ORIGINAL ARTICLE

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

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ABSTRACT

BACKGROUND

Patients with metastatic triple-negative breast cancer have a poor prognosis. Sacituzumab govitecan is an antibody–drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), which is expressed in the majority of breast cancers, coupled to SN-38 (topoisomerase I inhibitor) through a proprietary hydrolyzable linker.

METHODS

In this randomized, phase 3 trial, we evaluated sacituzumab govitecan as compared with single-agent chemotherapy of the physician's choice (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with relapsed or refractory metastatic triple-negative breast cancer. The primary end point was progression-free survival (as determined by blinded independent central review) among patients without brain metastases.

RESULTS

A total of 468 patients without brain metastases were randomly assigned to receive sacituzumab govitecan (235 patients) or chemotherapy (233 patients). The median age was 54 years; all the patients had previous use of taxanes. The median progression-free survival was 5.6 months (95% confidence interval [CI], 4.3 to 6.3; 166 events) with sacituzumab govitecan and 1.7 months (95% CI, 1.5 to 2.6; 150 events) with chemotherapy (hazard ratio for disease progression or death, 0.41; 95% CI, 0.32 to 0.52; P<0.001). The median overall survival was 12.1 months (95% CI, 10.7 to 14.0) with sacituzumab govitecan and 6.7 months (95% CI, 5.8 to 7.7) with chemotherapy (hazard ratio for death, 0.48; 95% CI, 0.38 to 0.59; P<0.001). The percentage of patients with an objective response was 35% with sacituzumab govitecan and 5% with chemotherapy. The incidences of key treatment-related adverse events of grade 3 or higher were neutropenia (51% with sacituzumab govitecan and 33% with chemotherapy), leukopenia (10% and 5%), diarrhea (10% and <1%), anemia (8% and 5%), and febrile neutropenia (6% and 2%). There were three deaths owing to adverse events in each group; no deaths were considered to be related to sacituzumab govitecan treatment.

CONCLUSIONS

Progression-free and overall survival were significantly longer with sacituzumab govitecan than with single-agent chemotherapy among patients with metastatic triple-negative breast cancer. Myelosuppression and diarrhea were more frequent with sacituzumab govitecan. (Funded by Immunomedics; ASCENT ClinicalTrials.gov number, NCT02574455; EudraCT number, 2017-003019-21.)

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Patients with metastatic triple-negative breast cancer (defined by a lack of tumor-cell expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 [HER2]) have poor survival outcomes.[1,2] Although immunotherapy has shown promising first-line clinical activity, single-agent chemotherapy remains standard for previously treated (beyond first-line) metastatic triple-negative breast cancer.[2-4] However, chemotherapy is associated with low response rates and short progression-free survival.[5-9]

Sacituzumab govitecan is an antibody–drug conjugate composed of an antitrophoblast cell-surface antigen 2 (Trop-2) IgG1 kappa antibody coupled to SN-38, the active metabolite of irinotecan and a topoisomerase I inhibitor,[10] through a proprietary hydrolyzable linker.[11,12] Trop-2 is a transmembrane calcium signal transducer that is highly expressed in multiple tumor types, including breast cancer (>90%).[13-15] After administration, the anti–Trop-2 monoclonal antibody binds to Trop-2 expressed on the tumor-cell surface and allows for targeted delivery of SN-38 to tumor cells.[12,16] Because free SN-38 is membrane-permeable, it may elicit antitumor effects in adjacent tumor cells (bystander effect) before internalization of the antibody–drug conjugate through hydrolysis of the linker or by intracellular SN-38 release after internalization.[12,14,17-20]

A phase 1–2, single-group, basket trial (IMMU-132-01) evaluated sacituzumab govitecan monotherapy in metastatic, epithelial cancers.[21-23] In the cohort of 108 patients with metastatic triple-negative breast cancer, an objective response rate of 33%, a median progression-free survival of 5.5 months, and a median overall survival of 13.0 months was observed with sacituzumab govitecan.[23] These results provided the basis for accelerated approval by the Food and Drug Administration (FDA) in April 2020, with full approval contingent on the results of the confirmatory phase 3 trial.[24] Here we provide the primary results of the confirmatory phase 3 ASCENT trial, a global, open-label, randomized trial evaluating the efficacy and safety of sacituzumab govitecan as compared with chemotherapy of the physician's choice (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with relapsed or refractory metastatic triple-negative breast cancer (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Methods

Patients

We enrolled patients with metastatic triple-negative breast cancer that was relapsed or refractory to two or more previous standard chemotherapy regimens (no upper limit) for unresectable, locally advanced or metastatic disease; previous therapy had to include a taxane (for any indication). Patients had to have triple-negative breast cancer according to standard American Society of Clinical Oncology–College of American Pathologists criteria.[25] Patients with stable brain metastases for at least 4 weeks before treatment were eligible for the trial but were excluded from the primary end-point analysis. Additional details are provided in the Supplementary Appendix.

