ORIGINAL ARTICLE

Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer

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ABSTRACT

BACKGROUND

Standard chemotherapy is associated with low response rates and short progression-free survival among patients with pretreated metastatic triple-negative breast cancer. Sacituzumab govitecan-hziy is an antibody–drug conjugate that combines a humanized monoclonal antibody, which targets the human trophoblast cell-surface antigen 2 (Trop-2), with SN-38, which is conjugated to the antibody by a cleavable linker. Sacituzumab govitecan-hziy enables delivery of high concentrations of SN-38 to tumors.

METHODS

We conducted a phase 1/2 single-group, multicenter trial involving patients with advanced epithelial cancers who received sacituzumab govitecan-hziy intravenously on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxic effects. A total of 108 patients received sacituzumab govitecan-hziy at a dose of 10 mg per kilogram of body weight after receiving at least two previous anticancer therapies for metastatic triple-negative breast cancer. The end points included safety; the objective response rate (according to Response Evaluation Criteria in Solid Tumors, version 1.1), which was assessed locally; the duration of response; the clinical benefit rate (defined as a complete or partial response or stable disease for at least 6 months); progression-free survival; and overall survival. Post hoc analyses determined the response rate and duration, which were assessed by blinded independent central review.

RESULTS

The 108 patients with triple-negative breast cancer had received a median of 3 previous therapies (range, 2 to 10). Four deaths occurred during treatment; 3 patients (2.8%) discontinued treatment because of adverse events. Grade 3 or 4 adverse events (in ≥10% of the patients) included anemia and neutropenia; 10 patients (9.3%) had febrile neutropenia. The response rate (3 complete and 33 partial responses) was 33.3% (95% confidence interval [CI], 24.6 to 43.1), and the median duration of response was 7.7 months (95% CI, 4.9 to 10.8); as assessed by independent central review, these values were 34.3% and 9.1 months, respectively. The clinical benefit rate was 45.4%. Median progression-free survival was 5.5 months (95% CI, 4.1 to 6.3), and overall survival was 13.0 months (95% CI, 11.2 to 13.7).

CONCLUSIONS

Sacituzumab govitecan-hziy was associated with durable objective responses in patients with heavily pretreated metastatic triple-negative breast cancer. Myelotoxic effects were the main adverse reactions. (Funded by Immunomedics; IMMU-132-01 ClinicalTrials.gov number, NCT01631552.)

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Triple-negative breast cancer, which is defined by a lack of tumor-cell expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2),[1,2] accounts for approximately 15% of invasive breast cancers[3-5] and is associated with aggressive tumor biology and a poor prognosis. Triple-negative breast cancer is more common in younger women than in older women and in black persons than in persons of other races and ethnic groups, and it is often associated with visceral metastases.[2,4]

Although targeted therapies have benefited patients with other subtypes of breast cancer, and several targeted therapies for hormone-receptor–positive and HER2-positive breast cancer have recently been approved for use,[6-9] sequential single-agent chemotherapy remains the standard of care for patients with metastatic triple-negative breast cancer.[7,10] Recently, a progression-free survival of 7.2 months was reported with investigational use of atezolizumab and nab-paclitaxel combination therapy in previously untreated patients with metastatic triple-negative breast cancer.[11] However, a majority of patients have disease progression after receiving first-line therapy, and standard therapeutic options are limited to chemotherapy. Standard chemotherapy is associated with low response rates (10 to 15%) and short progression-free survival (2 to 3 months) among patients with pretreated metastatic triple-negative breast cancer.[12-16] Overall survival among patients with this form of breast cancer has not changed over the past 20 years[6]; this highlights the need for advances in therapeutic options for these patients.

Sacituzumab govitecan-hziy (IMMU-132; Immunomedics) is an antibody–drug conjugate in which SN-38 (an active metabolite of irinotecan), a topoisomerase I inhibitor, is coupled to the humanized antitrophoblast cell-surface antigen 2 (Trop-2) monoclonal antibody hRS7 IgG1κ through the cleavable CL2A linker.[17] Trop-2, a transmembrane calcium signal transducer, is overexpressed in many epithelial cancers, and it stimulates cancer-cell growth.[18,19] Trop-2 is detected in breast cancer cells, including those in triple-negative breast cancer,[19,20] and its expression is reported in more than 85% of tumors.[21,22] On binding to Trop-2, hRS7 (in free or conjugated form) is internalized and delivers SN-38 into the tumor cell.[23] In addition, because of the cleavable linker, SN-38 is released in tumors both intracellularly and in the tumor microenvironment, thereby allowing for the delivery of therapeutic concentrations of the drug in bystander cells to which the conjugate has not bound. Sacituzumab-bound tumor cells are killed by intracellular uptake of SN-38, and adjacent tumor cells are killed by the extracellular release of SN-38.[24]

