The Impact of High Body Mass Index on the Safety and Efficacy of Sacituzumab Govitecan in Patients With Metastatic Triple-Negative Breast Cancer From ASCENT

Poster # 189P

ASCENT (NCT02574455)

Laura García-Estévez[1], Aditya Bardia[2], Hope S Rugo[3], Lisa A Carey[4], Véronique C Diéras[5], Sibylle Loibl[6], Martine Piccart[7], Luca Gianni[8], Kevin Kalinsky[9], Joyce O'Shaughnessy[10], Sara A Hurvitz[11], Eliza Harting[12], Theresa Valdez[12], See C Phan[12], Catherine Lai[12], Javier Cortes[13]

[1]MD Anderson Cancer Center, Madrid, Spain; [2]David Geffen School of Medicine, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [3]University of California-San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [4]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; [5]Centre Eugène Marquis, Rennes, France; [6]Hämatologisch-Onkologische Gemeinschaftspraxis am Bethanien-Krankenhaus, Frankfurt, Germany; [7]Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Bruxelles, Belgium; [8]Gianni Bonadonna Foundation, Milano, Italy; [9]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [10]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA; [11]Fred Hutchinson Cancer Center and University of Washington Medicine, Seattle, WA, USA; [12]Gilead Sciences, Inc., Foster City, CA, USA; [13]International Breast Cancer Center (IBCC), Pangaea Oncology, Quirónsalud Group, Barcelona, Spain & Universidad Europea de Madrid, Madrid, Spain

Conclusions

- To our knowledge, this is the first study evaluating the impact of BMI on treatment outcomes with ADCs
- SG demonstrated improved efficacy vs TPC and a manageable safety profile in patients from all evaluated BMI subgroups from ASCENT
- 24% of overweight and 41% of obese patients had a reduction in SG dose due to an adverse event; however, the efficacy of SG was maintained in these patients; 3% and 8% of patients, respectively, discontinued SG due to an adverse event
- Clinical benefit with SG could be maintained by using available adverse event management strategies, including dose reductions
- 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

Plain Language Summary

- Sacituzumab govitecan (SG) is a drug that is approved to treat metastatic triple-negative breast cancer and other types of breast cancer in several countries
- This study analyzed the effect of body mass index (BMI) on participants treated with SG or chemotherapy – BMI groups analyzed were underweight and normal weight, overweight, and obese
- In all BMI groups tested, participants treated with SG lived approximately 2 to 3 times longer without their disease getting worse, and more participants had their tumors get smaller or disappear, compared with those who were treated with chemotherapy
- Although more overweight and obese participants had changes to their SG dose due to side effects than underweight and normal-weight participants, they still benefited from SG treatment

References: **1**. Rugo HS, et al. *Future Oncol*. 2020;16:705-15. **2**. Trodelvy® (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; February 2023. **3.** European Medicines Agency. Trodelvy® [summary of product characteristics]. County Cork, Ireland: Gilead Sciences Ireland UC; 2021. **4.** Pharmaceutical Technology. www.pharmaceutical-technology.com/news/everest-trodelvy-breast-cancer/. Accessed March 7, 2024. **5.** BioPharma APAC. https://biopharmaapac.com/news/89/12582/-singapore-hsa-approval-marks-the-first-in-a-series-of-expected-approvals-of-trodelvy-in-asia.html. Accessed March 7, 2024. **6.** Korea Biomedical Review. https://www.koreabiomed.com/news/articleView.html?idxno=21060. Accessed March 7, 2024. **7.** Bardia A, et al. *N Engl J Med*. 2021;384:1529-41. **8.** Bardia A, et al. *J Clin Oncol*. Published online February 29, 2024. https://doi.org/10.1200/JCO.23.01409. Accessed March 12, 2024. **9.** World Health Organization. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed March 7, 2024.

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Correspondence: Laura García-Estévez, lgestevez@mdanderson.es

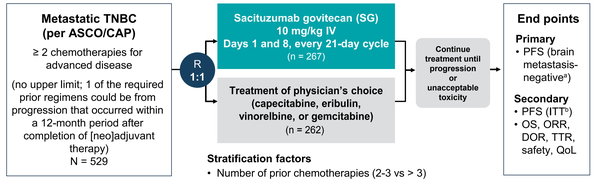
Introduction

- Sacituzumab govitecan (SG) is a Trop-2–directed antibody-drug conjugate (ADC) designed with a hydrolysable linker attached to SN-38, the active metabolite of irinotecan[1]
  - SG is approved in multiple countries for the treatment of relapsed or refractory metastatic triple-negative breast cancer (mTNBC) based on results from the global, phase 3 ASCENT study[2-7]
- In ASCENT (N = 529), significantly longer progression-free survival (PFS; hazard ratio [HR], 0.43; 95% CI, 0.35-0.54) and overall survival (OS; HR, 0.51; 95% CI, 0.41-0.62) were observed with SG vs chemotherapy treatment of physician's choice (TPC) in all patients, including those with brain metastases (data cutoff: March 11, 2020; median follow-up of 17.7 months); these results were maintained with longer follow-up[7,8]
- The incidence of worldwide adult obesity has more than doubled since 1990, and the World Health Organization now classifies it as a global crisis[9]
- The impact of body mass index (BMI) on treatment outcomes, especially for ADCs like SG that have weight-based dosing, is unclear and remains an area of active research
- In this analysis, we report the impact of BMI on efficacy and safety of SG vs TPC among patients with mTNBC from the ASCENT study