Trial Design and Treatment

Patients were randomly assigned in a 1:1 ratio to receive sacituzumab govitecan (Trodelvy; Immunomedics, a subsidiary of Gilead Sciences) at a dose of 10 mg per kilogram of body weight intravenously on days 1 and 8 of each 21-day cycle or single-agent chemotherapy as determined before randomization: eribulin (1.4 mg per square meter of body-surface area [North America] or 1.23 mg per square meter [Europe] intravenously on days 1 and 8 of a 21-day cycle), vinorelbine (25 mg per square meter intravenously on day 1 weekly), capecitabine (1000 to 1250 mg per square meter orally twice daily on days 1 to 14 of a 21-day cycle), or gemcitabine (800 to 1200 mg per square meter intravenously on days 1, 8, and 15 of a 28-day cycle). Patients were stratified at randomization according to the number of previous chemotherapy regimens for advanced disease (2 or 3 vs. >3), the presence of known brain metastases at baseline (yes vs. no), and geographic region (North America vs. rest of the world). Treatment was continued until disease progression, unacceptable toxic effects, withdrawal from the trial, or death, whichever occurred first. No crossover to the sacituzumab govitecan group was allowed on progression with chemotherapy.

Polymorphisms in the gene encoding uridine diphosphate glucuronosyltransferase 1A1 (e.g., homozygosity for *UGT1A1*28*) are associated with SN-38 glucuronidation and an increased risk of hematologic toxic effects with sacituzumab govitecan.[18,23] Therefore, inhibitors and inducers of *UGT1A1* were used with caution.

TRIAL OVERSIGHT

The trial was approved by the institutional review board or ethics committee at each investigational site before initiation and was performed in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines for Good Clinical Practice, the FDA Code of Federal Regulations, national and local drug and data-protection laws, and other applicable regulatory requirements. All the patients provided written informed consent before enrollment.

The sponsor team, including former and current employees, designed and conducted the trial and gathered data in collaboration with the trial investigators. Trial oversight was provided by the trial steering committee and an independent data and safety monitoring committee. The data analysis was performed by Immunomedics, with statistical service rendered by Covance. The first author, with members of the steering committee and sponsor, guided the initial manuscript draft after an agreement to publish with editorial assistance from professional medical writers funded by the sponsor. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available at NEJM.org). All drafts of the manuscript were reviewed and approved by the authors.

ASSESSMENTS

The primary end point was progression-free survival (as determined by blinded independent central review) among patients without known baseline brain metastases (measured by computed tomography [CT] or magnetic resonance imaging [MRI] according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1[26]). Screening for brain metastasis was not mandatory. This prespecified primary end point, approved by regulatory authorities, allowed for investigation of the clinical benefit of sacituzumab govitecan in patients with metastatic triple-negative breast cancer without the confounding effects of brain metastases, a poor prognostic factor. Progression-free survival among patients with brain metastases will be reported separately. Secondary end points included overall survival, progression-free survival (investigator assessment), objective response, and safety. Imaging (CT or MRI) was performed every 6 weeks for 36 weeks, then every 9 weeks thereafter, until disease progression leading to treatment discontinuation. Responses required confirmatory scans 4 to 6 weeks later. Patients were contacted every 4 weeks to assess survival during long-term follow-up.

Safety was evaluated in all treated patients according to the *Medical Dictionary for Regulatory Activities*, version 22.1, and the severity of adverse events was coded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Premedication for infusion reactions was recommended, antiemetics and supportive measures were allowed, and diarrhea was treated at its onset (details are provided in the Methods section in the Supplementary Appendix).

STATISTICAL ANALYSIS

Anticipated enrollment was 488 patients, including patients with or without brain metastases at baseline, with a 15% cap for patients with brain metastases. The efficacy analyses involved the patients without brain metastases at baseline as well as the full trial population. Under the assumption of a hazard ratio for disease progression or death (sacituzumab govitecan vs. chemotherapy) of 0.667, 315 events of progression or death would provide an estimated 95% power to detect a significant between-group difference in progression-free survival in the primary efficacy population; the expected progression-free survival with sacituzumab govitecan was 4.5 months, as compared with 3 months with chemotherapy of the physician's choice. To control for type I error at a two-sided alpha level of 0.05, a hierarchical testing procedure (gatekeeping) was implemented for testing progression-free and overall survival. On the unanimous recommendation of the data and safety monitoring committee, the trial was halted in March 2020, and the process to conduct a final analysis was initiated owing to compelling evidence of efficacy.

Progression-free survival was defined as the time from randomization until objective tumor progression or death or was censored at the last radiographic assessment for patients without progression or death. Progression-free survival, overall survival, and response duration were analyzed with the use of the Kaplan–Meier method, with medians and corresponding 95% confidence intervals determined according to the Brookmeyer and Crowley method with log–log transformation. The 95% confidence intervals were not adjusted for multiplicity and cannot be used to

infer treatment effects. Treatment effect was compared with the use of a stratified log-rank test. Hazard ratios and their 95% confidence intervals were estimated with the use of a stratified Cox proportional-hazards model. The percentage of patients with an objective response was compared between the treatment groups with the use of the stratified Cochran–Mantel–Haenszel method. The same stratification factors that were used for the randomization were used in the stratified efficacy analyses.