IMMU-132-01 is a phase 1/2, basket design, open-label, single-group, multicenter trial involving patients with various types of advanced solid cancers who have received at least one previous therapy for metastatic disease. Preliminary results for 69 patients with metastatic triple-negative breast cancer have been reported.[25] In 2016, sacituzumab govitecan-hziy was assigned a "breakthrough therapy" designation by the Food and Drug Administration (FDA) for the treatment of patients with metastatic triple-negative breast cancer who have received at least two previous therapies for metastatic disease, and, accordingly, the protocol was amended to require further enrollment in a more defined population of patients with metastatic triple-negative breast cancer who had received at least two lines of previous therapy, including previous taxane therapy. Here, we report updated results for all patients who received sacituzumab govitecan-hziy as a third-line or higher line of therapy for metastatic triple-negative breast cancer at the clinically selected dose level of 10 mg per kilogram of body weight.

METHODS

TRIAL DESIGN AND OVERSIGHT

Eligibility criteria that were previously described for patients with metastatic triple-negative breast cancer[25] also apply to the overall trial population (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). Sacituzumab govitecan-hziy was administered as an intravenous infusion on days 1 and 8 of 21-day cycles until disease progression or unacceptable adverse events. In case of severe treatment-related adverse events, dose reductions of 25% were allowed for the first occurrence and of 50% for the second occurrence, with treatment discontinuation at the third occurrence. Hematopoietic growth factors or blood transfusions were allowed at the investigator's discretion; however, prophylactic treatment before the first dose (cycle 1, day 1) was not allowed. All patients with metastatic triple-negative breast cancer in the

efficacy data set received treatment at a starting dose of 10 mg per kilogram.

The sponsor, Immunomedics, designed the trial and gathered the data. Data analysis was performed by Veristat and by authors who are employed by Immunomedics. All the authors assume responsibility for the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol, which is available at NEJM.org. The first draft of the manuscript was written by the first author with the sponsor and a medical writer paid by the sponsor. All the authors contributed to the writing, review, and revision of the manuscript.

EFFICACY EVALUATIONS

Staging computed tomography (CT) and magnetic resonance imaging (MRI) were performed at baseline and at 8-week intervals from the start of treatment until disease progression requiring discontinuation of treatment. Confirmatory CT and MRI were performed no sooner than 4 weeks after an initial partial or complete response. Subsequent imaging was performed at 8-week intervals after the confirmatory imaging.

The primary efficacy end point was the objective response rate. Assessment of response was performed according to Response Evaluation Criteria in Solid Tumors, version 1.1. Local assessments were used for treatment decisions and for the primary efficacy analysis. Other efficacy end points were the time to response and the duration of response in patients who had a response, the clinical benefit rate (defined as a complete or partial response or stable disease for at least 6 months), and progression-free and overall survival.

Blinded independent central review of staging scans was also obtained for the 56 patients (of the 108 with metastatic triple-negative breast cancer) who had complete or partial remission, or at least a 20% reduction in the baseline sum of the diameters of the target lesions, according to local site evaluation. This blinded independent review, which was performed by Intrinsic Imaging, included reviews by two independent radiologists and a third adjudicating radiologist, if needed.

Table 1. Characteristics of the Patients at Baseline.

Characteristic	Patients (N=108)
Sex — no. (%)	
Female	107 (99.1)
Male	1 (0.9)
Median age (range) — yr	55 (31–80)
Race or ethnic group — no. (%)*	
White	82 (75.9)
Black	8 (7.4)
Asian	3 (2.8)
Other or not specified†	15 (13.9)
ECOG performance-status score — no. (%)‡	
0	31 (28.7)
1	77 (71.3)
Previous anticancer regimens — median no. (range)	3 (2–10)
Previous use of taxanes or anthracyclines for metastatic or nonmetastatic disease — no. (%)	
Taxanes	106 (98.1)
Anthracyclines	93 (86.1)
Previous use of chemotherapy drugs for metastatic disease — no. (%)	
Cyclophosphamide	20 (18.5)
Platinum agents	74 (68.5)
Gemcitabine	59 (54.6)
Fluoropyrimidine agents	56 (51.9)
Eribulin	49 (45.4)
Vinorelbine	17 (15.7)
Previous use of checkpoint inhibitors — no. (%)	18 (16.7)
Most common sites of disease — no. (%)	
Visceral organ§	83 (76.9)
Lung or pleura	61 (56.5)
Liver	45 (41.7)
Other visceral organ: adrenal glands, pancreas, and kidneys	7 (6.5)
Nonvisceral site	25 (23.1)

* Race or ethnic group was reported by the patients.
† Eleven patients did not indicate or declined to indicate their race or ethnic group; four identified as Native American, Dominican, Hispanic, or mixed race.
‡ The Eastern Cooperative Oncology Group (ECOG) performance-status scale ranges 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.
§ Visceral organs were defined as solid organs, excluding the brain.

