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ORIGINAL ARTICLE

The association of high body mass index with the safety and efficacy of sacituzumab govitecan in patients with metastatic triple-negative breast cancer from the ASCENT study

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Available online xxx

Background: Sacituzumab govitecan (SG) is a trophoblast cell-surface antigen 2-directed antibody—drug conjugate (ADC) approved in multiple countries for relapsed/refractory metastatic triple-negative breast cancer (mTNBC) based on results from the phase III ASCENT study. The incidence of obesity has grown to epidemic proportions in recent decades; it is unclear what impact this has on treatment outcomes, especially for ADCs like SG that have weight-based dosing. We report the association of body mass index (BMI) with efficacy and safety of SG versus chemotherapy among patients with mTNBC from the ASCENT study.

Patients and methods: This *ad hoc* subgroup analysis included patients from the intent-to-treat population of ASCENT who received SG at 10 mg/kg of body weight or chemotherapy. BMI, assessed at baseline, was classified as normal (18.5 to $<$25 kg/m^2), overweight (25 to $<$30 kg/m^2), and obese ($\geq$30 kg/m^2).

Results: A total of 509 patients were included. Longer progression-free survival was observed with SG versus chemotherapy in patients from all BMI subgroups [normal: 4.2 versus 2.1 months, hazard ratio (HR) 0.48, 95% confidence interval (CI) 0.34-0.67, $P < 0.0001$; overweight: 4.6 versus 1.5 months, HR 0.31, 95% CI 0.20-0.47, $P < 0.0001$; obese: 5.9 versus 2.6 months, HR 0.34, 95% CI 0.21-0.53, $P < 0.0001$]. SG also led to improved overall survival and objective response rates versus chemotherapy in all evaluated BMI subgroups. With SG treatment, the incidence of treatment-emergent adverse events of grade $\geq$3, and those leading to dose reductions and study drug interruptions, was higher in patients with overweight and obese BMI compared with normal BMI; however, the rates of treatment discontinuation remained low and similar across the subgroups.

Conclusions: To our knowledge, this is the first study evaluating the association of BMI with outcomes with ADCs. SG demonstrated improved efficacy versus chemotherapy and a manageable safety profile in all evaluated BMI subgroups from ASCENT.

Key words: sacituzumab govitecan, metastatic triple-negative breast cancer, body mass index, obesity, antibody—drug conjugate

INTRODUCTION

The worldwide incidence of adult obesity more than doubled between 1990 and 2022. The World Health Organization (WHO) now classifies obesity as a global crisis. Obesity is described by the WHO as a body mass index (BMI) $\geq$30 kg/m^2; individuals with a BMI of 25-29 kg/m^2 are

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considered overweight.[1] Obesity has been linked to an increased risk of, and mortality from, several common cancers, including breast cancer in postmenopausal women, and can lead to increased treatment-related adverse events (AEs) that may have an impact on treatment choices.[2] Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer, characterized by a lack of estrogen/progesterone receptor expression and no overexpression of human epidermal growth factor receptor 2 (HER2), that has limited treatment options and poor prognosis.[3-5]

In a retrospective cohort study of 329 patients with HER2-positive metastatic breast cancer (mBC) who were treated with first-line trastuzumab-based regimens, high BMI ($\geq$25 kg/m^2) was not associated with a significant difference in progression-free survival (PFS) and overall survival (OS) compared with normal/underweight BMI ($<$25 kg/m^2).[6] A preplanned analysis of the global, randomized PALLAS trial of ~5700 patients with hormone receptor-positive, HER2-negative, early-stage breast cancer who were treated with endocrine therapy alone or in combination with the cyclin-dependent kinase 4/6 inhibitor palbociclib showed that, compared with patients with a normal BMI (18.5 to $<$25 kg/m^2), there was significantly less neutropenia, thrombocytopenia, and early discontinuation of palbociclib in patients with overweight/obese BMI. No statistically significant differences were observed in the invasive disease-free survival between patients with obese/overweight BMI and those with normal BMI.[7] Similarly, studies of patients with mBC treated with chemotherapy in the first line have not found any association between BMI and survival outcomes including PFS and OS.[8,9] However, in a meta-analysis of 13 studies with ~9000 patients who had early TNBC, an association was found between overweight BMI and shorter disease-free survival and OS.[10] Additionally, a retrospective French cohort study that included ~1800 patients with metastatic TNBC (mTNBC) showed that being overweight seemed to have a slightly protective effect on OS.[11] There is a need for more studies that explore the association of BMI with treatment outcomes in patients with mTNBC.