RESULTS

PATIENT CHARACTERISTICS

A total of 529 patients with triple-negative breast cancer were enrolled between November 2017 and September 2019 at 88 sites in seven countries and were randomly assigned in a 1:1 ratio to receive sacituzumab govitecan or single-agent chemotherapy. A total of 61 patients had brain metastases at baseline, and 468 patients had no evidence of brain metastases (primary trial population for the analysis of efficacy); 235 patients were assigned to receive sacituzumab govitecan and 233 patients to receive single-agent chemotherapy prespecified by the investigator (54% eribulin, 20% vinorelbine, 13% capecitabine, and 12% gemcitabine). A total of 32 patients who were assigned to receive chemotherapy received no trial drug (26 patients) or withdrew consent (6 patients) before treatment; these 32 patients are included in the efficacy analysis but not in the safety analyses.

Patients had a median age of 54 years (range, 27 to 82); previous treatments included taxanes (100%), anthracyclines (82%), carboplatin (66%), inhibitors of programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) (27%), and poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors (7%) (Table 1). Patients had discontinued their previous treatment primarily because of progressive disease (78%); 3% had discontinued because of adverse events. Approximately 30% of the patients were not triple-negative at initial diagnosis, and this discordance between primary tumor staining and metastatic recurrence underscores the importance of obtaining biopsy samples at the time of recurrence. At the time of data cutoff (March 11, 2020), 15 of 235 patients (6%) continued to receive sacituzumab govitecan and 0 of 233 patients continued to receive chemotherapy (Fig. S2).

EFFICACY IN PATIENTS WITHOUT BRAIN METASTASES

As of the March 11, 2020, data cutoff, the median follow-up time from patients' randomization date was 17.7 months (range, 5.8 to 28.1). The median progression-free survival as determined by central review (primary end point) was 5.6 months (95% confidence interval [CI], 4.3 to 6.3) with sacituzumab govitecan and 1.7 months (95% CI, 1.5 to 2.6) with chemotherapy (hazard ratio for disease progression or death, 0.41; 95% CI, 0.32 to 0.52; P<0.001) (Table 2 and Fig. 1A). Progression-free survival as determined by central review was consistent with investigator assessments (5.5 months with sacituzumab govitecan and 1.7 months with chemotherapy; hazard ratio for disease progression or death, 0.35; 95% CI, 0.28 to 0.44) (Fig. S3). The median overall survival was 12.1 months (95% CI, 10.7 to 14.0) with sacituzumab govitecan and 6.7 months (95% CI, 5.8 to 7.7) with chemotherapy (hazard ratio for death, 0.48; 95% CI, 0.38 to 0.59; P<0.001) (Table 2 and Fig. 1B).

The progression-free survival benefit of sacituzumab govitecan over chemotherapy was consistently observed across all predefined subgroups (Fig. 2), including patients 65 years of age or older (median, 7.1 vs. 2.4 months), those with more than three previous therapies (5.6 vs. 2.5 months), those with previous use of PD-1 or PD-L1 inhibitors (4.2 vs. 1.6 months), those with triple-negative breast cancer at initial diagnosis (5.7 vs. 1.6 months), those without triple-negative breast cancer at initial diagnosis (4.6 vs. 2.3 months), and those with liver metastases (4.2 vs. 1.5 months). Subgroup analyses of median overall survival similarly favored sacituzumab govitecan over chemotherapy (Fig. S4).

The percentage of patients with an objective response was 35% with sacituzumab govitecan and 5% with chemotherapy (Table 2 and Fig. 1C). Clinical benefit was also noted in all subgroups evaluated (Fig. S5). The median duration of response was 6.3 months (95% CI, 5.5 to 9.0) with sacituzumab govitecan and 3.6 months (95% CI, 2.8 to could not be estimated) with chemotherapy (hazard ratio, 0.39; 95% CI, 0.14 to 1.07) (Fig. S6). The median time to response was 1.5 months (range, 0.7 to 10.6) with sacituzumab

govitecan and 1.5 months (range, 1.3 to 4.2) with chemotherapy.

EFFICACY IN THE FULL POPULATION

Among all randomly assigned patients (with or without brain metastases), the median progression-free survival was 4.8 months (95% CI, 4.1 to 5.8) with sacituzumab govitecan and 1.7 months (95% CI, 1.5 to 2.5) with chemotherapy (hazard ratio for disease progression or death, 0.43; 95% CI, 0.35 to 0.54) (Table 2 and Fig. 1D). The median overall survival was 11.8 months (95% CI, 10.5 to 13.8) with sacituzumab govitecan and 6.9 months (95% CI, 5.9 to 7.7) with chemotherapy (hazard ratio, 0.51; 95% CI, 0.41 to 0.62) (Fig. S7).

SAFETY

The safety population consisted of the 482 patients who received at least one treatment dose (258 in the sacituzumab govitecan group and 224 in the chemotherapy group). The median relative dose intensity with sacituzumab govitecan was 99.7%; patients received sacituzumab govitecan for a median of 4.4 months (maximum, 22.9 months). Overall, 99.6% of the patients in the sacituzumab govitecan group and 99.1% of those in the chemotherapy group received preinfusion or concomitant medication (see the Results section in the Supplementary Appendix).