SAFETY EVALUATIONS

Safety evaluations included assessments of adverse events and serious adverse events, laboratory safety evaluations, vital signs, physical examination, and 12-lead electrocardiography (ECG). A 12-lead ECG was to be performed at baseline, after completion of the infusion on day 1 of every even-numbered treatment cycle, at the end of treatment, and at the end of the trial. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 20.0, and severity was graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. For events

Table 2. Summary of Adverse Events in Patients Receiving Sacituzumab Govitecan-hziy.*

Adverse Event	Patients (N=108)		
	Any Grade	Grade 3	Grade 4
	number of patients with event (percent)		
Any adverse event	108 (100)	71 (66)	21 (19)
Gastrointestinal disorders	102 (94)	21 (19)	0
Nausea	72 (67)	7 (6)	0
Diarrhea	67 (62)	9 (8)	0
Vomiting	53 (49)	7 (6)	0
Constipation	37 (34)	1 (1)	0
Abdominal pain†	27 (25)	1 (1)	0
Mucositis‡	15 (14)	0	0
General disorders and administration-site conditions	82 (76)	10 (9)	0
Fatigue and asthenia	59 (55)	9 (8)	0
Peripheral edema	17 (16)	0	0
Pyrexia	13 (12)	0	0
Blood and lymphatic system disorders	80 (74)	25 (23)	15 (14)
Neutropenia§	69 (64)	28 (26)	17 (16)
Anemia	54 (50)	12 (11)	0
Metabolism and nutrition disorders	70 (65)	21 (19)	2 (2)
Decreased appetite	32 (30)	0	0
Hyperglycemia	26 (24)	3 (3)	1 (1)
Hypomagnesemia	23 (21)	1 (1)	0
Hypokalemia	19 (18)	2 (2)	0
Hypophosphatemia	16 (15)	10 (9)	0
Dehydration	14 (13)	4 (4)	0
Skin and subcutaneous tissue disorders	66 (61)	5 (5)	0
Alopecia	39 (36)	0	0
Rash¶	30 (28)	2 (2)	0
Pruritus	17 (16)	0	0
Dry skin	15 (14)	1 (1)	0
Abnormal values	62 (57)	22 (20)	6 (6)
Decreased white-cell count	23 (21)	9 (8)	3 (3)
Prolonged activated partial thromboplastin time	15 (14)	2 (2)	0
Increased aspartate aminotransferase level	15 (14)	1 (1)	0
Increased alanine aminotransferase level	15 (14)	1 (1)	0
Decreased weight	15 (14)	0	0
Increased blood alkaline phosphatase level	12 (11)	2 (2)	0
Increased blood lactate dehydrogenase level	11 (10)	0	0
Nervous system disorders	59 (55)	4 (4)	0
Headache	23 (21)	1 (1)	0
Dizziness	22 (20)	0	0
Neuropathy‖	20 (19)	0	0
Dysgeusia	12 (11)	0	0

Table 2. (Continued.)

Adverse Event	Patients (N=108)		
	Any Grade	Grade 3	Grade 4
	number of patients with event (percent)		
Infections and infestations	56 (52)	11 (10)	2 (2)
Respiratory infection**	23 (21)	3 (3)	0
Urinary tract infection	22 (20)	3 (3)	0
Musculoskeletal and connective-tissue disorders	56 (52)	0	0
Back pain	24 (22)	0	0
Arthralgia	17 (16)	0	0
Pain in extremity	11 (10)	0	0
Respiratory, thoracic, and mediastinal disorders	55 (51)	4 (4)	1 (1)
Cough and productive cough	21 (19)	0	0
Dyspnea	20 (19)	2 (2)	1 (1)
Psychiatric disorders	27 (25)	1 (1)	0
Insomnia	15 (14)	0	0

