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Impact of UGT1A1 Status on the Safety Profile of Sacituzumab Govitecan in the Phase 3 ASCENT Study in Patients With Metastatic Triple-Negative Breast Cancer

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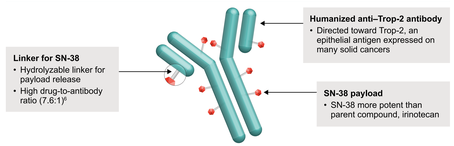
BACKGROUND

- 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) composed 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 (April 2020) 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]
- Starting at a 10 mg/kg dose was found to have a manageable safety profile with better efficacy than lower doses[8]

SACITUZUMAB GOVITECAN

Figure 1. Sacituzumab Govitecan Antibody-Drug Conjugate



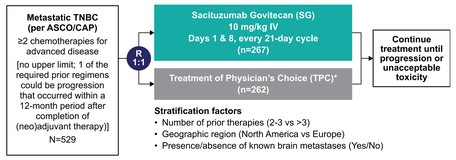
Trop-2, trophoblast cell surface antigen 2.

- The landmark confirmatory phase 3 ASCENT study is the first with Trop-2–directed ADC (SG) in pretreated mTNBC to demonstrate a significant survival improvement over standard single-agent chemotherapy with a manageable safety profile[3]:
  - Key grade ≥3 treatment-related adverse events (TRAEs; SG vs treatment of physician's choice [TPC]): neutropenia, diarrhea, leukopenia, anemia, and febrile neutropenia
- Further safety analyses of ASCENT were conducted, including
  - Additional descriptive detailed safety analyses of AEs of interest
  - A post-hoc analysis of time to onset and duration of key AEs
  - Evaluating whether patients with uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) polymorphisms are at increased safety risk since reduced or diminished uridine diphosphate-glucuronosyltransferase enzymatic activity prevents SN-38 glucuronidation and inactivation and is associated with hematologic toxicity

METHODS

- ASCENT is a phase 3 confirmatory trial of SG vs single-agent chemotherapy of physician's choice, which included eribulin, vinorelbine, gemcitabine, or capecitabine (**Figure 2**)
- We report a post-hoc analysis of the time to onset and duration of neutropenia and diarrhea in the safety population and the impact of dose reductions and interruptions on efficacy evaluated
- Exploratory safety analyses by *UGT1A1* allele status were performed
- Further descriptive analyses on alopecia, nausea, and vomiting along with AE management strategies are provided
- Data cutoff for analysis is March 11, 2020

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



*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent centralized and blinded group of radiology experts who will be assessing tumor response using RECIST 1.1 criteria in patients with/without brain metastasis at baseline. ‡The full population includes all randomized patients (with and without brain metastases).
ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists; *BRCA*, breast cancer gene; 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; Trop-2, trophoblast cell surface antigen 2; TTR, time to response; UGT, uridine diphosphate glucuronosyltransferase.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

RESULTS

PATIENT DISPOSITION

- Of the 529 patients enrolled in ASCENT, 482 patients (SG, n=258; TPC, n=224) were included in the safety population (all patients who received ≥1 dose of study treatment) (**Table 1**)
  - 47 randomized patients did not receive treatment (SG, n=9 [3%]; TPC, n=38 [15%])
- At data cutoff, 17 patients (7%) remained on treatment in the SG arm; no patients remain on treatment in the TPC arm
- The primary reason for discontinuation (SG vs TPC) was disease progression (86% vs 82%)

Table 1. Patient Disposition

Safety Population*	SG (n=258)	TPC (n=224)†
Remain on treatment—no. (%)	17 (7)	0
Discontinued treatment—no. (%)	241 (93)	224 (100)
Disease progression	222 (86)	184 (82)
Adverse event	10 (4)	8 (4)
Withdrawal of consent	5 (2)	18 (8)
Investigator decision	3 (1)	5 (2)
Death	1 (<1)‡	4 (2)
Other	0	5 (2)§

*All patients who received ≥1 dose of study treatment. †Patients in the TPC arm received: eribulin (n=139); vinorelbine (n=52); gemcitabine (n=38); capecitabine (n=33). ‡This was considered unlikely related to SG treatment. §Due to treatment delay >3 weeks (n=4) and unacceptable toxicity (n=1).
SG, sacituzumab govitecan; TPC, treatment of physician's choice.

PATIENTS

- Baseline characteristics were balanced between the SG and TPC arms (**Table 2**)

Table 2. Demographics and Patient Characteristics

	SG (n=258)	TPC (n=224)
Female, no. (%)	256 (99)	224 (100)
Median age —y (range)	54 (27–82)	54 (30–81)
<50 y	92 (36)	71 (32)
50-64 y	117 (45)	105 (47)
≥65 y	49 (19)	48 (21)
ECOG PS—no. (%)		
0	117 (45)	93 (42)
1	141 (55)	131 (58)
Race or ethnic group—no. (%)		
White	211 (82)	172 (77)
Black	25 (10)	31 (14)
Asian	11 (4)	9 (4)
Other	11 (4)	12 (5)
Brain metastasis at randomization—no. (%)		
Yes	30 (12)	23 (10)
No	228 (88)	201 (90)
Median no. of anticancer regimens*— (range)	4 (2–17)	4 (2–14)
No. of prior chemotherapies—no. (%)		
2-3	178 (69)	158 (71)
>3	80 (31)	66 (29)
*BRCA*1/2 mutational status†—no. (%)		
Negative	145 (56)	123 (55)
Positive	19 (7)	20 (9)
Original diagnosis of TNBC‡—no. (%)		
Yes	184 (71)	156 (70)
No	74 (29)	68 (30)
Median time from metastatic diagnosis—mo (range)	17.1 (0.1–202.9)	15.5 (-0.4–95.8)