The most common treatment-related adverse events of any grade were neutropenia (63% with sacituzumab govitecan and 43% with chemotherapy), diarrhea (59% and 12%), nausea (57% and 26%), alopecia (46% and 16%), fatigue (45% and 30%), and anemia (34% and 24%) (Table 3). The most frequent treatment-related adverse events of grade 3 or higher were neutropenia (51% with sacituzumab govitecan and 33% with chemotherapy), leukopenia (10% and 5%), diarrhea (10% and <1%), anemia (8% and 5%), and febrile neutropenia (6% and 2%). In the sacituzumab govitecan group, treatment-related adverse events involving rash of any grade (in 22 patients [9%] overall; 1 patient with a grade 3 event) and ocular toxic effects (in 12 patients [5%]; no patients with an event of grade >1) occurred with low incidence, and no neuropathy of greater than grade 2 was observed. No grade 1 or 2 interstitial lung disease was reported, and grade 3 pneumonitis developed in 1 patient (see the Results section in the Supplementary Appendix). In the chemotherapy group, treatment-related adverse events involving rash of any grade (in 3 patients [1%] overall; 1 patient with a grade 3 event), ocular toxic effects (in 6 patients [3%]; no patients with an event of grade >2), and neuropathy of greater than grade 2 (2 patients [1%]) occurred at low frequency, and no interstitial lung disease was reported.

Neutropenia was managed with dose reduction, dose delay, or both and with growth-factor support after day 1 of cycle 1. The incidence of grade 3 and 4 febrile neutropenia was 5% and 1%, respectively, with sacituzumab govitecan and 2% and less than 1%, respectively, with chemotherapy. Concomitant growth-factor support was given to 49% of the patients treated with sacituzumab govitecan and 23% of those treated with chemotherapy. (For dose-modification recommendations for severe neutropenia and nonneutropenic toxic effects, see Fig. S8.) Diarrhea (predominantly of grade 1) was a common adverse event; the incidence of grade 3 diarrhea was 10% with sacituzumab govitecan and less than 1% with chemotherapy, and no grade 4 events were noted in either group (Table 3).

Serious treatment-related adverse events were reported in 39 patients (15%) treated with sacituzumab govitecan and 19 patients (8%) treated with chemotherapy. Dose reductions due to adverse events occurred with similar frequency in the two groups (22% of the patients who received sacituzumab govitecan and 26% of those who received chemotherapy). Adverse events leading to treatment discontinuation were infrequent, occurring in 12 patients (5%) in each group. A total of 3 patients treated with sacituzumab govitecan and 3 treated with chemotherapy died owing to adverse events (in the sacituzumab govitecan group, owing to respiratory failure [2 patients] and postobstructive pneumonia [1 patient]; in the chemotherapy group, owing to neutropenic sepsis, sepsis, and general physical health deterioration related to progressive disease [1 patient each]). None of the deaths in the sacituzumab govitecan group were deemed to be treatment-related, whereas one death in the chemotherapy group was deemed to be treatment-related (neutropenic sepsis; see the Results section in the Supplementary Appendix).

Table 1. Baseline Characteristics and Previous Treatment of Patients without Brain Metastases.*

Characteristic	Sacituzumab Govitecan (N=235)	Chemotherapy (N=233)†
Sex — no. (%)		
Female	233 (99)	233 (100)
Male	2 (1)	0
Median age (range) — yr	54 (29–82)	53 (27–81)
Race or ethnic group — no. (%)‡		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG performance-status score at screening — no. (%)§		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
Germline *BRCA1* or *BRCA2* mutation status — no. (%)¶		
Negative	133 (57)	125 (54)
Positive‖	16 (7)	18 (8)
Triple-negative breast cancer at initial diagnosis — no. (%)		
Yes	165 (70)	157 (67)
No**	70 (30)	76 (33)
Median time from diagnosis of metastatic disease to enrollment (range) — mo††	15.8 (0–202.9)	15.2 (0–140.1)
Major tumor locations — no. (%)‡‡		
Lung	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Axillary lymph nodes	57 (24)	73 (31)
Bone§§	48 (20)	55 (24)
Median no. of previous anticancer regimens (range) ¶¶	3 (1–16)	3 (1–12)
Previous chemotherapy regimens — no. (%)		
2 or 3	166 (71)	164 (70)
>3	69 (29)	69 (30)
Previous chemotherapy drugs — no. (%)‖‖		
Taxanes	235 (100)	233 (100)
Anthracyclines	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous use of PARP inhibitors — no. (%)	17 (7)	18 (8)
Previous use of PD-1 or PD-L1 inhibitors — no. (%)	67 (29)	60 (26)

* PARP denotes poly(adenosine diphosphate–ribose) polymerase, PD-1 programmed death 1, and PD-L1 programmed death ligand 1.
† The chemotherapy group included patients randomly assigned to receive eribulin (126 patients), vinorelbine (47), capecitabine (31), and gemcitabine (29).
‡ Race was reported by the patients.

Table 1. (Continued.)