* Shown are the adverse events of any grade (according to Common Terminology Criteria for Adverse Events [CTCAE], version 4.0) that occurred in at least 10% of the patients. The *Medical Dictionary for Regulatory Activities* system organ class and preferred terms are reported whenever possible.
† This category includes abdominal pain, abdominal distention, upper abdominal pain, abdominal discomfort, and abdominal tenderness.
‡ This category includes stomatitis and mucosal inflammation.
§ This category includes neutropenia and decreased neutrophil counts. Febrile neutropenia of all grades was observed in 10 patients (9%), and grade 3 and grade 4 febrile neutropenia was observed in 7 patients (6%) and 2 patients (2%), respectively.
¶ This category includes maculopapular rash, generalized rash, dermatitis acneiform, and skin disorder.
‖ This category includes peripheral neuropathy, paresthesia, peripheral sensory neuropathy, and hypoesthesia.
** This category includes upper respiratory tract infection, viral upper respiratory tract infection, lower respiratory tract infection, pneumonia, influenza, bronchitis, and respiratory syncytial virus infection.

with varying severity, the maximum reported grade was used in summaries. The safety evaluation for the cohort of patients with metastatic triple-negative breast cancer was the same as that for the overall trial population.

STATISTICAL ANALYSIS

Details of the statistical analyses have been described previously.[25] When the cohort of patients with metastatic triple-negative breast cancer was evaluated to identify those who received sacituzumab govitecan-hziy at a dose of 10 mg per kilogram and had received at least two previous therapies for metastatic disease, the target group included 108 patients. The response rate and the exact 95% confidence intervals were calculated with the use of the Clopper–Pearson method. Progression-free and overall survival and time-to-event end points were analyzed with the use of Kaplan–Meier methods, with medians and corresponding 95% confidence intervals determined according to the Brookmeyer and Crowley method with log–log transformation. Subgroup analyses were used to evaluate the effect of patient factors and previous cancer treatments.

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

RESULTS

PATIENT POPULATION

A total of 108 patients with metastatic triple-negative breast cancer (median age, 55 years) were enrolled between June 2013 and February 2017. The

patients had been heavily pretreated (median of 3 previous anticancer regimens [range, 2 to 10]). A total of 106 of these patients (98%) had received taxanes and 93 (86%) had received anthracyclines. The baseline demographic characteristics of the patients are summarized in Table 1. At the time of data cutoff (December 1, 2017), the median duration of follow-up among the 108 patients with metastatic triple-negative breast cancer was 9.7 months (range, 0.3 to 36.5). Eight of these patients were continuing to receive treatment. A total of 100 patients (92.6%) had discontinued treatment, and in 86 of these patients (80%), discontinuation was because of disease progression. Other reasons for discontinuation are listed in Table S1 in the Supplementary Appendix.

SAFETY

The 108 patients with metastatic triple-negative breast cancer received a mean of 18.7 doses of sacituzumab govitecan-hziy (range, 1 to 102), or 9.6 cycles (range, 1 to 51), with a median duration of exposure of 5.1 months (range, 0.03 to 36.1). A total of 99 patients (92%) received preinfusion medications (acetaminophen, antihistamines, H_2 antagonists, glucocorticoids, antiemetics, anxiolytics, and atropine). The most common adverse events were nausea, diarrhea, fatigue, neutropenia, and anemia, and the most common adverse events of grade 3 or higher (>5% incidence) included neutropenia, anemia, and a decreased white-cell count, as outlined in Table 2. Diarrhea (predominantly grade 1) was a common adverse event (in 62% of the patients overall); the incidence of CTCAE grade 2 diarrhea was 14%, and the incidence of at least grade 3 diarrhea was 8%. No peripheral neuropathy of grade 3 or higher was reported. Four patients (4%) had adverse events leading to death during treatment (details are provided in the Results section in the Supplementary Appendix). Serious adverse events were reported in 35 patients (32%); the most common (>2% incidence) were febrile neutropenia (in 7% of the patients), vomiting (in 6%), nausea (in 4%), diarrhea (in 3%), and dyspnea (in 3%).

Adverse events leading to interruption of treatment occurred in 48 of the 108 patients (44%); the most common reason was neutropenia. Three patients (3%) discontinued treatment because of adverse events; 2 patients discontinued because of drug-related events, and 1 patient discontinued because of hypertension, which was thought by the investigator not to be drug-related. Transient changes in laboratory safety values that occurred during treatment included decreases in blood-cell counts and alterations in biochemical values, which generally recovered by the end of treatment.

