Analysis of Patients Without an Initial Triple-Negative Breast Cancer Diagnosis in the Phase 3 ASCENT Study of Sacituzumab Govitecan in Metastatic TNBC

Poster 258P

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ASCENT Clinical Trial

Background

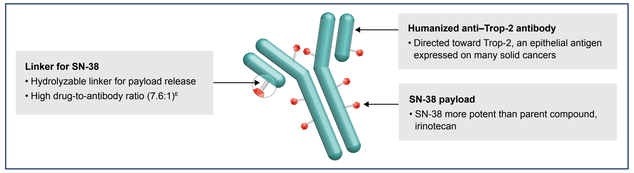
Metastatic Triple-Negative Breast Cancer (mTNBC)

- mTNBC is a heterogenous disease with few treatment options and poor outcomes[1-3]
- Single-agent chemotherapy remains standard for previously treated mTNBC, but is associated with low response rates and short progression-free survival (PFS)[4-7]
- While 88% of breast cancers are initially diagnosed as hormone receptor (HR)-positive and/or human epidermal growth factor receptor 2 (HER2)-positive,[8,9] discordance in receptor status from initial diagnosis through relapse/disease is common, most often involving positive-to-negative changes in receptor status[10-14]
- Loss of HR or HER2 expression between primary and recurrent breast tumors is associated with poorer survival compared with receptor stability between primary and recurrent tumors[11-13]
- Patients with mTNBC who have had altered receptor status since initial breast cancer diagnosis thus represent a population with an unmet need for novel therapies

Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed Antibody-Drug Conjugate

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[15,16]
- SG is distinct from other antibody-drug conjugates (ADCs; **Figure 1**)[17-21]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody
  - Hydrolysis of the linker releases SN-38 extracellularly in the tumor microenvironment (bystander effect)
- Granted U.S. Food and Drug Administration (FDA) approval for mTNBC and FDA accelerated approval for metastatic urothelial cancer[20]
- Results from the confirmatory ASCENT study demonstrated a significant survival improvement of SG over chemotherapy, with a manageable safety profile in the second-line or greater mTNBC setting[21]
  - Median PFS of 5.6 vs 1.7 months (HR, 0.41; *P*<0.001)
  - Median overall survival (OS) of 12.1 vs 6.7 months (HR, 0.48; *P*<0.001)

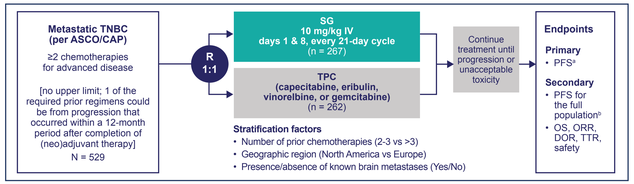
Figure 1. Sacituzumab Govitecan Antibody-Drug Conjugate



Methods

- This prespecified subgroup analysis assessed the clinical impact of SG in the subgroup of patients who did not have TNBC at initial diagnosis (prior to enrollment in ASCENT)
- TNBC status prior to enrollment in ASCENT was determined by local assessment of most recent biopsy or other pathology specimen per American Society of Clinical Oncology/College of American Pathologists criteria (**Figure 2**)
  - Negativity for estrogen receptor (ER) and progesterone receptor (PR) defined as <1% of cells expressing ER and PR by immunohistochemistry (IHC)
  - Negativity for HER2 defined as 0 or 1+ by IHC, or if IHC 2+, then fluorescence in situ hybridization (FISH)-negative
- Median PFS and objective response rate (ORR) in the population without known brain metastases (BMNeg) were assessed by blind independent central review (BICR) per RECIST 1.1
- Safety population included all patients who received ≥1 dose of study treatment
- Data cutoff was March 11, 2020

Figure 2. ASCENT: A Phase 3 Confirmatory Study of SG in Refractory/Relapsed mTNBC (NCT02574455)



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[a] 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.
[b] 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; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Results

Patients

- Of the 468 patients in the BMNeg population, 70/235 (30%) in the SG arm and 76/233 (33%) in the treatment of physician's choice (TPC) arm did not have TNBC at initial diagnosis
- Demographics and baseline characteristics across the SG and TPC arms were generally balanced (**Table 1**)
  - Of note, patients without TNBC at initial diagnosis received a median of 5 prior anticancer regimens
  - In the overall ASCENT study population, patients received a median of 4 prior anticancer regimens[21]
  - In the SG vs TPC arms, 27% vs 29% of patients received prior cyclin-dependent kinase (CDK) 4/6 inhibitors, respectively
- At data cutoff, 4 patients (6%) in the SG arm remained on treatment, whereas no patients in the TPC arm remained on treatment
  - The most common reason for treatment discontinuation was disease progression (84% vs 72%)
- Median treatment duration for the SG vs TPC arms was 5.1 vs 1.2 months
- Median duration of follow-up for the SG vs TPC arms was 10.6 vs 6.1 months