§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating that the patient is fully active with no restrictions, 1 indicating that the patient is ambulatory and able to carry out work of a light or sedentary nature but restricted in physically strenuous activity, and higher numbers indicating increasing degrees of disability.
¶ Patients who did not undergo *BRCA1* or *BRCA2* germline testing or who had inconclusive results are not included.
‖ Among the patients with *BRCA1* or *BRCA2* mutations at baseline, 10 of 16 (62%) in the sacituzumab govitecan group and 11 of 18 (61%) in the chemotherapy group had previously received PARP inhibitors.
** Patients whose initial diagnosis was hormone receptor–positive or human epidermal growth factor receptor 2–positive breast cancer had a median time from diagnosis of metastatic disease to enrollment of 22.5 months (range, 2.1 to 202.9) in the sacituzumab govitecan group and 21.2 months (range, 1.1 to 140.1) in the chemotherapy group.
†† The time from diagnosis of metastatic disease is defined as number of days from the date of first diagnosis of metastasis to the date of trial entry divided by 30.4375.
‡‡ Tumor locations were based on independent central review of target and nontarget lesions at baseline.
§§ Patients with bone-only disease were not permitted in the trial.
¶¶ Anticancer regimens refer to any previous regimens for metastatic or locally advanced disease or in the neoadjuvant context that were used to treat an eligible patient with breast cancer. Previous therapy in the adjuvant context is excluded from this count.
‖‖ Shown are most common chemotherapy drugs used. Taxanes include paclitaxel, nab-paclitaxel, and docetaxel. Anthracyclines include doxorubicin, daunorubicin, epirubicin, and different formulations of these agents.

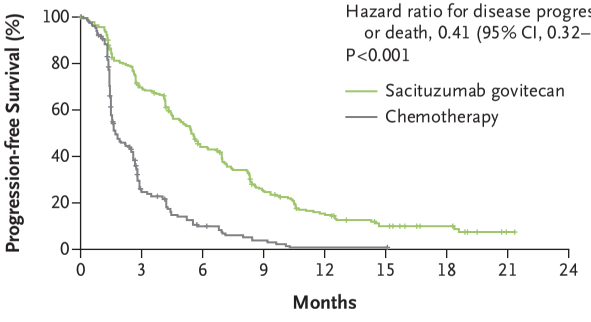
Table 2. Summary of Treatment Efficacy, as Determined by Independent Central Review.*

Variable	Patients without Brain Metastases		Full Population†	
	Sacituzumab Govitecan (N=235)	Chemotherapy (N=233)	Sacituzumab Govitecan (N=267)	Chemotherapy (N=262)
Median progression-free survival (95% CI) — mo	5.6 (4.3–6.3)	1.7 (1.5–2.6)	4.8 (4.1–5.8)	1.7 (1.5–2.5)
Hazard ratio for disease progression or death (95% CI)	0.41 (0.32–0.52)‡		0.43 (0.35–0.54)	
Median overall survival (95% CI) — mo	12.1 (10.7–14.0)	6.7 (5.8–7.7)	11.8 (10.5–13.8)	6.9 (5.9–7.7)
Hazard ratio for death (95% CI)	0.48 (0.38–0.59)‡		0.51 (0.41–0.62)	
Objective response — no. of patients (%)§	82 (35)	11 (5)	83 (31)	11 (4)
Complete response	10 (4)	2 (1)	10 (4)	2 (1)
Partial response	72 (31)	9 (4)	73 (27)	9 (3)
Clinical benefit — no. of patients (%)¶	105 (45)	20 (9)	108 (40)	21 (8)
Stable disease — no. of patients (%)	81 (34)	62 (27)	96 (36)	71 (27)
Stable disease for ≥6 mo	23 (10)	9 (4)	25 (9)	10 (4)
Progressive disease — no. of patients (%)	54 (23)	89 (38)	65 (24)	100 (38)
Response could not be evaluated — no. of patients (%)‖	18 (8)	71 (30)	23 (9)	80 (31)
Median time to response (95% CI) — mo	1.5 (0.7–10.6)	1.5 (1.3–4.2)	1.5 (0.7–10.6)	1.5 (1.3–4.2)
Median duration of response (95% CI) — mo	6.3 (5.5–9.0)	3.6 (2.8–NE)	6.3 (5.5–9.0)	3.6 (2.8–NE)
Hazard ratio (95% CI)	0.39 (0.14–1.07)			

* NE denotes could not be estimated.
† The full population includes all randomly assigned patients (with and without brain metastases).
‡ P<0.001.
§ An objective response was defined as a complete response or partial response.
¶ Clinical benefit was defined as a complete response, a partial response, or stable disease with a duration of at least 6 months.
‖ Response could not be evaluated for a variety of reasons, including a lack of postbaseline images or unreadable images.

A Progression-free Survival among Patients without Brain Metastases

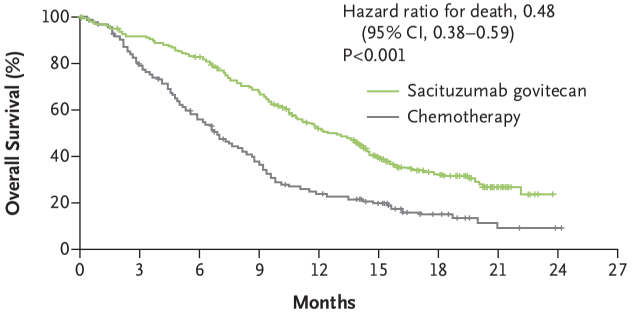
	No. of Patients	No. of Events	Median Progression-free Survival (mo (95% CI))
Sacituzumab Govitecan	235	166	5.6 (4.3–6.3)
Chemotherapy	233	150	1.7 (1.5–2.6)



No. at Risk								
Sacituzumab govitecan	235	154	91	49	28	15	9	1
Chemotherapy	233	39	14	5	1	1	0	0