EFFICACY

In Figure 1A, a waterfall plot shows the breadth and depth of responses according to local assessment in 108 patients with metastatic triple-negative breast cancer. The response rate was 33.3% (36 of 108 patients), including complete responses in 3 patients (2.8%). The clinical benefit rate (including stable disease for at least 6 months) was 45.4% (49 of 108 patients). In Figure 1B, a swimmer plot shows the onset and durability of response in each of the 36 patients who had an objective response. In these patients, the median time to response was 2.0 months (range, 1.6 to 13.5), and the median duration of response was 7.7 months (95% confidence interval [CI], 4.9 to 10.8). The response rate (34.3% [95% CI, 25.4 to 44.0]) and median duration of response (9.1 months [95% CI, 4.6 to 11.3]) according to blinded independent review were similar to those determined by local assessment (Table S5 in the Supplementary Appendix). According to local assessment, the estimated probability that a patient would have a response at 6 months was 59.7%, and the estimated probability that a patient would have a response at 12 months was 27.0% (Fig. S2 in the Supplementary Appendix). At the database cutoff date, 6 patients had long-term responses with a response for more than 12 months (range, 12.7 to 30.4). Table 3 summarizes the results according to investigator assessment.

We evaluated the response to sacituzumab govitecan-hziy in a variety of patient subgroups (Table S6 in the Supplementary Appendix) and found no meaningful differences in response rates according to patient age, the onset of metastatic disease, the number of previous therapies, or the presence or absence of visceral metastases. The response rate was 44% (8 of 18) among patients who had received previous checkpoint inhibitors; however, these results and those of all the reported subgroups should be interpreted with caution given the small number of patients available, which led to wide confidence intervals.

At the time of data cutoff, 94 patients (87.0%) had disease progression and 77 patients (71.3%) had died. The median progression-free survival

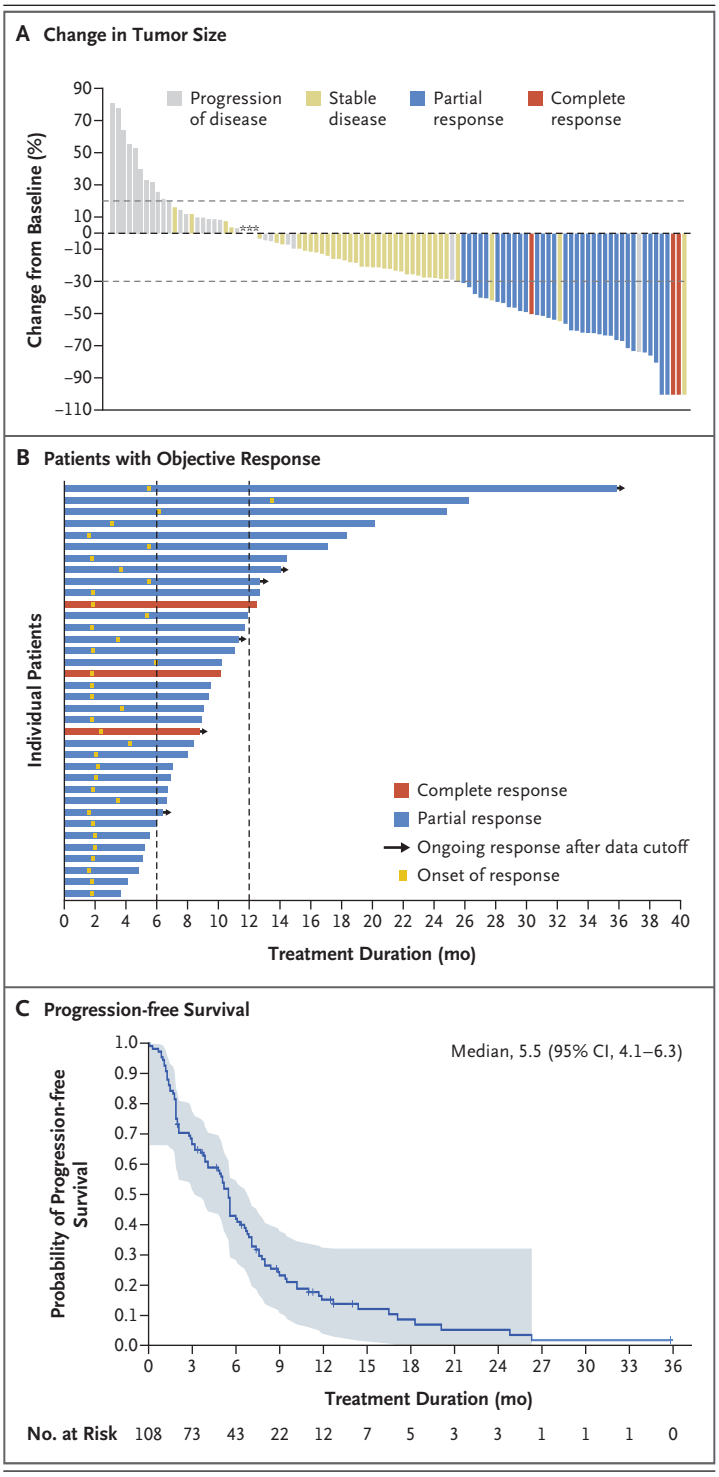

Figure 1. Response and Survival among 108 Patients with Metastatic Triple-Negative Breast Cancer.