Table 1. Demographics and Baseline Characteristics of Patients Without TNBC at Initial Diagnosis

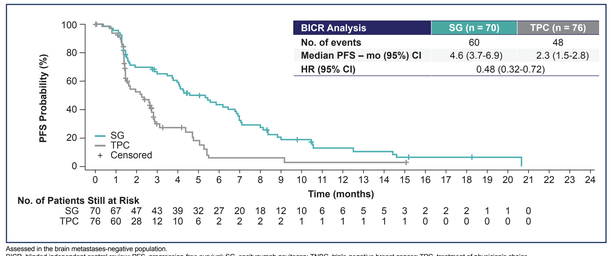
	SG (n = 70)	TPC (n = 76)
Female—no. (%)	69 (99)	76 (100)
Median age (range)—y	56 (31-74)	55 (27-80)
Race or ethnic group—no. (%)		
White	58 (83)	62 (82)
Black	6 (9)	5 (7)
Asian	3 (4)	4 (5)
Other or not specified	3 (4)	5 (7)
ECOG performance status—no. (%)		
0	28 (40)	26 (34)
1	42 (60)	50 (66)
Number of prior chemotherapies—no. (%)		
2-3	41 (59)	46 (61)
>3	29 (41)	30 (39)
Median prior anticancer regimens[a]—no. (range)	5 (2-17)	5 (2-14)
Previous use of checkpoint inhibitors—no. (%)	17 (24)	23 (30)
Previous use of CDK4/6 inhibitors—no. (%)	19 (27)	22 (29)
Previous use of anti-HER2 therapy—no. (%)	14 (20)	13 (17)
Previous use of PI3K inhibitors—no. (%)	2 (3)	0
Previous use of PARP inhibitors—no. (%)	4 (6)	5 (7)
Setting of prior systemic therapies—no. (%)		
Adjuvant	54 (77)	55 (72)
Neoadjuvant	30 (43)	30 (39)
Metastatic	69 (99)	76 (100)
Locally advanced disease	2 (3)	1 (1)
ER <1% of tumor cells—no. (%)	70 (100)	76 (100)
PR <1% of tumor cells—no. (%)	70 (100)	76 (100)
Diagnosis of HER2 negativity—no. (%)		
IHC 0	31 (44)	37 (49)
IHC 1	16 (23)	13 (17)
FISH	23 (33)	26 (34)
***BRCA1/2* mutational status—no. (%)**		
Negative	43 (61)	36 (47)
Positive	6 (9)	4 (5)
Trop-2 expression—no. (%)		
(High) H-score >200-300	27 (39)	22 (29)
(Medium) H-score 100-200	12 (17)	13 (17)
(Low) H-score 0-<100	7 (10)	7 (9)

Assessed in the brain metastasis-negative population.
[a] Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting.
BRCA, breast cancer gene; CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; FISH; fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; H-score, histological score; IHC, immunohistochemistry; PARP poly (adenosine diphosphate-ribose) polymerase; PI3K, phosphoinositide 3 kinase; PR, progesterone receptor; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice; y, years.

Efficacy

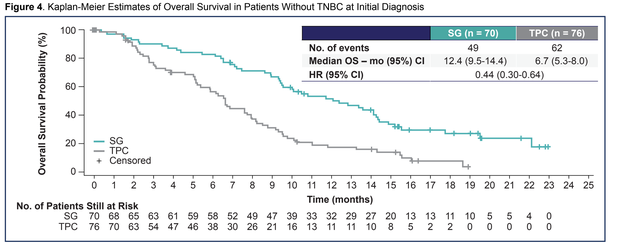
- In this patient subgroup, median PFS (BICR) with SG vs TPC was 4.6 vs 2.3 months (HR, 0.48; 95% CI, 0.32-0.72; **Figure 3**)
- Median OS with SG vs TPC was 12.4 vs 6.7 months (HR, 0.44; 95% CI, 0.30-0.64; **Figure 4**)
- ORR (BICR) with SG vs TPC was 31% vs 4% (**Table 2**)
  - In the SG arm, 1 patient (1%) had a complete response (CR) and 21 patients (30%) had a partial response (PR)
  - In the TPC arm, 1 patient (1%) had a CR and 2 patients (3%) had a PR
  - Median duration of response (DOR) was 5.6 vs 3.5 months (HR, 0.31; 95% CI, 0.05-2.01)
- Efficacy outcomes for SG in patients without TNBC at initial diagnosis were similar to those of SG in the overall BMNeg population and the total ASCENT study population (**Table 2**)[21]
- Among patients who did not have TNBC at initial diagnosis and who had received a prior CDK4/6 inhibitor, the ORR was 21% with SG and 5% with TPC (**Table 3**)
  - Median DOR was 4.2 vs 2.9 months (HR, 1.14; 95% CI, 0.10-13.27)