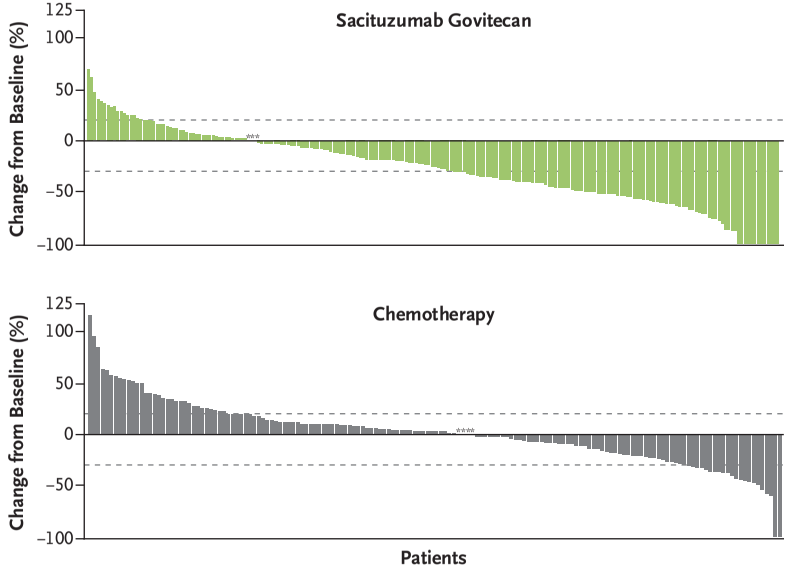
B Overall Survival among Patients without Brain Metastases

	No. of Patients	No. of Events	Median Overall Survival (mo (95% CI))
Sacituzumab Govitecan	235	155	12.1 (10.7–14.0)
Chemotherapy	233	185	6.7 (5.8–7.7)



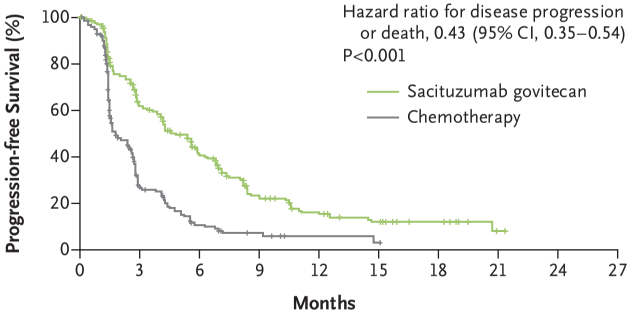
No. at Risk									
Sacituzumab govitecan	235	214	190	153	107	70	37	13	0
Chemotherapy	233	173	117	74	45	30	11	3	1

C Change in Tumor Size among Patients without Brain Metastases



D Progression-free Survival in the Full Population

	No. of Patients	No. of Events	Median Progression-free Survival (mo (95% CI))
Sacituzumab Govitecan	267	190	4.8 (4.1–5.8)
Chemotherapy	262	171	1.7 (1.5–2.5)



No. at Risk								
Sacituzumab govitecan	267	145	82	38	23	14	8	1
Chemotherapy	262	41	13	6	2	1	0	0

Figure 1 (facing page). Efficacy Results in Patients without Brain Metastases at Baseline and in the Full Population.
Panels A and B show progression-free and overall survival, respectively, among patients without brain metastases. Progression-free survival was determined by blinded independent central review according to Response Evaluation Criteria in Solid Tumors, version 1.1. Panel C shows a waterfall plot of the best percent change in the sum of the diameters of target lesions in patients without brain metastases who had at least one response assessment by central review (212 patients in the sacituzumab govitecan group and 160 in the chemotherapy group). Asterisks at 0 denote patients who had no change from baseline in tumor size. Panel D shows progression-free survival among all randomly assigned patients (with or without brain metastases).

DISCUSSION

This phase 3, randomized clinical trial involving patients with metastatic triple-negative breast cancer showed a significant benefit of sacituzumab govitecan, a Trop-2–directed antibody–drug conjugate, over chemotherapy with respect to progression-free survival (hazard ratio for disease progression or death, 0.41; P<0.001) and overall survival (hazard ratio for death, 0.48; P<0.001). The benefit with sacituzumab govitecan was seen in all clinical and prespecified subgroups, including patients who received previous treatment with PD-1 or PD-L1 inhibitors. The percentage of patients with an objective response was higher with sacituzumab govitecan than with chemotherapy (35% vs. 5%). A similar clinical benefit in progression-free and overall survival was observed in the full trial population of patients with or without brain metastases.