Panel A shows a waterfall plot of the best percent change from baseline in the sum of the diameters of the target lesions (longest diameter for non-nodal lesions and short axis for nodal lesions). In 3 patients (2 with stable disease and 1 with progressive disease) (asterisks), the best percent change was zero. The dashed lines at 20% and –30% indicate progressive disease and partial response, respectively, according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Additional details are provided in the Results section in the Supplementary Appendix. Panel B shows a swimmer plot of the objective responses (according to RECIST, version 1.1) from the start of treatment to disease progression, as determined by local assessment. At the time of the analysis, 6 patients had a continuing response. The vertical dashed lines show the response at 6 months and 12 months, which are clinically meaningful end points for patients with metastatic triple-negative breast cancer. Panel C shows a Kaplan–Meier analysis of progression-free survival among the 108 patients.

was 5.5 months (95% CI, 4.1 to 6.3); the estimated probability of progression-free survival was 41.9% at 6 months and 15.1% at 12 months (Fig. 1C). The median overall survival was 13.0 months (95% CI, 11.2 to 13.7); the estimated probability of survival was 78.5% at 6 months and 51.3% at 12 months (Fig. S3 in the Supplementary Appendix).

To analyze efficacy in relation to the aggressiveness of the clinical course and to address concerns regarding relatively indolent tumor biologic characteristics in the trial population, we compared the duration of treatment with sacituzumab govitecan-hziy with that of previous anticancer treatment in the 108 patients with metastatic triple-negative breast cancer for whom data were available. The median duration of treatment with sacituzumab govitecan-hziy (5.1 months) was approximately twice that with the previous anticancer treatment (2.5 months); this highlights the clinical activity and lack of cross-resistance with this antibody–drug conjugate (Fig. 2).

DISCUSSION

Among patients with metastatic triple-negative breast cancer who had received at least two previous therapies for metastatic disease (median, three) and who received treatment with sacituzumab govitecan-hziy, the response rate was 33.3%, the median duration of response was 7.7 months, the median progression-free survival was 5.5 months, and the median overall survival was 13.0 months. Efficacy was observed in patients who had received taxanes and anthracyclines, suggesting a lack of cross-resistance to previous cyto-

Table 3. Summary of Treatment Efficacy, According to Local Assessment.

Variable	Patients (N=108)
Complete response — no. of patients (%)	3 (2.8)
Partial response — no. of patients (%)	33 (30.6)
Stable disease — no. of patients (%)	40 (37.0)
Progressive disease — no. of patients (%)	28 (25.9)
Not evaluated — no. of patients (%)*	4 (3.7)
Objective response rate†	
No. of patients	36
% of patients (95% CI)	33.3 (24.6–43.1)
Clinical benefit rate‡	
No. of patients	49
% of patients (95% CI)	45.4 (35.8–55.2)
Median duration of response (95% CI) — mo	7.7 (4.9–10.8)

* These patients could not be evaluated because of death, transfer to hospice, withdrawal due to clinical progression, or withdrawal due to grade 4 neutropenia before any radiologic assessment of response.
† The objective response rate is the percentage of patients with a complete response or partial response.
‡ The clinical benefit rate is the percentage of patients with a complete response or partial response or stable disease for at least 6 months.

toxic chemotherapy. The duration of treatment with sacituzumab govitecan-hziy was longer than with the immediate previous antitumor therapy (5.1 months vs. 2.5 months); this provides further evidence of clinical activity in patients with difficult-to-treat metastatic triple-negative breast cancer. Although a subgroup analysis based on the patients' age, the onset of metastatic disease, the number of previous therapies, or the presence or absence of visceral metastases showed no meaningful differences in outcomes, the small number of patients led to wide confidence intervals, and thus the homogeneity of clinical outcomes observed in these subgroups is weak and should be interpreted with caution.