Figure 3. Kaplan-Meier Estimates of Progression-Free Survival in Patients Without TNBC at Initial Diagnosis



Assessed in the brain metastases-negative population.
BICR, blinded independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

Figure 4. Kaplan-Meier Estimates of Overall Survival in Patients Without TNBC at Initial Diagnosis



Assessed in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

Table 2. Efficacy Outcomes

	Patients Without TNBC at Initial Diagnosis		Overall BMNeg Population		ITT Population	
	SG (n = 70)	TPC (n = 76)	SG (n = 235)	TPC (n = 233)	SG (n = 267)	TPC (n = 262)
Median PFS—mo (95% CI)	4.6 (3.7-6.9)	2.3 (1.5-2.8)	5.6 (4.3–6.3)	1.7 (1.5–2.6)	4.8 (4.1-5.8)	1.7 (1.5-2.5)
HR (95% CI)	0.48 (0.32-0.72)		0.41 (0.32−0.52), *P*<0.001		0.43 (0.35−0.54)	
Median OS—mo (95% CI)	12.4 (9.5-14.4)	6.7 (5.3-8.0)	12.1 (10.7−14.0)	6.7 (5.8–7.7)	11.8 (10.5-13.8)	6.9 (5.9-7.7)
HR (95% CI)	0.44 (0.30-0.64)		0.48 (0.38−0.59), *P*<0.001		0.51 (0.41-0.62)	
ORR—no. (%)	22 (31)	3 (4)	82 (35)	11 (5)	83 (31)	11 (4)
Best overall response—no. (%)						
CR	1 (1)	1 (1)	10 (4)	2 (1)	10 (4)	2 (1)
PR	21 (30)	2 (3)	72 (31)	9 (4)	73 (27)	9 (3)
SD	26 (37)	24 (32)	81 (34)	62 (27)	96 (36)	71 (27)
SD >6 months	9 (13)	2 (3)	23 (10)	9 (4)	25 (9)	10 (4)
PD	18 (26)	24 (32)	54 (23)	89 (38)	65 (24)	100 (38)
NE	4 (6)	25 (33)	18 (8)	71 (30)	23 (9)	80 (31)
CBR[a]—no. (%)	31 (44)	5 (7)	105 (45)	20 (9)	108 (40)	21 (8)

[a] CBR is defined as the percentage of patients with a confirmed best overall response of CR, PR, and SD ≥6 months.
BMNeg, brain metastases-negative; CBR, clinical benefit rate; CR, complete response; DOR, duration of response; ITT, intent-to-treat; mo, month(s); NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

Table 3. Treatment Responses in Patients Without TNBC at Initial Diagnosis Who Received Prior CDK4/6 Inhibitor

	SG (n = 19)	TPC (n = 22)
ORR—no. (%)	4 (**21**)	1 (**5**)
Best overall response—no. (%)		
CR	0	0
PR	4 (21)	1 (5)
SD	10 (53)	6 (27)
SD >6 months	2 (11)	0
PD	3 (16)	7 (32)
NE	2 (11)	8 (36)
CBR[a]—no. (%)	6 (32)	1 (5)

[a] CBR is defined as the percentage of patients with a confirmed best overall response of CR, PR, and SD ≥6 months.
CBR, clinical benefit rate; CDK, cyclin-dependent kinase; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

Safety

- The most common treatment-related adverse events (TRAEs; SG vs TPC) were neutropenia, diarrhea, nausea, alopecia, fatigue, and anemia (**Table 4**)
- Key grade ≥ 3 TRAEs (SG vs TPC) were neutropenia (59% vs 40%), leukopenia (12% vs 9%), anemia (8% vs 7%), and diarrhea (7% vs 0%)
  - 2 patients each in the SG and TPC arms experienced febrile neutropenia, both of grade 3 (each 3%)
- Dose reduction due to TRAEs occurred in 16% vs 25% of patients in the SG vs TPC arms
  - Most common reasons for dose reduction were neutropenia (9% vs 25%) and diarrhea (4% vs 0%)
- Discontinuations due to treatment-emergent adverse events occurred in 5% SG vs 7% TPC
- There were no treatment-related deaths in either arm

Table 4. TRAEs Any Grade (≥ 20%) and Grade ≥ 3 (≥ 5%) in Patients Without TNBC at Initial Diagnosis