Sacituzumab govitecan (SG) is a trophoblast cell-surface antigen 2 (Trop-2)-directed antibody–drug conjugate (ADC) composed of an anti-Trop-2 monoclonal antibody attached to SN-38, a potent topoisomerase I inhibitor, through a hydrolyzable linker.[12,13] The hydrolyzable linker facilitates rapid release of the SN-38 payload into Trop-2-expressing cancer cells and subsequently to surrounding cancer cells (bystander effect).[12,13] SG is currently approved for use in multiple countries for patients with unresectable, locally advanced or metastatic TNBC after at least two prior systemic therapies (at least one in the metastatic setting)[14-18] based on the phase III, global, randomized ASCENT study (NCT02574455) that enrolled 529 patients.[19] In ASCENT, after a median follow-up of 17.7 months, SG treatment resulted in significantly longer PFS [hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.35-0.54] and OS (HR 0.51, 95% CI 0.41-0.62) versus chemotherapy treatment of physician's choice, including in patients with brain metastases; these results were maintained at the final analysis.[19,20]

SG has body weight-based dosing and is administered at 10 mg/kg of body weight intravenously on days 1 and 8 of each 21-day cycle. In pivotal studies of SG in breast cancer, there was no dose cap for patients with a high BMI.[19,21] Pharmacokinetic studies of SG have shown that body weight correlates with volume of drug distribution and clearance and support the approved dosing regimen.[22] Clinical trials of systemic breast cancer treatments do not often report BMI or other adiposity measurements, making it unclear how BMI affects treatment outcomes and toxicities.[23] This is especially relevant for ADCs like SG that have weight-based dosing. In addition, considering that the mechanism of action of SG includes the bystander effect in the tumor microenvironment, evaluation of the extent to which excess adipose tissue could affect drug efficacy by interfering with this bystander effect is of interest.

In this analysis we report the relationship of BMI with the efficacy and safety of SG versus chemotherapy among patients with mTNBC from the ASCENT study. To our knowledge, this is the first study evaluating the association of BMI with treatment outcomes with ADCs.

PATIENTS AND METHODS

The study design of ASCENT has been described previously.[19] Briefly, patients with mTNBC who had relapsed or were refractory to two or more previous standard chemotherapy regimens for unresectable locally advanced or metastatic disease were enrolled. TNBC was defined according to the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) criteria as estrogen/progesterone receptor expression $<$1% and HER2 immunohistochemistry 0, 1+, 2+/*in situ* hybridization-negative.[4,5] Patients were randomized in a 1 : 1 ratio to receive SG or chemotherapy (capecitabine, eribulin, vinorelbine, or gemcitabine). Stratification was based on number of prior chemotherapy regimens (2-3 versus $>$3), presence of brain metastases at baseline (yes versus no), and geographic region (North America versus rest of the world).

SG was administered at 10 mg/kg of body weight intravenously on days 1 and 8 of each 21-day cycle. Eribulin was administered at 1.4 mg/m^2 (North America) or 1.23 mg/m^2 (Europe) of body surface area intravenously on days 1 and 8 of each 21-day cycle, vinorelbine at 25 mg/m^2 intravenously on day 1 weekly, capecitabine at 1000-1250 mg/m^2 orally twice daily on days 1-14 of each 21-day cycle, and gemcitabine at 800-1200 mg/m^2 intravenously on days 1, 8, and 15 of each 28-day cycle. There were no dosage caps (i.e. maximum dose) placed on SG or chemotherapy doses within the study. The primary endpoint was PFS by independent, centralized review for patients without known baseline brain metastases; secondary endpoints included PFS in the full intent-to-treat (ITT) population, which included patients with and without brain metastases, OS, objective response rate (ORR), duration of response and time to response in the ITT population, and safety.

This *ad hoc* subgroup analysis included patients with and without brain metastases from the full ITT population of ASCENT. BMI (kg/m^2) was calculated as the patient's weight in kilograms (kg) divided by the square of their height in meters (m^2). BMI was assessed at baseline and was classified as follows: underweight (<18.5 kg/m^2), normal (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥30 kg/m^2). Since the number of patients with underweight BMI was too small to draw meaningful conclusions, and to avoid complicating the analysis, they were excluded from this *ad hoc* analysis.

Efficacy was evaluated in all patients in the ITT population of ASCENT by independent, centralized review based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Median PFS and OS values were estimated using the Kaplan–Meier method, and 95% CIs were computed using the Brookmeyer–Crowley method. An unstratified Cox regression analysis was used to determine HRs. This was an *ad hoc* analysis with descriptive statistics, and *P* values reported are nominal for exploratory purposes only and no formal testing was carried out.

The safety population included all patients who received at least one dose of the study drug. Safety was evaluated starting on the first dose of study treatment and until 30 days after the last dose according to the *Medical Dictionary for Regulatory Activities*, version 22.1. The severity of AEs was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

This was an *ad hoc* analysis of the ASCENT clinical trial. The ASCENT study protocol was approved by the institutional review boards or ethics committee at each investigational site, and the trial was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and other applicable regulatory requirements. All patients in ASCENT provided written informed consent to participate.

RESULTS

Patient characteristics and disposition

A total of 509 patients from ASCENT were included in this analysis. Results presented are as of the final database lock on 25 February 2021. In the SG and chemotherapy groups, there were 8 and 11 patients with underweight BMI (<18.5 kg/m^2), respectively, who were excluded from this *ad hoc* analysis. There were 222 patients (44%) with normal BMI and 287 (56%) with high BMI. Among the patients with high BMI, 155 (30%) had overweight BMI and 132 (26%) had obese BMI (Table 1).

