (14) | 8 (3) | 0 |
| Abdominal pain | 34 (13) | 12 (4) | 2 (1) | 17 (7) | 4 (2) | 0 |
| Others, No. (%) | | | | | | |
| Alopecia | 123 (46) | 105 (39) | 0 | 41 (16) | 18 (7) | 0 |
| Fatigue | 100 (37) | 37 (14) | 15 (6) | 73 (29) | 31 (12) | 6 (2) |
| Asthenia | 53 (20) | 26 (10) | 5 (2) | 37 (15) | 19 (8) | 2 (1) |
| Decreased appetite | 41 (15) | 9 (3) | 1 (< 1) | 34 (14) | 13 (5) | 1 (< 1) |
| Neuropathy[f] | 23 (9) | 8 (3) | 3 (1) | 38 (15) | 16 (6) | 6 (2) |

NOTE. Assessed in the safety population.

Abbreviations: AE, adverse event; SG, sacituzumab govitecan.

[a]Patients may report more than one event per preferred term. AEs were coded using Medical Dictionary for Regulatory Activities v24.0, and AE severity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

[b]Combined preferred terms of neutropenia and neutrophil count decreased.

[c]Combined preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased.

[d]Combined preferred terms of leukopenia and WBC count decreased.

[e]Combined preferred terms of lymphopenia and lymphocyte count decreased.

[f]Combined preferred terms of gait disturbance, hypoesthesia, muscular weakness, neuropathy peripheral, paresthesia, and peripheral sensory neuropathy.

context of the totality of efficacy data from this trial in the late-line setting, which all favored SG over chemotherapy, with a substantially higher proportion of patients alive and progression-free at all landmark time points. This novel agent directed to a highly expressed target may represent an important treatment option for these patients, addressing a critical unmet medical need. In accordance with the NCCN Guidelines for Breast Cancer, SG is a preferred therapy option for patients with HR+/HER2− cancers after prior treatment including endocrine therapy, a CDK4/6i and at least two lines of chemotherapy (including a taxane) for advanced breast cancer.[21] Neutropenia and diarrhea are known AEs with SG and should be prevented and managed according to established guidelines.[28-32] Additional phase III studies evaluating SG in HR+ breast cancer are underway, including GBG102-SASCIA (ClinicalTrials.gov identifier: NCT04595565)[33] and EVER-132-002 (ClinicalTrials.gov identifier: NCT04639986).


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Sacituzumab Govitecan in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer**

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[a]Denotes members of the TROPiCS-02 scientific steering committee.