Study Design and Methods

- This was an ad hoc subgroup analysis from the ASCENT study (Figure 1)
- Patients from the full intent-to-treat population of ASCENT who received SG at 10 mg/kg of body weight or TPC were included
- Patients did not have their dosage capped for high BMI
- BMI was assessed at baseline and was classified as follows:
  - Underweight/normal (< 25 kg/m^2)
  - Overweight (25 to < 30 kg/m^2)
  - Obese (≥ 30 kg/m^2)
- Results presented are as of February 25, 2021

Figure 1. ASCENT (NCT02574455) Study Design



Stratification factors
- Number of prior chemotherapies (2-3 vs > 3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (Yes/No)

Adapted from Bardia A, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med*. 2021;384:1529-41. [a]PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST v1.1 criteria in patients without brain metastasis. [b]The ITT population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastases.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; ITT, intent-to-treat; IV, intravenous; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TNBC, triple-negative breast cancer; TTR, time to response.

Results

Patient Population

- Baseline characteristics were generally similar across the BMI categories (Table 1)
- Of the 528 patients included in this analysis, 287 (54%) had high BMI
  - 155 patients (29%) were overweight
  - 132 patients (25%) were obese

Results

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Underweight/Normal[a] (< 25 kg/m^2)		Overweight (25 to < 30 kg/m^2)		Obese (≥ 30 kg/m^2)	
	SG (n = 127)	TPC (n = 114)	SG (n = 71)	TPC (n = 84)	SG (n = 68)	TPC (n = 64)
Median age, years	53	53	56	55	53	52
Female, n (%)	126 (> 99)	114 (100)	70 (99)	84 (100)	68 (100)	64 (100)
BMI,[b] kg/m^2, mean (SD)	21.8 (2.08)	21.6 (2.33)	27.4 (1.39)	27.3 (1.46)	35.7 (5.18)	35.2 (4.99)
ECOG PS at screening, n (%)						
0	61 (48)	49 (43)	29 (41)	37 (44)	31 (46)	22 (34)
1	66 (52)	65 (57)	42 (59)	47 (56)	37 (54)	42 (66)
Prior systemic therapies, median (range)	4 (2-11)	4 (2-14)	4 (2-17)	4 (2-14)	4 (2-11)	4 (2-11)

[a]Includes 8 and 11 underweight patients (BMI < 18.5 kg/m^2) in the SG and TPC groups, respectively. [b]BMI is calculated as BMI (kg/m^2) = (weight in kg)/(height in m)^2.
BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Efficacy Outcomes

- Longer PFS and OS (Figure 2) and higher objective response rate and clinical benefit rate were observed with SG vs TPC in all evaluated BMI subgroups (Table 2)
- Standard chemotherapy showed reduced objective response rates in overweight and obese patients compared with those in the underweight/normal subgroup; however, the activity of SG was maintained in all evaluated BMI subgroups

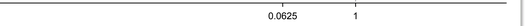
Figure 2. Forest Plots of PFS by Independent Review (A) and OS (B)

A

BMI Subgroup	Median PFS, Months (95% CI) SG	TPC	HR (95% CI)	*P* Value
Underweight/normal (< 25 kg/m^2) (n = 241)	4.2 (2.9-5.6)	1.9 (1.5-2.8)	0.503 (0.366-0.692)	< .0001
Overweight (25 to < 30 kg/m^2) (n = 155)	4.6 (3.3-6.3)	1.5 (1.4-1.6)	0.310 (0.203-0.473)	< .0001
Obese (≥ 30 kg/m^2) (n = 132)	5.9 (4.1-8.3)	2.6 (1.6-3.0)	0.337 (0.212-0.534)	< .0001

B

BMI Subgroup	Median OS, Months (95% CI) SG	TPC	HR (95% CI)	*P* Value
Underweight/normal (< 25 kg/m^2) (n = 241)	10.9 (9.4-13.0)	6.2 (4.8-7.1)	0.554 (0.418-0.735)	< .0001
Overweight (25 to < 30 kg/m^2) (n = 155)	10.8 (9.0-14.2)	6.7 (5.2-8.9)	0.511 (0.354-0.735)	.0003
Obese (≥ 30 kg/m^2) (n = 132)	14.9 (11.2-16.8)	8.7 (6.7-9.8)	0.451 (0.304-0.670)	< .0001