Patient baseline characteristics were well balanced across the BMI categories (Table 1). The median age was 52-56 years across treatment groups and BMI categories, and the median number of prior systemic therapies was four in all subgroups. The mean (standard deviation) BMIs for SG and chemotherapy, respectively, were 22.1 kg/m^2 (1.69) and 22.1 kg/m^2 (1.81) in the normal subgroup, 27.4 kg/m^2 (1.39) and 27.3 kg/m^2 (1.46) in the overweight subgroup, and 35.7 kg/m^2 (5.18) and 35.2 kg/m^2 (4.99) in the obese subgroup (Table 1).

Efficacy by BMI subgroups

In the ITT population of ASCENT, SG was consistently associated with clinically meaningful improvements in efficacy outcomes versus chemotherapy, regardless of BMI.

Table 1. Patient baseline demographics and disease characteristics

Characteristic	Normal[a] (BMI 18.5 to <25 kg/m^2)		Overweight (BMI 25 to <30 kg/m^2)		Obese (BMI ≥30 kg/m^2)	
	SG (*n* = 119)	Chemo (*n* = 103)	SG (*n* = 71)	Chemo (*n* = 84)	SG (*n* = 68)	Chemo (*n* = 64)
Median age, years (range)	53 (29-82)	53 (27-81)	56 (27-80)	55 (30-80)	53 (31-74)	52 (34-80)
Female, *n* (%)	119 (100)	103 (100)	70 (99)	84 (100)	68 (100)	64 (100)
BMI,[b] kg/m^2, mean (SD)	22.1 (1.69)	22.1 (1.81)	27.4 (1.39)	27.3 (1.46)	35.7 (5.18)	35.2 (4.99)
Race						
White	100 (84)	88 (85)	57 (80)	57 (68)	50 (74)	47 (73)
Black	8 (7)	5 (5)	7 (10)	17 (20)	13 (19)	12 (19)
Asian	6 (5)	5 (5)	4 (6)	4 (5)	2 (3)	0
Other	5 (4)	5 (5)	3 (4)	6 (7)	3 (4)	5 (8)
ECOG PS at screening, *n* (%)						
0	59 (50)	44 (43)	29 (41)	37 (44)	31 (46)	22 (34)
1	60 (50)	59 (57)	42 (59)	47 (56)	37 (54)	42 (66)
Brain metastases at study entry, *n* (%)						
Yes	17 (14)	8 (8)	7 (10)	12 (14)	7 (10)	7 (11)
No	102 (86)	95 (92)	64 (90)	72 (86)	61 (90)	57 (89)
Prior systemic therapies, median (range)	4 (2-11)	4 (2-14)	4 (2-17)	4 (2-14)	4 (2-11)	4 (2-11)
Prior PD-1/PD-L1 therapy, *n* (%)						
Yes	38 (32)	30 (29)	20 (28)	25 (30)	18 (26)	18 (28)
No	81 (68)	73 (71)	51 (72)	59 (70)	50 (74)	46 (72)

BMI, body mass index; Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; SD, standard deviation; SG, sacituzumab govitecan.
[a]Patients with underweight BMI (<18.5 kg/m^2) in the SG (*n* = 8) and chemotherapy (*n* = 11) groups are not included.
[b]BMI is calculated as BMI (kg/m^2) = (weight in kg)/(height in m)^2.

Median PFS as determined by independent central review with SG versus chemotherapy was 4.2 months (95% CI 2.9-5.6 months) and 2.1 months (95% CI 1.5-2.8 months), respectively, in patients with normal BMI (HR 0.48, 95% CI 0.34-0.67, $P < 0.0001$), 4.6 months (95% CI 3.3-6.3 months) and 1.5 months (95% CI 1.4-1.6 months), respectively, in patients with overweight BMI (HR 0.31, 95% CI 0.20-0.47, $P < 0.0001$), and 5.9 months (95% CI 4.1-8.3 months) and 2.6 months (95% CI 1.6-3.0 months), respectively, in patients with obese BMI (HR 0.34, 95% CI 0.21-0.53, $P < 0.0001$) (Figure 1A). Consistent results were observed when the overweight and obese BMI subgroups were combined (high BMI, $\geq$25 kg/m^2). Median PFS was 5.7 months (95% CI 4.2-7.0 months) with SG and 1.6 months (95% CI 1.5-2.6 months) with chemotherapy (HR 0.33, 95% CI 0.24-0.45, $P < 0.0001$) in this subgroup.

Median OS was improved with SG versus chemotherapy in patients with normal BMI [11.2 months (95% CI 9.4-13.5 months) versus 6.2 months (95% CI 4.7-7.1 months), HR 0.54, 95% CI 0.40-0.72, $P < 0.0001$], overweight BMI [10.8 months (95% CI 9.0-14.2 months) versus 6.7 months (95% CI 5.2-8.9 months), HR 0.51, 95% CI 0.35-0.74, $P = 0.0003$], and obese BMI [14.9 months (95% CI 11.2-16.8 months) versus 8.7 months (95% CI 6.7-9.8 months), HR 0.45, 95% CI 0.30-0.67, $P < 0.0001$] (Figure 1B). In the subgroup of patients with high BMI ($\geq$25 kg/m^2), median OS was 13.4 months (95% CI 10.5-14.9 months) with SG and 7.7 months (95% CI 5.9-9.1 months) with chemotherapy (HR 0.48, 95% CI 0.37-0.63, $P < 0.0001$).

