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Poster PD13-07

Subgroup Analysis of Patients With Brain Metastases From the Phase 3 ASCENT Study of Sacituzumab Govitecan Versus Chemotherapy in Metastatic Triple-Negative Breast Cancer

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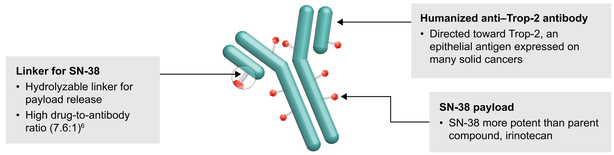
BACKGROUND

- Trophoblast cell surface antigen 2 (Trop-2) is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- Sacituzumab govitecan (SG) is a novel antibody-drug conjugate (ADC) comprised of an anti–Trop-2 monoclonal antibody conjugated to SN-38 (an active metabolite of irinotecan) via a unique hydrolyzable linker (**Figure 1**)
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- SG was granted accelerated approval by the FDA for patients with metastatic triple-negative breast cancer (mTNBC) who have received at least 2 prior therapies for metastatic disease and fast-track designation in metastatic urothelial cancer[7]

Figure 1: Sacituzumab Govitecan Antibody-Drug Conjugate

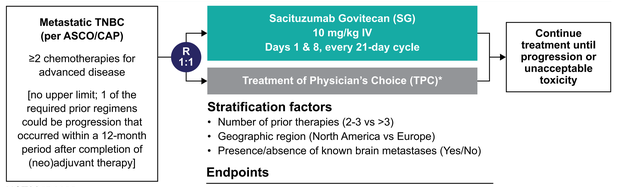


Trop-2, trophoblast cell surface antigen 2.

- ASCENT is the first phase 3 study with Trop-2–directed ADC (SG) in pretreated mTNBC to demonstrate a significant survival improvement versus standard single-agent chemotherapy with a tolerable safety profile (**Figure 2**)
- SN-38 can cross the blood–brain barrier and is a drug partner in central nervous system (CNS) disease regimens[8-10]
  - In a model of breast cancer brain metastases, liposomal SN-38 accumulated in metastatic lesions and significantly increased median survival versus vehicle[10]
  - Previous studies in adults have noted manageable toxicities, including diarrhea, with SN-38[8]
- Activity with SG has been observed in intracranial xenograft models[11,12]
  - Preliminary results of SG in patients with breast cancer and known or suspected parenchymal brain metastases show that 4 of 7 patients were progression free at 279, 202, 175, and 161 days[12]

METHODS

Figure 2: ASCENT Study Design



NCT02574455

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

Endpoints

Primary
- PFS†

Secondary
- PFS for the full population‡
- OS, ORR, DOR, TTR, QoL, safety

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

- In a subgroup analysis from ASCENT, the efficacy and safety of SG were evaluated in patients with stable brain metastases
- Brain MRIs were required in patients with known brain metastases
  - Patients were eligible if they had stable CNS disease for ≥4 weeks by MRI *(defined as ≥2 weeks from discontinuation of antiseizure medication and corticosteroid dose [≤20 mg prednisone equivalent] that was stable or decreasing for ≥2 weeks before randomization)*
  - Brain MRIs were required throughout the study
- The primary endpoint was progression-free survival (PFS) per independent central review (RECIST v1.1) in brain metastases-negative patients
- Secondary endpoints included PFS per investigator review, PFS in the full population (in patients with/without brain metastases) by central review, objective response rate (ORR), overall survival (OS), and safety
- Data cutoff for analysis was March 11, 2020

RESULTS

PATIENT DISPOSITION

- Of the 529 patients enrolled in ASCENT, 61 patients (SG, n=32; treatment of physician's choice [TPC], n=29) were included in the brain metastases-positive population (**Table 1**)
  - Of these 61 patients, 2 (6%) in the SG arm and 6 (21%) in the TPC arm did not receive treatment
- At the data cutoff, 2 patients (6%) with brain metastases treated with SG are continuing treatment for 16.2 months and 6.3 months; no patients remain on treatment in the TPC arm
- Primary reasons for discontinuation (SG vs TPC) were disease progression (72% vs 62%) and adverse events (13% vs 3%)