Although cross-trial comparisons should be made with caution, the results with single-agent chemotherapy (control group) that were observed in this trial are broadly consistent with survival rates in previous studies.[5-9] The KEYNOTE-119 trial, which involved patients who were less

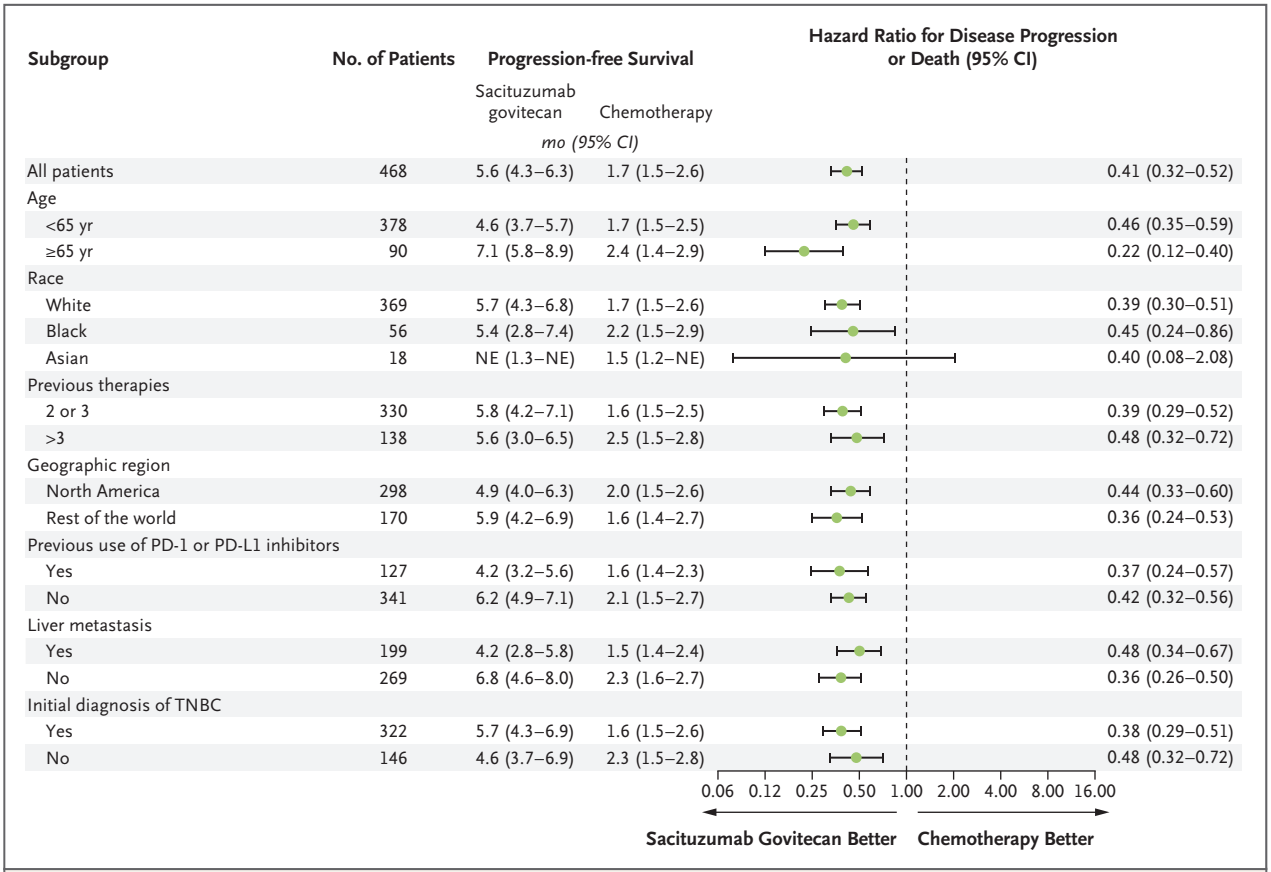


Figure 2. Subgroup Analysis of Progression-free Survival.
NE denotes could not be evaluated, PD-1 programmed death 1, PD-L1 programmed death ligand 1, and TNBC triple-negative breast cancer.

Table 3. Summary of Treatment-Related Adverse Events in the Safety Population.*

Adverse Event	Sacituzumab Govitecan (N=258)			Chemotherapy (N=224)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	252 (98)	117 (45)	48 (19)	192 (86)	71 (32)	33 (15)
Hematologic event						
Neutropenia†	163 (63)	88 (34)	44 (17)	96 (43)	45 (20)	29 (13)
Anemia‡	89 (34)	20 (8)	0	54 (24)	11 (5)	0
Leukopenia§	41 (16)	23 (9)	3 (1)	25 (11)	10 (4)	2 (1)
Thrombocytopenia¶	14 (5)	2 (1)	2 (1)	25 (11)	3 (1)	0
Febrile neutropenia	15 (6)	12 (5)	3 (1)	5 (2)	4 (2)	1 (<1)
Gastrointestinal event						
Diarrhea	153 (59)	27 (10)	0	27 (12)	1 (<1)	0
Nausea	147 (57)	6 (2)	1 (<1)	59 (26)	1 (<1)	0
Vomiting	75 (29)	2 (1)	1 (<1)	23 (10)	1 (<1)	0
Constipation	44 (17)	0	0	32 (14)	0	0
Abdominal pain	29 (11)	3 (1)	0	9 (4)	1 (<1)	0
General disorders and administration-site conditions						
Fatigue	115 (45)	8 (3)	0	68 (30)	12 (5)	0
Asthenia	31 (12)	2 (1)	0	23 (10)	3 (1)	0
Skin and subcutaneous disorders: alopecia‖	119 (46)	0	0	35 (16)	0	0
Metabolism and nutrition disorders: decreased appetite	51 (20)	4 (2)	0	32 (14)	1 (<1)	0
Nervous system disorders**††	64 (25)	1 (<1)	0	53 (24)	5 (2)	0
Respiratory, thoracic, and mediastinal disorders††	41 (16)	5 (2)‡‡	0	17 (8)	1 (<1)	0
Musculoskeletal and connective-tissue disorders††	32 (12)	0	0	28 (12)	3 (1)	0
Infections and infestations††	30 (12)	6 (2)	1 (<1)	22 (10)	4 (2)	3 (1)