ORR with SG was 24% (95% CI 17% to 33%) in patients with normal BMI, 34% (95% CI 23% to 46%) in patients with overweight BMI, and 40% (95% CI 28% to 52%) in patients with obese BMI (Table 2). Among patients treated with chemotherapy, ORR was 7% (95% CI 3% to 14%), 1% (95% CI 0% to 7%), and 2% (95% CI 0% to 8%) in the normal, overweight, and obese subgroups, respectively (Table 2). Improvement in ORR was also observed when the overweight/obese subgroups were combined [37% (95% CI 29% to 45%) with SG versus 1% (95% CI <1% to 5%) with chemotherapy]. Additional efficacy outcomes including clinical benefit rate and best overall response are presented in Table 2.

Exposure and safety

Treatment-emergent AEs (TEAEs) of grade $\geq$3 with SG were observed at higher rates in the overweight and obese BMI subgroups (78% and 77%, respectively) compared with the normal BMI subgroup (68%). The incidence of treatment-emergent serious AEs was also higher in the overweight and obese subgroups (34% and 33%, respectively) compared with the normal subgroup (18%) (Table 3).

The rate and number of dose reductions with SG due to any reason was the highest in patients from the obese subgroup (44%), the majority of whom received only one

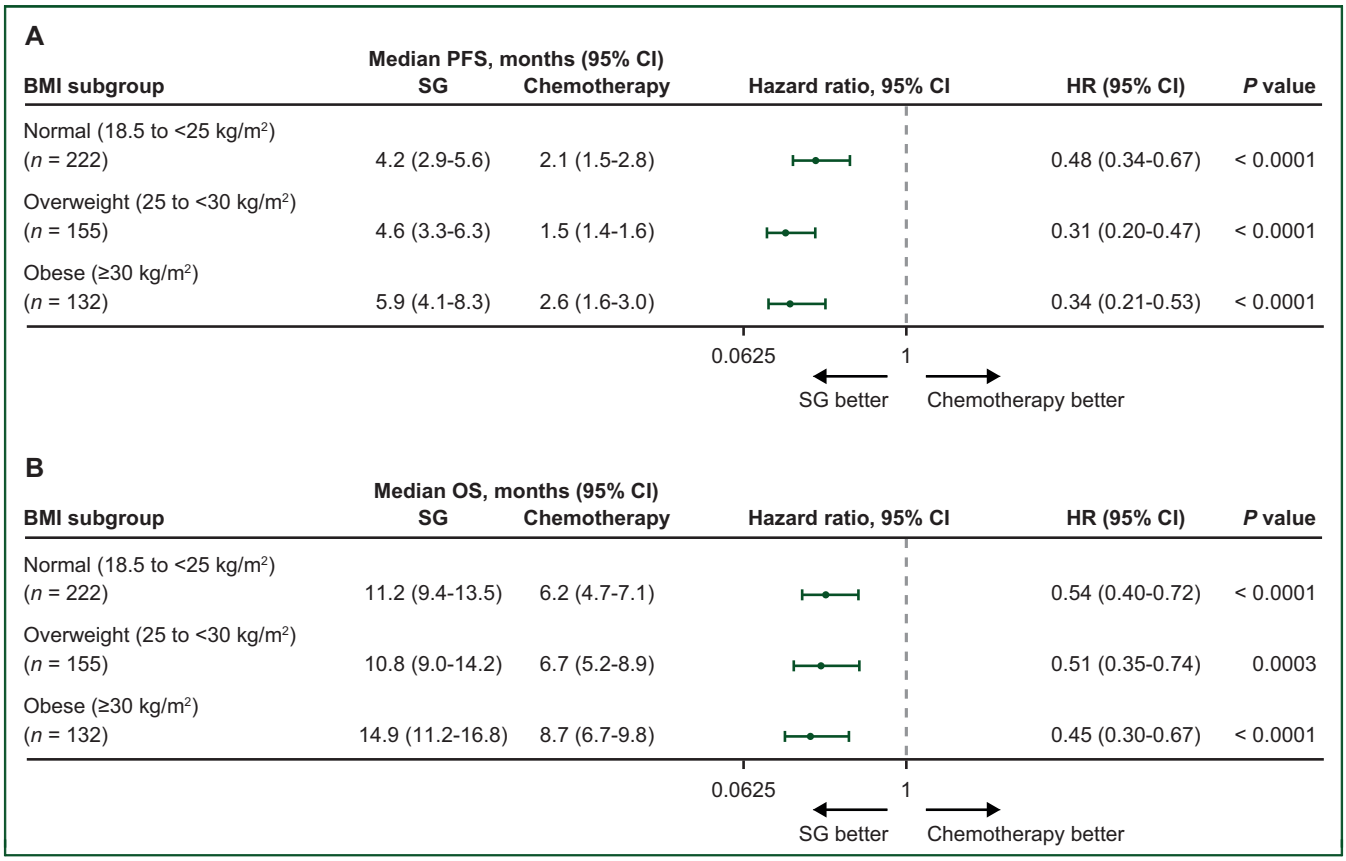

Figure 1. Forest plots of PFS. By independent review (A) and OS (B).
BMI, body mass index; Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