		SG (n = 74)			TPC (n = 68)		
TRAE[a]		All grade, n (%)	Grade 3, n (%)	Grade 4, n (%)	All grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Hematologic	Neutropenia[b]	54 (73)	28 (38)	16 (22)	32 (47)	17 (25)	10 (15)
	Anemia[c]	23 (31)	6 (8)	0	17 (25)	5 (7)	0
	Leukopenia[d]	12 (16)	8 (11)	1 (1)	10 (15)	4 (6)	2 (3)
Gastrointestinal	Nausea	46 (62)	2 (3)	0	18 (26)	1 (1)	0
	Diarrhea	46 (62)	5 (7)	0	8 (12)	0	0
	Vomiting	22 (30)	0	0	7 (10)	1 (1)	0
Other	Fatigue	37 (50)	1 (1)	0	22 (32)	5 (7)	0
	Alopecia	35 (47)	0	0	6 (9)	0	0
	Decreased appetite	19 (26)	0	0	12 (18)	0	0

Assessed in the safety population.
2 patients each in the SG and TPC arms experienced febrile neutropenia, both of grade 3.
[a] Patients may report more than 1 event per preferred term. AEs were coded using MedDRA v22.1, and AE severity was graded per NCI CTCAE v4.03. [b] Combined preferred terms of 'neutropenia' and 'neutrophil count decreased'. [c] Combined preferred terms of 'anemia', 'hemoglobin decreased', and 'red blood cell count decreased'. [d] Combined preferred terms of 'leukopenia' and 'white blood cell count decreased'.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for AE; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice; TRAE, treatment-related adverse event.

Conclusions

- In the ASCENT trial, approximately one-third of patients did not have TNBC at initial breast cancer diagnosis; in this subgroup, treatment with SG demonstrated superior efficacy over TPC in this subgroup of patients, similar to that of SG in the overall BMNeg population and the total ASCENT study population[21]
  - Median PFS of 4.6 vs 2.3 months (**HR, 0.48; 95% CI, 0.32-0.72**)
  - Median OS of 12.4 vs 6.7 months (**HR, 0.44; 95% CI, 0.30-0.64**)
  - ORR of 31% vs 4% in the overall subgroup
  - ORR of 21% vs 5% in patients who received prior CDK4/6 inhibitors in this subgroup
- SG has a manageable safety profile in this subgroup of patients
  - Treatment discontinuations due to AEs were low (5%)
  - No treatment-related deaths were reported with SG
- However, ER and PR IHC were not performed centrally on the initial breast cancer diagnostic tissue nor on the trial qualifying tissue; this and the small number of patients in the non-TNBC at diagnosis subset limit interpretation of the presented data
- SG should be further evaluated as a treatment option for patients with subtypes other than TNBC, including those who previously received CDK4/6 inhibitors
- Ongoing studies will evaluate SG in the post-neoadjuvant setting for HER2-negative breast cancer (SASCIA, NCT04595565), and in HR-positive, HER2-negative metastatic breast cancer (TROPiCS-02, NCT03901339)

References

1. Berrocal JK, et al. *Am J Hematol Oncol*. 2017;13:16-19.
2. Kohler BA, et al. *J Natl Cancer Inst*. 2015;107:djv048.
3. Plasilova ML, et al. *Medicine*. 2016;95:35(e4614).
4. Brufsky A, et al. *Breast Cancer Res Treat*. 2012;133:1067-1075.
5. Pivot X, et al. *Ann Oncol*. 2016;27:1525-1531.
6. Perez EA, et al. *Breast Cancer Res Treat*. 2010;121:261-271.
7. Park IH, et al. *Cancer Res Treat*. 2019;51:43-52.
8. American Cancer Society. *Breast Cancer Facts & Figures*. 2019-2020.
9. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. National Cancer Institute.
10. Aurilio G, Disalvatore D, Pruneri G, et al. *Eur J Cancer*. 2014;50:277-289.
11. Dieci MV, Barbieri E, Piacentini F, et al. *Ann Oncol*. 2013;24:101-108.
12. Lindstrom LS, Karlsson E, Wilking UM, et al. *J Clin Oncol*. 2012;30:2601-2608.
13. Liedtke C, Broglio K, Moulder S, et al. *Ann Oncol*. 2009;20:1953-1958.
14. Niikura N, Liu J, Hayashi N, et al. *J Clin Oncol*. 2012;30:593-599.
15. Goldenberg DM, et al. *Expert Opin Biol Ther*. 2020;20:871-885.
16. Nagayama A, et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980.
17. Cardillo TM, et al. *Bioconjugate Chem*. 2015;26:919-931.
18. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496-22512.
19. Govindan SV, et al. *Mol Cancer Ther*. 2013;12:968-978.
20. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021.
21. Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541.

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