BMI, body mass index; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Table 2. Responses by Independent Review

	Underweight/Normal (< 25 kg/m^2)		Overweight (25 to < 30 kg/m^2)		Obese (≥ 30 kg/m^2)	
	SG (n = 127)	TPC (n = 114)	SG (n = 71)	TPC (n = 84)	SG (n = 68)	TPC (n = 64)
Objective response rate,[a] % (95% CI)	25 (18-34)	8 (4-15)	34 (23-46)	1 (0-7)	40 (28-52)	2 (0-8)
Odds ratio (95% CI)	3.9 (1.8-8.7)		42.4 (5.6-323.4)		41.5 (5.4-317.3)	
Clinical benefit rate,[b] % (95% CI)	35 (27-44)	11 (6-19)	41 (29-53)	5 (1-12)	50 (38-62)	6 (2-15)
Odds ratio (95% CI)	4.3 (2.2-8.4)		13.8 (4.6-41.9)		15.0 (4.9-45.9)	

[a]Objective response rate is defined as the best confirmed overall response of either CR or PR. [b]Clinical benefit rate is defined as those patients with best response as CR or PR or SD ≥ 6 months.
CR, complete response; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

SG Exposure and Safety Outcomes

- The rate of dose interruption was higher, and more serious adverse events were observed, in patients from the overweight and obese BMI subgroups (Table 3)
- The rate and number of dose reductions was the highest in patients from the obese subgroup, the majority of whom received only 1 dose reduction
- The most common adverse events (≥ 5%) leading to SG dose reductions were neutropenia in the underweight/normal and overweight subgroups, and neutropenia, diarrhea, nausea, and febrile neutropenia in the obese subgroup
- The rates of treatment-emergent adverse events leading to SG discontinuation and death were low and similar across the BMI subgroups

Table 3. SG Exposure and Safety Summary

	All Patients N = 258	Underweight/ Normal (< 25 kg/m^2) n = 125	Overweight (25 to < 30 kg/m^2) n = 67	Obese (≥ 30 kg/m^2) n = 66
Exposure				
Median time to first dose reduction (range), months	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)	19 (15)	18 (27)	29 (44)
1	52 (20)	17 (14)	14 (21)	21 (32)
2	14 (5)	2 (2)	4 (6)	8 (12)
Safety, n (%)				
Any TEAEs	257 (100)	125 (100)	66 (99)	66 (100)
TEAEs grade ≥ 3	188 (73)	85 (68)	52 (78)	51 (77)
Treatment-emergent serious AEs	69 (27)	24 (19)	23 (34)	22 (33)
TEAEs leading to SG interruption	162 (63)	72 (58)	43 (64)	47 (71)
TEAEs leading to SG discontinuation	12 (5)	5 (4)	2 (3)	5 (8)
TEAEs leading to SG dose reduction	57 (22)	14 (11)	16 (24)	27 (41)
TEAEs leading to death	1 (< 1)	1 (< 1)	0 (0)	0 (0)

Percentages based on the number of patients in the safety population in each subgroup. Treatment-emergent adverse event defined as an adverse event with a start date on or after the date of the first dose of study treatment and up to 30 days after the date of the last dose of study treatment.
AE, adverse event; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

- Neutropenia was the most frequently observed TEAE of grade ≥ 3 in all evaluated BMI subgroups (Table 4)
- Grade ≥ 3 neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, and infections occurred at a higher incidence in obese patients compared with underweight and normal-weight patients (Table 4)
- Diarrhea and infection led to SG treatment discontinuation in 1 obese patient each. No obese patients discontinued SG treatment due to neutropenia, leukopenia, anemia, or febrile neutropenia

Table 4. Most Common Grade ≥ 3 TEAEs (≥ 10%) Observed With SG

TEAE, n (%)	All Patients N = 258	Underweight/ Normal (< 25 kg/m^2) n = 125	Overweight (25 to < 30 kg/m^2) n = 67	Obese (≥ 30 kg/m^2) n = 66
Neutropenia	135 (52)	64 (51)	33 (49)	38 (58)
Leukopenia	27 (11)	10 (8)	6 (9)	11 (17)
Diarrhea	30 (12)	8 (6)	9 (13)	13 (20)
Infections and infestations[a]	25 (10)	8 (6)	9 (13)	8 (12)
Anemia	24 (9)	6 (5)	8 (12)	10 (15)
Febrile neutropenia	15 (6)	2 (2)	5 (8)	8 (12)

Percentages based on the number of patients in the safety population in each subgroup. Treatment-emergent adverse event defined as an adverse event with a start date on or after the date of the first dose of study treatment and up to 30 days after the date of the last dose of study treatment.
[a]Defined as all preferred terms within the system organ class infections and infestations.
SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.