Table 2. Summary of antitumor activity

	Normal[a] (BMI 18.5 to <25 kg/m^2)		Overweight (BMI 25 to <30 kg/m^2)		Obese (BMI ≥30 kg/m^2)	
	SG (n = 119)	Chemo (n = 103)	SG (n = 71)	Chemo (n = 84)	SG (n = 68)	Chemo (n = 64)
ORR[b], *n* (%)	29 (24)	7 (7)	24 (34)	1 (1)	27 (40)	1 (2)
95% CI	17-33	3-14	23-46	0-7	28-52	0-8
Odds ratio	4.42		42.38		41.49	
95% CI	1.84-10.59		5.56-323.39		5.43-317.26	
CBR[c], *n* (%)	41 (34)	10 (10)	29 (41)	4 (5)	34 (50)	4 (6)
95% CI	26-44	5-17	29-53	1-12	38-62	2-15
Odds ratio	4.89		13.81		15.00	
95% CI	2.30-10.39		4.55-41.91		(4.90-45.89)	
BOR[d], *n* (%)						
CR	2 (2)	1 (1)	5 (7)	0	3 (4)	1 (2)
PR	27 (23)	6 (6)	19 (27)	1 (1)	24 (35)	0
SD	50 (42)	28 (27)	24 (34)	18 (21)	21 (31)	23 (36)
SD ≥6 months	12 (10)	3 (3)	5 (7)	3 (4)	7 (10)	3 (5)
PD	31 (26)	37 (36)	17 (24)	38 (45)	14 (21)	20 (31)
NE	9 (8)	31 (30)	6 (9)	27 (32)	6 (9)	20 (31)

BMI, body mass index; BOR, best overall response; CBR, clinical benefit rate; Chemo, chemotherapy; CI, confidence interval; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SG, sacituzumab govitecan.

[a]Patients with underweight BMI (<18.5 kg/m^2) in the SG (n = 8) and chemotherapy (n = 11) groups are not included.

[b]ORR is defined as the best confirmed overall response of either CR or PR.

[c]Clinical benefit rate is defined as the best response of CR or PR or SD ≥6 months.

[d]Best overall response derived based on independent review-assessed tumor response at each tumor assessment according to RECIST 1.1.

dose reduction (Table 4). A reduction in SG dose due to a TEAE was observed in 10%, 24%, and 41% of patients in the normal, overweight, and obese BMI subgroups, respectively (Table 3). The most common (≥5% in any subgroup) AEs of any grade leading to SG dose reductions were neutropenia in the normal and overweight subgroups, and neutropenia, diarrhea, nausea, and febrile neutropenia in the obese subgroup.

TEAEs led to SG dose interruption in 58% of patients with normal BMI, 64% of patients with overweight BMI, and 71% of patients with obese BMI. The rates of TEAEs leading to SG discontinuation and death were low and similar across the BMI subgroups (Table 3).

The most frequent (≥10% in any subgroup) grade ≥3 TEAEs observed with SG were neutropenia, leukopenia, diarrhea, infections and infestations (defined as any infection or infestation), anemia, and febrile neutropenia. All of these grade ≥3 TEAEs occurred at a higher incidence in patients with obese BMI compared with patients with normal BMI (Table 3). Neutropenia was the most frequently

Table 3. Safety summary and most common grade ≥3 TEAEs (≥10% in any subgroup) observed with SG

	All patients treated with SG N = 258	Normal[a] (BMI 18.5 to <25 kg/m^2) n = 117	Overweight (BMI 25 to <30 kg/m^2) n = 67	Obese (BMI ≥30 kg/m^2) n = 66
Safety summary, *n* (%)				
Any TEAEs	257 (100)	117 (100)	66 (99)	66 (100)
TEAEs grade ≥3	188 (73)	79 (68)	52 (78)	51 (77)
Any-grade treatment-emergent serious AEs	69 (27)	21 (18)	23 (34)	22 (33)
Any-grade TEAEs leading to SG interruption	162 (63)	68 (58)	43 (64)	47 (71)
Any-grade TEAEs leading to SG discontinuation	12 (5)	5 (4)	2 (3)	5 (8)
Any-grade TEAEs leading to SG dose reduction	57 (22)	12 (10)	16 (24)	27 (41)
Any-grade TEAEs leading to death	1 (<1)	1 (<1)	0 (0)	0 (0)
Most common grade ≥3 TEAEs, *n* (%)				
Neutropenia	135 (52)	61 (52)	33 (49)	38 (58)
Leukopenia	27 (10)	10 (9)	6 (9)	11 (17)
Diarrhea	30 (12)	6 (5)	9 (13)	13 (20)
Infections and infestations[b]	25 (10)	7 (6)	9 (13)	8 (12)
Anemia	24 (9)	6 (5)	8 (12)	10 (15)
Febrile neutropenia	15 (6)	2 (2)	5 (7)	8 (12)

Percentages are based on the number of patients in the safety population in each subgroup. TEAE is defined as an AE with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment.

AE, adverse event; BMI, body mass index; SG, sacituzumab govitecan; TEAEs, treatment-emergent adverse events.

[a]Patients with underweight BMI (<18.5 kg/m^2) in the SG (n = 8) and chemotherapy (n = 11) groups are not included.