Table 1: Patient Disposition

Brain Metastases-Positive Population	SG (n=32)	TPC (n=29)
Randomized—no.	32	29
Randomized (not treated)—no. (%)	2 (6)	6 (21)
Safety population (treated)*—no. (%)	30 (94)	23 (79)
Remain on treatment—no. (%)	2 (6)	0
Discontinued treatment—no. (%)	28 (88)	23 (79)
Disease progression	23 (72)	18 (62)
Adverse event	4 (13)†	1 (3)†
Withdrawal of consent	1 (3)	1 (3)
Investigator decision	0	1 (3)
Death	0	0
Other	0	2 (7)‡

*All patients who received ≥1 dose of study treatment.
†One patient in the SG arm discontinued due to sepsis and thrombocytopenia (considered treatment-related) and 1 patient in the TPC arm due to fatigue (considered possibly treatment-related).
‡Due to treatment delay >3 weeks.
SG, sacituzumab govitecan; TPC, treatment of physician's choice.

DEMOGRAPHICS AND PATIENT CHARACTERISTICS

- Baseline characteristics were balanced between the SG and TPC arms (**Table 2**)
  - All patients were female and had a median of 5 prior anticancer regimens in both treatment arms

Table 2: Demographics and Patient Characteristics

	SG (n=32)	TPC (n=29)
Female—no. (%)	32 (100)	29 (100)
Median age—yr (range)	53 (27-80)	51 (34-81)
Race or ethnic group—no. (%)		
White	27 (84)	22 (76)
Black	0	6 (21)
Asian	4 (13)	0
Other or not specified	1 (3)	1 (3)
ECOG PS—no. (%)		
0	13 (41)	10 (34)
1	19 (59)	19 (66)
BRCA1/2 mutational status—no. (%)		
Positive	4 (13)	5 (17)
Negative	17 (53)	21 (72)
Missing	11 (34)	3 (10)
Original diagnosis of TNBC*—no. (%)		
Yes	27 (84)	23 (79)
No	5 (16)	6 (21)
Prior anticancer regimens†—median no. (range)	5 (2-9)	5 (2-10)
Previous use of checkpoint inhibitors—no. (%)	12 (38)	14 (48)
Most common sites of disease‡—no. (%)		
Lung only	23 (72)	18 (62)
Bone	14 (44)	8 (28)
Liver	9 (28)	13 (45)

Assessed in the brain metastasis-positive population. *Patients on study either had TNBC at initial diagnosis or had hormone receptor-positive disease that converted to hormone-negative at time of study entry. †Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting. ‡Based on independent central review of target and non-target lesions at baseline.
BRCA, breast cancer gene; ECOG PS, Eastern Cooperative Oncology Group performance status; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

RESPONSES

- The ORR and clinical benefit rate (CBR) per blind independent central review (BICR) assessment for patients treated with SG versus TPC were 3% versus 0% ORR and 9% versus 3% CBR, respectively (**Table 3**)
  - Per investigator assessment, the ORR was 9% for SG versus 3% for TPC
  - More patients achieved stable disease in the SG arm versus the TPC arm (47% vs 31%)

Table 3: Responses (BICR Analysis)

	Brain Metastases-Positive (N=61)	
	SG (n=32)	TPC (n=29)
ORR—no. (%)	1 (3)	0
CBR—no. (%)*	3 (9)	1 (3)
Best overall response—no. (%)		
CR	0	0
PR	1 (3)	0
SD	15 (47)	9 (31)
SD >6 months	2 (6)	1 (3)
PD	11 (34)	11 (38)
Not evaluable	5 (16)	9 (31)

*CBR is defined as the percentage of patients with a confirmed best overall response of CR or PR and SD ≥6 months.
BICR, blind independent central review; CBR, clinical benefit rate; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

SURVIVAL OUTCOMES

- Median PFS was 2.8 months for SG versus 1.6 months for TPC per BICR assessment, with a hazard ratio (HR) of 0.65 (95% CI, 0.35-1.22) (**Table 4**)
  - PFS rates were higher for SG versus TPC at 3 months (41% vs 28%) and at 9 months (9% vs 0%)
- Median OS was 6.8 months for SG versus 7.5 months for TPC (HR [95% CI], 0.87 [0.47-1.63]) (**Table 5**)

Table 4: Progression-Free Survival

	Brain Metastases-Positive (N=61)	
BICR Analysis	SG (n=32)	TPC (n=29)
No. of events	24	21
Median PFS—mo (95% CI)	2.8 (1.5-3.9)	1.6 (1.3-2.9)
HR (95% CI)	0.65 (0.35-1.22)	
PFS rate—% (95% CI)		
At 3 months	41.4 (23.7-58.3)	27.7 (11.4-46.9)
At 6 months	9.0 (0.9-29.2)	6.9 (0.6-24.9)
At 9 months	9.0 (0.9-29.2)	0
At 12 months	9.0 (0.9-29.2)	0