The most relevant adverse events in patients with metastatic triple-negative breast cancer, as well as in the larger population of patients with multiple tumor types who received sacituzumab govitecan-hziy, included neutropenia and diarrhea, which were managed with routine supportive care according to general practice guidelines (i.e., early intervention with granulocyte colony-stimulating factor and early intervention for diarrhea). Few patients discontinued treatment because of adverse events. Severe drug-related neuropathy or cardiac adverse events, which may limit the duration of treatment with cytotoxic agents in this patient population,[26] were not observed. Hypersensitivity events of grade 3 or higher that were associated with infusion of monoclonal antibodies were infrequent (in 3 patients [3%]). Four deaths occurred during treatment (within 30 days after the last dose of sacituzumab govitecan-hziy); all deaths were attributed by the investigators to disease progression, and none were considered to be related to sacituzumab govitecan-hziy (see the Results section in the Supplementary Appendix). The safety profile of sacituzumab govitecan-hziy in the 108 patients with metastatic triple-negative breast cancer was generally consistent with that in the overall safety population of 420 patients who had a variety of tumor types (Table S3 in the Supplementary Appendix).

The long-term efficacy of the various treatment options for patients with metastatic triple-negative breast cancer (serial application of single agents) is limited.[12-14,16] Poor outcomes seen in patients with metastatic triple-negative breast cancer, as compared with other breast cancer subtypes, are partly explained by the lack of actionable driver mutations or established molecular targets, thereby leaving sequential single-agent chemotherapy as the main treatment approach.[7,10] Sacituzumab govitecan-hziy is an antibody–drug conjugate with Trop-2 as the target of recognition; it can deliver cytotoxic chemotherapy to tumors, including adjacent cancer cells, in concentrations that are higher than those with standard chemotherapy and may reduce toxic effects in normal tissues that do not express the target.[24] High expression of Trop-2 in triple-negative breast cancer and its association with a poor prognosis suggest that it is a rational therapeutic target in this patient population.[19,21]

The cytotoxic component of sacituzumab govitecan-hziy is SN-38, a highly potent topoisomerase I inhibitor and metabolite of irinotecan. The cytotoxic activity of SN-38 delivered through sacituzumab govitecan-hziy is 100 to 1000 times as high as that of irinotecan.[27] In animal models, the tumor-to-serum area under the curve ratio for SN-38 was 20 to 40 times as high with sacituzumab govitecan-hziy as it was with irinotecan, whereas concentrations that were 20 to 136 times as high as those with irinotecan were delivered into the tumor.[24] Clinically, serum concentrations of glucuronidated SN-38, the molecular species most strongly associated with toxic effects, were

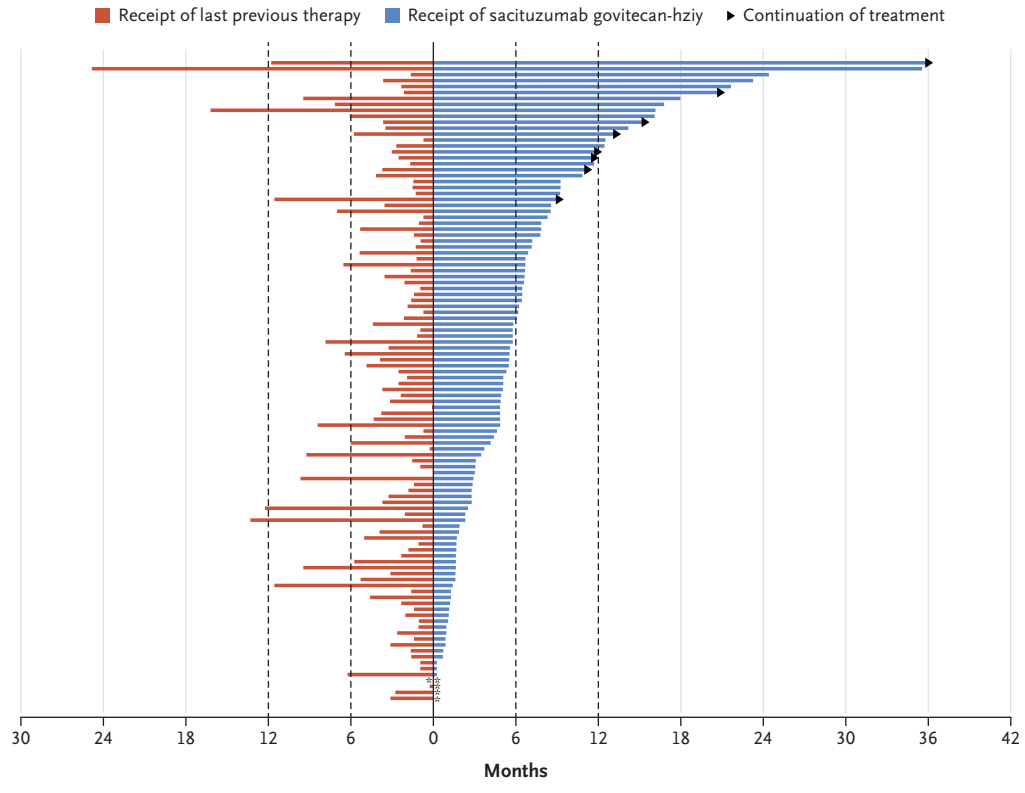

Figure 2. Duration of Treatment with Sacituzumab Govitecan-hziy and with the Last Previous Therapy in the 108 Patients with Metastatic Triple-Negative Breast Cancer.