[b]Defined as all preferred terms within the system organ class infections and infestations.

observed grade ≥3 TEAE in all evaluated BMI subgroups (Table 3). Of the most frequent TEAEs, one event of infection led to discontinuation of SG treatment in each of the normal and overweight BMI subgroups. One event of infection and one event of diarrhea led to discontinuation of SG treatment in one patient each in the obese BMI subgroup. No patients with obese BMI discontinued SG treatment due to neutropenia, leukopenia, anemia, or febrile neutropenia.

Among all patients treated with SG ($N = 258$), the median relative dose intensity was 91%. It was 94% in patients with normal BMI, 90% in patients with overweight BMI, and 85% in patients with obese BMI. The median time to first dose reduction was similar across the BMI subgroups (1.7 months in patients with normal BMI and 1.8 months in patients with overweight and obese BMIs) (Table 4).

DISCUSSION

To our knowledge, this is the first study that evaluates the association of BMI with treatment outcomes with ADCs in breast cancer. In this *ad hoc* exploratory analysis, SG demonstrated improved efficacy versus chemotherapy and a manageable safety profile in patients from all evaluated BMI subgroups (normal, overweight, and obese) in the phase III ASCENT study. Longer PFS and OS, and higher ORRs, were observed with SG compared with chemotherapy.

SG had a manageable safety profile in patients from all evaluated BMI subgroups. Despite the lower median relative dose intensity in patients with overweight/obese BMI compared with those with normal BMI, the incidence of grade ≥3 TEAEs, treatment-emergent serious AEs, TEAEs leading to dose reduction, and TEAEs leading to study drug interruption was higher in patients with overweight and obese BMI than in those with normal BMI. This observation seems paradoxical but could be influenced by several factors. Patients with obese BMI have different physiology and metabolism compared with patients with normal BMI, possibly leading to markedly altered pharmacokinetics of several drugs. Moreover, patients with obesity are also at a higher risk of developing comorbidities such as high blood pressure, diabetes, and cardiovascular disease.[24,25] Overall, 24% of patients with overweight BMI and 41% of patients with obese BMI had a reduction in SG dose due to an adverse event; however, SG demonstrated improved efficacy versus chemotherapy in these groups of patients despite the dose reductions. Additionally, the incidence of TEAEs leading to discontinuation of SG treatment in the overweight and obese subgroups was low (3% and 8%, respectively), and similar compared with that in the normal BMI subgroup (4%). AE management strategies, including active monitoring, early intervention and dose modifications, enabled patients across BMI subgroups to derive clinical benefit from SG treatment.

In the current descriptive analysis with SG treatment, higher BMI was associated with numerically improved ORR, PFS, and OS compared with normal BMI. Similar results have been observed in an observational cohort study of 12 999 patients with mBC from 18 French comprehensive cancer centers in which underweight BMI was found to be an independent negative prognostic factor for both OS and PFS, while OS was higher in patients with TNBC who had an overweight BMI. Patients included in that study were not treated with a specific type of therapy.[11] The impact of BMI on specific cancer types, or treatments such as immune checkpoint inhibitors, has been documented.[26-28] In a systematic literature review and meta-analysis of follow-up studies of breast cancer survivors, obesity was associated with poor OS among 213 075 patients with localized breast cancer who were studied.[27] In a meta-analysis of 203 studies involving >6 million patients, it was found that, overall, obesity was associated with worse outcomes in patients with breast, colorectal, and uterine cancers. However, in certain cancer types such as lung cancer, renal cell carcinoma, and melanoma, patients with obesity had improved survival outcomes compared with those without obesity.[28] In another meta-analysis of 5279 patients with cancer who were treated with immune checkpoint inhibitors, a positive association was observed between high BMI and improved OS and PFS.[26] The association between BMI and cancer outcomes is complex, with some variations based on cancer type, stage, and specific treatments that have been investigated. There is a significant need for additional studies to better understand these complexities.

Population pharmacokinetic analyses of SG in patients with mTNBC and other solid tumors have been described.

Table 4. SG exposure

	All patients treated with SG $N = 258$	Normal[a] (BMI 18.5 to <25 kg/m^2) $n = 117$	Overweight (BMI 25 to <30 kg/m^2) $n = 67$	Obese (BMI ≥30 kg/m^2) $n = 66$
Median relative dose intensity,[b] % (range)	91 (41-112)	94 (55-107)	90 (44-103)	85 (41-112)
Median time to first dose reduction, months (range)	1.8 (0.5-18.7)	1.7 (0.7-7.5)	1.8 (0.5-9.7)	1.8 (0.7-18.7)
Patients with dose reductions, *n* (%)	66 (26)	17 (15)	18 (27)	29 (44)
1	52 (20)	15 (13)	14 (21)	21 (32)
2	14 (5)	2 (2)	4 (6)	8 (12)

Percentages based on the number of patients in the safety population in each subgroup.
BMI, body mass index; SG, sacituzumab govitecan.
[a]Patients with underweight BMI (<18.5 kg/m^2) in the SG ($n = 8$) and chemotherapy ($n = 11$) groups are not included.
[b]Relative dose intensity defined as the cumulative dosage received (mg/kg)/total assigned dosage (mg/kg). Number of planned doses in the denominator adjusted for early or delayed doses. Relative dose intensity values are >100% for some patients because of rounding and protocol-specified rule to not change the dose unless the patient's body weight fluctuated >10%.