* Shown are adverse events of any grade that occurred in at least 10% of the patients in either treatment group and adverse events of grade 3 or higher that occurred in at least 5% of the patients in either treatment group. The safety population included all the patients who received at least one dose of trial treatment, irrespective of status with respect to brain metastases at baseline.
† The neutropenia category included neutropenia and decreased neutrophil count.
‡ The anemia category included anemia, decreased hemoglobin level, and decreased red-cell count.
§ The leukopenia category included leukopenia and decreased white-cell count.
¶ The thrombocytopenia category included thrombocytopenia and decreased platelet count.
‖ With respect to skin and subcutaneous disorders, there was one grade 3 rash in each of the sacituzumab govitecan and chemotherapy groups.
** There were no grade 3 or 4 neuropathy events with sacituzumab govitecan. In the chemotherapy group, there were grade 3 events of peripheral neuropathy (in two patients) and peripheral sensory neuropathy (in two patients).
†† For this category, the overall incidence of adverse events of any grade was at least 10%, but the incidence of all individual adverse events of any grade was 5% or less.
‡‡ There was one case of grade 3 pneumonitis in the sacituzumab govitecan group (see the Supplementary Appendix); there were none in the chemotherapy group.

heavily pretreated than those in the ASCENT trial, compared second- or third-line pembrolizumab with standard chemotherapy; efficacy outcomes were aligned with historical expectations of single-agent chemotherapy (median progression-free survival of 3.3 months and median overall survival of 10.8 months).[9] A pooled analysis of two phase 3 studies (EMBRACE and Study 301) included 428 patients with triple-negative breast cancer: 243 patients received eribulin, and 185 received control (treatment of the physician's choice in EMBRACE and capecitabine in Study 301). The pooled analysis showed a 2.8-month median progression-free survival and 12.9-month median overall survival with eribulin and a 2.6-month progression-free survival and 8.2-month overall survival with standard chemotherapy.[27]

Sacituzumab govitecan has toxic effects that may require management; however, our trial showed a low incidence of treatment discontinuation due to adverse events (5%). Sacituzumab govitecan was administered over a long duration, up to 22.9 months (median, 4.4 months). The most clinically relevant grade 3 or 4 adverse events with sacituzumab govitecan were neutropenia and diarrhea, which were managed with established supportive care measures. The incidence of treatment-related pneumonitis or interstitial lung disease was low, with only one patient having reversible grade 3 pneumonitis in the context of multiple confounding factors.

Although sacituzumab govitecan is the only antibody–drug conjugate approved for metastatic triple-negative breast cancer in the United States, antibody–drug conjugates have been established as treatment options in HER2-positive breast cancer.[28] Both ado-trastuzumab emtansine (T-DM1)[29] and fam-trastuzumab deruxtecan-nxki (DS-8201a)[30] are approved for patients with HER2-positive disease. Ado-trastuzumab emtansine combines trastuzumab with a microtubule inhibitor DM1 through a thioether linker, with toxic effects (e.g., thrombocytopenia and hepatotoxic effects) associated with the cytotoxic component.[29] Fam-trastuzumab deruxtecan-nxki combines an anti-HER2 fam-trastuzumab with a topoisomerase inhibitor, deruxtecan (an exatecan derivative), as its payload, with toxic effects (myelosuppression, diarrhea, and the rare but known toxic effect of potentially fatal interstitial lung disease) associated with the cytotoxic component.[31]

Potential limitations of the current trial included the number of patients assigned to the chemotherapy group (32) who withdrew consent before the initiation of trial treatment or who decided not to start trial treatment. The comparison of sacituzumab govitecan with multiple standard-of-care chemotherapies also provided some challenges owing to the heterogeneity of safety risks associated with each chemotherapy agent, and the trial was not powered to examine differences between the individual agents. Tissue biopsies were optional rather than protocol-mandated immediately before trial entry.

Sacituzumab govitecan is a first-in-class, Trop-2–directed antibody–drug conjugate[18]; it showed a significant benefit with respect to progression-free and overall survival as compared with standard-of-care chemotherapy. Toxic effects, particularly myelosuppression and diarrhea, were more frequent with sacituzumab govitecan than with chemotherapy. Multiple studies of sacituzumab govitecan involving patients with breast cancer are under way, including evaluation of the agent as neoadjuvant therapy in early triple-negative breast cancer (NeoSTAR [ClinicalTrials.gov number, NCT04230109]), as adjuvant therapy (GBG102-SASCIA [EudraCT number, 2019-004100-35]), in the metastatic context in combination with immunotherapy-based regimens (Morpheus-TNBC [ClinicalTrials.gov number, NCT03424005] and Saci-IO TNBC [NCT04468061]) or with a PARP inhibitor (NCT04039230) in advanced triple-negative breast cancer, and in hormone receptor–positive and HER2-negative metastatic breast cancer (TROPiCS-02 [NCT03901339]).

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APPENDIX

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