Asterisks indicate patients who received therapy for only 1 day. The vertical dashed lines at 6 months and 12 months show the clinically meaningful end points for patients with metastatic triple-negative breast cancer. When the month and year were available, a missing start date was imputed as the 15th of the month, and a missing end date was imputed as the last day of the month.

substantially lower than those of SN-38 with sacituzumab govitecan-hziy and substantially lower than glucuronidated SN-38 concentrations reported with irinotecan.[28] This may explain the considerably lower discontinuation rates and clinically relevant lower rates of grade 3 or 4 gastrointestinal toxic effects in this trial than in trials of irinotecan. Although toxic effects associated with sacituzumab govitecan-hziy are similar to those of irinotecan, these data suggest that sacituzumab govitecan-hziy has a better side-effect profile and is less likely to be associated with more severe adverse effects.[29] The less severe nature of these adverse events with sacituzumab govitecan-hziy was reflected in the low incidences of adverse events leading to treatment discontinuation (3%) and death during treatment (4%), as well as in the absence of grade 3 or 4 neurotoxicity.

Toxic effects of irinotecan, especially neutropenia, have been associated with *UGT1A1*28* homozygosity[30,31] and with other variants of *UGT1A1* or *DPYD*.[32-34] The incidence of neutropenia increased numerically with the number of **28* copies, whereas this pattern was not observed for other adverse events of interest such as diarrhea (Table S4 in Supplementary Appendix). However, the results are based on a retrospective, exploratory analysis, and additional validation is needed before they can be used for clinical decision making related to sacituzumab govitecan-hziy.

Among the few studies involving pretreated patients with metastatic breast cancer, one of the largest, EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin), involved 762 patients who had received a median of four previous chemotherapy regimens,

and 19% had triple-negative breast cancer.[26] Adverse events leading to discontinuation of treatment occurred in 13% of the patients receiving eribulin and 15% receiving treatment of the physician's choice (any single-agent chemotherapy, hormone, or radiotherapy). In the EMBRACE study, the incidence of neutropenia was 52% with eribulin (the incidence of grade 4 neutropenia was 24%) and 30% with the physician's choice (grade 4 neutropenia, 7%) and the response rate was 12% with eribulin (duration of response, 4.2 months) and 5% with the physician's choice (duration of response, 6.7 months). The response rate of 33% and the duration of response of 7.7 months reported with sacituzumab govitecan-hziy compare favorably.[26] In addition, topoisomerase inhibition may have advantages over microtubule inhibition in these patients, given that altered DNA repair pathways are common in triple-negative breast cancer.[35] Furthermore, confirmed objective responses were noted in patients who had received previous programmed death 1–based therapy or programmed death ligand 1–based therapy, suggesting a lack of cross-resistance with immune checkpoint inhibitors and the potential usefulness of combination therapy.

Direct comparison with other chemotherapy approaches was not possible in this trial because of its noncomparative design. However, we used the response rate as the primary end point, which is less subject to bias than progression-free survival in a single-group trial and has been used for accelerated approval in other oncology trials,[36-38] with only a small portion of indications under the accelerated approval program failing to verify clinical benefit.[39] A confirmatory multicenter, randomized, phase 3 trial (ASCENT; ClinicalTrials.gov number, NCT02574455) is currently recruiting patients in North America and Europe to compare sacituzumab govitecan-hziy with the physician's choice of four single-agent types of chemotherapy (capecitabine, gemcitabine, vinorelbine, and eribulin) in patients with metastatic triple-negative breast cancer that is refractory or relapsed after at least two previous forms of chemotherapy (including a taxane).

In conclusion, sacituzumab govitecan-hziy (IMMU-132) had efficacy with a 33% response rate in a heavily pretreated population of patients with metastatic triple-negative breast cancer. Diarrhea and myelosuppression were the primary adverse events, and discontinuation rates were low.

Editor's note: After this article went to press, the trial sponsor was informed by the FDA that the suffix "-hziy" had not yet been formally approved.

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APPENDIX

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