For pharmacokinetic parameters of SG, body weight was a statistically significant covariate; however, it had a limited impact on exposure as predicted relative exposure was in the 80%-125% range. Moreover, the effect of body weight on exposure was accounted for by the body weight-based dosing regimen.[22] Exposure response analyses of SG in patients with mTNBC have demonstrated dependence of the efficacy and safety of SG on serum exposure.[29] Overall, the approved dosing regimen of SG was supported by these pharmacokinetic analyses.[22,29] The manageable safety profile and clinical benefit of SG across all evaluated BMI subgroups in the current analysis further supports weight-based dosing of SG.

There are some limitations of the current analysis, including the *ad hoc* nature of the analysis that was not powered for statistical testing. BMI was only assessed at baseline and could have changed throughout the course of treatment; it is unclear what impact this may have on outcomes. Additionally, the number of Asian patients was low, especially in the obese BMI subgroup, and the applicability of the results to this patient population is limited.

Conclusions

SG demonstrated improved efficacy versus chemotherapy and a manageable safety profile in patients from all evaluated BMI subgroups, including patients with a high BMI ($\geq$25 kg/m^2). Although more patients with overweight and obese BMI had SG dose modifications owing to TEAEs than patients with normal BMI, they still benefited from SG treatment. Among the patients treated with SG who received dose reductions, a majority received only one dose reduction, and the rates of treatment discontinuation due to an AE remained low. The results from this *ad hoc* analysis show that high BMI does not negatively impact efficacy outcomes with SG in patients with relapsed or refractory mTNBC.

ACKNOWLEDGEMENTS

We thank the patients and their caregivers for their participation and commitment to clinical research. Thank you to the clinical trial investigators and their team members, without whom this work would not have been possible. Medical writing and editorial assistance was provided by Sonal S. Joshi, PhD, of Parexel, and funded by Gilead Sciences, Inc.

FUNDING

This work was supported by Gilead Sciences, Inc (no grant number).

DISCLOSURE

LGE reports speaker fees and honoraria from Daiichi Sankyo, Gilead Sciences, Inc., MSD, and SANED; travel grants from Gilead Sciences, Inc.; participation on a data safety monitoring or advisory board for MSD; and other institutional financial or non-financial interests for Roche. AB reports receiving grants to their institution from AstraZeneca/Daiichi Sankyo, Eli Lilly, Genentech, Gilead Sciences, Inc., Menarini, Merck, Novartis, Pfizer, and Sanofi; speaker fees and honoraria from AstraZeneca/Daiichi Sankyo, Eli Lilly, Genentech, Gilead Sciences, Inc., Menarini, Merck, Novartis, Pfizer, and Sanofi; and travel grants from AstraZeneca/Daiichi Sankyo, Eisai, Genentech, Gilead Sciences, Inc., Lilly, Menarini, Merck, Mersana, Novartis, Pfizer, and Sanofi. HSR reports receiving grants to their institution from AstraZeneca, Daiichi Sankyo, F Hoffmann-La Roche/Genentech, Gilead Sciences, Inc., Lilly, Merck, Novartis, Pfizer, OBI Pharma, Stemline Therapeutics, and Ambrx; and speaker fees and honoraria from NAPO, Chugai, and Puma. LAC reports receiving grants to their institution from AstraZeneca, NanoString Technologies, SeaGen, and Veracyte. VCD reports receiving consulting fees from Lilly, Roche Genentech, AstraZeneca, Seagen, Eisai Roche, Novartis, Pfizer, Daiichi Sankyo, Gilead Sciences, Inc., and Menarini; speaker fees and honoraria from Roche, Pfizer, AstraZeneca, Novartis, Lilly, Daiichi Sankyo, and Roche; travel grants from AstraZeneca, Daiichi Sankyo, Roche, Pfizer, Lilly, Novartis, and MSD; and participation on a data safety monitoring or advisory board for Sanofi Aventis, AstraZeneca, and Roche Genentech. SL reports receiving grants to their institution, and consulting fees/speaker fees/honoraria from AstraZeneca, AbbVie, Agendia, Amgen, BioNTech, Celgene/BMS, Celcuity, DSI, Exact Science, Gilead Sciences, Inc., GSK, Incyte, Lilly, Medscape, Molecular Health, MSD, Novartis, Pierre Fabre, Pfizer, Relay, Roche, Sanofi, Seagen, Stemline/Menarini, Olema, Bayer, Bicycle, JAZZ Pharma, and BeiGene; royalties or licenses from VM Scope; travel grants from DSI, ESMO, ASCO, AGO Komission Mamma, and SGBCC; patents EP14153692.0, EP21152186.9, EP18209672, and EP24210258; receiving drugs for clinical trials from AstraZeneca, Celgene/BMS, Novartis, Pfizer, and Roche; and being an employee of GBG Forschungs GmbH. MP reports receiving grants to their institution from AstraZeneca, Lilly, Menarini, MSD, Novartis, Pfizer, Roche-Genentech, Servier, and Gilead Sciences, Inc.; consulting fees from AstraZeneca, Gilead Sciences, Inc., Lilly, Menarini, Mersana, MSD, Novartis, Pfizer, Roche-Genentech, Seattle Genetics, Seagen, NBE Therapeutics, and Summit Therapeutics; speaker fees and honoraria from AstraZeneca, Gilead Sciences, Inc., Lilly, Menarini, Mersana, MSD, Novartis, Pfizer, Roche-Genentech, Seattle Genetics, Seagen, NBE Therapeutics, and Summit Therapeutics; and participation on a data safety monitoring or advisory board for Oncolytics. LG reports consulting fees from Revolution Medicines, Zymeworks, Roche, Menarini Ricerche, Denali Therapeutics, and Synaffix; being a co-inventor of the European Patent application N. 12195182.6 and 12196177.5; and participation on a data safety monitoring or advisory board for Artemida Pharma Ltd., AstraZeneca, Daiichi-Sankyo, Roche, BeiGene, and Zymeworks. KK reports receiving grants from Lilly, Novartis, AstraZeneca, Genentech/Roche, Immunomedics, Merck, Seagen, Oncosec, 4D Pharma, Daiichi Sankyo/Zeneca, Puma Biotechnology, Mersana, Menarini Silicon Biosystems, Myovant Sciences, Takeda, Prelude Therapeutics, RayzeBio, eFFECTOR Therapeutics,