BICR, blind independent central review; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Table 5: Overall Survival

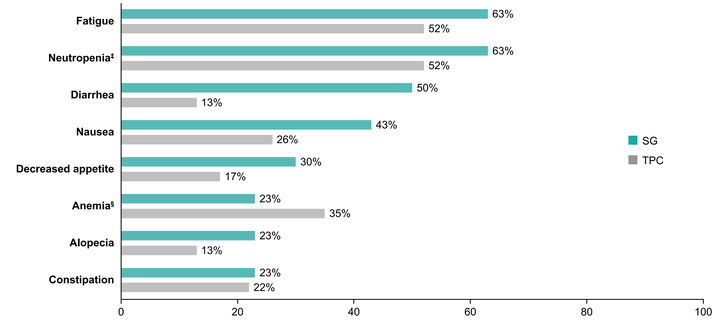
	Brain Metastases-Positive (N=61)	
	SG (n=32)	TPC (n=29)
No. of events	24	21
Median OS—mo (95% CI)	6.8 (4.7-14.1)	7.5 (4.7-11.1)
HR (95% CI)	0.87 (0.47-1.63)	

HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

TREATMENT-EMERGENT ADVERSE EVENTS

- The most common treatment-emergent adverse events for SG versus TPC were fatigue (63% vs 52%), diarrhea (50% vs 13%), neutropenia (43% vs 35%), and nausea (43% vs 26%) (**Figure 3**)
- One patient in the SG arm discontinued due to sepsis and thrombocytopenia (considered treatment-related) and 1 patient in the TPC arm due to fatigue (considered possibly treatment-related)
- There were no treatment-related deaths in either arm

Figure 3: TEAEs (All Grades, >20% of BMPos Patients Treated With SG)*



*Patients may report more than 1 event per preferred term. Adverse events were classified according to the MedDRA systems of preferred terms and system organ class. †Percentages are based on the number of BMPos patients treated (SG, n=30; TPC, n=23). ‡Combined preferred terms of 'neutropenia' and 'neutrophil count decreased.' §Combined preferred terms of 'anemia,' 'hemoglobin decreased,' and 'red blood cell count decreased.'
BMPos, brain-metastases positive; MedDRA, Medical Dictionary for Regulatory Activities; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

CASE STUDY*

- The patient of this case study is a White female, 52-years old at the time of enrollment, with *BRCA1/2*-positive mutation status and an Eastern Cooperative Oncology Group performance status of 0 at baseline
- The patient progressed on 3 prior anticancer regimens in the metastatic setting, and her best response to any of these therapies was stable disease
- At baseline, the patient had known brain metastases (2 non-target lesions) with a target lesion in the lymph node
  - Stereotactic radiosurgery to the left cerebellar hemisphere had been performed 7 months prior to study screening
  - At baseline, MRI showed metastases in the left cerebellum (1 lesion) and left inferior cerebellar hemisphere (1 lesion)
  - No concomitant medical, surgical, or radiotherapy procedures were carried out
  - After 15 cycles, 1 brain lesion (left cerebellum) was absent by contrast MRI; the second brain lesion (left inferior cerebellar hemisphere) was present throughout the course of treatment
- The patient received SG for approximately 21 months (29 treatment cycles)
  - Treatment was discontinued due to patient withdrawal of consent
  - During treatment, the patient achieved stable disease for approximately 11 months before achieving a partial response for 4 months
- During treatment, the patient experienced 4 treatment-related adverse events (grade 1 nausea [2 times], grade 2 alopecia, and grade 3 decreased neutrophil count)
  - The treatment dose was reduced due to the grade 3 decreased neutrophil count

*Disclaimer: The information contained in this case study is not representative of the study subgroup and cannot be generalized.

CONCLUSIONS

- Data interpretation in this subset with poor prognosis is limited by the small sample size
- In the phase 3 ASCENT study, SG was numerically better than TPC for tumor response and PFS, but not OS, in this exploratory analysis
- Safety profile was similar to the population without brain metastases for both study arms and consistent with previous reports
- SG is currently under clinical investigation for patients undergoing elective surgery for breast cancer brain metastases or recurrent glioblastoma (NCT03995706) based on promising preclinical and intracranial data

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