and Cullinan Oncology; and other financial or non-financial interests for their spouse for EQRX, and ADC Therapeutics. JOS reports consulting fees from AbbVie, Agendia, Amgen Biotechnology, Aptitude Health, AstraZeneca, Byondis, Carrick Therapeutics, BioNTech, Daiichi Sankyo, DAVA Oncology, Eisai, Fishawack Health, G1 Therapeutics, Genzyme, GlaxoSmithKline, Genentech, Gilead Sciences, Inc., Lilly, Loxo Oncology, Merck, Novartis, Ontada, Pfizer, Pierre Fabre Pharmaceuticals, Puma Biotechnology, Roche, Samsung Bioepis, Sanofi, Seagen, Stemline Therapeutics, Taiho Oncology, and Veru; and speaker fees and honoraria from AbbVie, Agendia, Amgen Biotechnology, Aptitude Health, AstraZeneca, Byondis, Carrick Therapeutics, BioNTech, Daiichi Sankyo, DAVA Oncology, Eisai, Fishawack Health, G1 Therapeutics, Genzyme, GlaxoSmithKline, Genentech, Gilead Sciences, Inc., Lilly, Loxo Oncology, Merck, Novartis, Ontada, Pfizer, Pierre Fabre Pharmaceuticals, Puma Biotechnology, Roche, Samsung Bioepis, Sanofi, Seagen, Stemline Therapeutics, Taiho Oncology, and Veru. SAH reports receiving grants to their institution from Ambrx, Amgen, Arvinas, AstraZeneca, Bayer, Celcuity, CytomX, Daiichi Sankyo, Dantari, Dignitana, Eli Lilly, Genentech/Roche, G1-Therapeutics, Gilead Sciences, Inc., Greenwich Life Sciences Inc., GSK, Immunomedics, Loxo, MacroGenics, Novartis, OBI Pharma, Orinove, Orum, Pfizer, Phoenix Molecular Designs, Ltd., Pieris, PUMA, Radius, Samumed, Sanofi, Seattle Genetics/Seagen, Stemline/Menarini, Jazz, and Zymeworks; royalties from Wolters Kluwer, Elsevier, McGraw Hill, and Sage; consulting fees to their institution from Briacell, BeiGene, BridgeBio, Daiichi Sankyo, Jazz/Zymeworks, Boehringer Ingelheim, Gilead Sciences, Inc., Luminate, Menarini, Mersana, MedSir, Novartis, Roche, BMS, and Arvinas/Pfizer; participation on a data safety monitoring or advisory board for Alliance Foundation, Quantum Leap, and InClin/Atossa; and stocks/stock options with RomTech. TV reports being an employee of Gilead Sciences, Inc.; and having stock or stock options with Gilead Sciences, Inc. and Novavax. EH, SP, and CL report being employees of and having stock or stock options with Gilead Sciences, Inc. JC reports receiving consulting fees from Roche, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Lilly, Merck Sharp & Dohme, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, HiberCell, BioInvent, GEMoaB, Gilead Sciences, Inc., Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, ExpreS2ion Biotechnologies, Jazz Pharmaceuticals, AbbVie, BridgeBio, BioNtech, Biocon, Circle Pharma, and Delcath Systems, Inc.; speaker fees and honoraria from Roche, Novartis, Eisai, Pfizer, Lilly, Merck Sharp & Dohme, Daiichi Sankyo, AstraZeneca, Gilead Sciences, Inc., and Stemline Therapeutics; travel grants from Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead Sciences, Inc., Merck Sharp & Dohme, and Stemline Therapeutics; patents WO 2014/199294 A (issued) and US 2019/0338368 A1 (licensed); stock or stock options with MAJ3 Capital, and Leuko (for a relative); and research funding to their institution from Roche, Ariad pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer Healthcare, Eisai, F. Hoffman-La Roche, Guardant Health, Merck Sharp & Dohme, Pfizer, Piqur Therapeutics, Iqvia, and Queen Mary University of London.

DATA SHARING

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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