Assessed in the safety population. *Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting. †Approximately 64% of patients in each arm consented and had known *BRCA*1/2 mutation status. ‡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.
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.

TREATMENT-RELATED ADVERSE EVENTS

- Median relative dose intensity with SG (cumulative dosage received/total assigned dosage × 100) was 99.7%
- The most common TRAEs in SG vs TPC patients, respectively, included neutropenia (63% vs 43%), diarrhea (59% vs 12%), nausea (57% vs 26%), alopecia (46% vs 16%), fatigue (45% vs 30%), and vomiting (29% vs 10%) (**Table 3**; **Figure 4**)
- No severe cardiovascular toxicity was observed with SG as well as no grade >1 ocular toxicity, no grade >2 neuropathy, and no grade >3 interstitial lung disease
- No treatment-related deaths were reported with SG; 1 treatment-related death (neutropenic sepsis) was reported with TPC
- AEs leading to treatment discontinuation were low in the safety population (SG, 4.7% vs TPC, 5.4%)

Table 3. TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)*

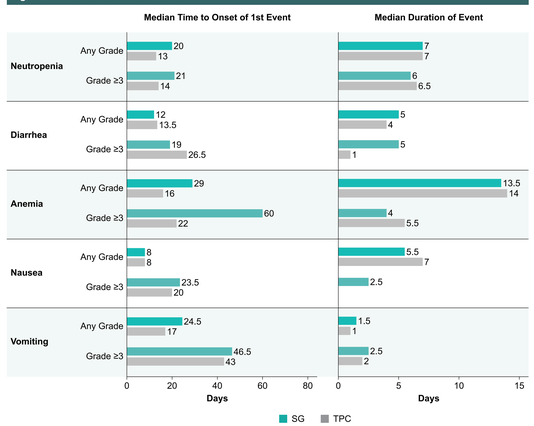
		SG (n=258)			TPC (n=224)		
	TRAE*	All grade, %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	Neutropenia†	63	34‡	17	43	20	13
	Anemia†	34	8	0	24	5	0
	Leukopenia§	16	9	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	Diarrhea	59	10	0	12	<1	0
	Nausea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

*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 and according to severity by NCI CTCAE v4.03. †Combined preferred terms of 'neutropenia' and 'decreased neutrophil count.' Due to overlapping reporting of events for these combined terms, all grades reported are not shown for the SG arm: grade 1: 19%; grade 2: 37%; grade ≥3: 51%. ‡The 46% reported previously did not properly account for duplication/overlap between events by grade. §Combined preferred terms of 'anemia,' 'hemoglobin decreased,' and 'red blood cell count decreased.' ¶Combined preferred terms of 'leukopenia' and 'decreased white blood cell count.'
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for AE; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related AE.

TIME TO ONSET AND DURATION (FIGURE 3)

- Median time to onset of 1st grade ≥3 treatment-related AEs of special interest (AESIs; SG vs TPC):
  - Neutropenia: 21 vs 14 days
  - Diarrhea: 19 vs 26.5 days
- Median duration of grade ≥3 treatment-related AESIs (SG vs TPC):
  - Neutropenia: 6 vs 6.5 days
  - Diarrhea: 5 vs 1 days

Figure 3. Time to Onset and Duration



Assessed in the safety population.
SG, sacituzumab govitecan; TPC, treatment of physician's choice.

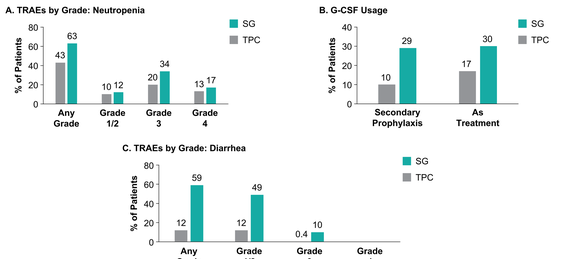
NEUTROPENIA

- Myeloid growth factor was used in neutropenia management as secondary prophylaxis and as treatment in 29% and 30% of patients, respectively, in the SG arm and 10% and 17% in the TPC arm (**Figure 4B**; **Figure 5**)
- No patients in the SG arm and 1% of patients in the TPC arm discontinued treatment due to treatment-related neutropenia
- Dose reductions due to treatment-related neutropenia or febrile neutropenia occurred for 11% and 19% of patients in the SG and TPC arms, respectively
- Dose interruptions due to treatment-related neutropenia or febrile neutropenia for 46% and 21% of patients in the SG and TPC arms, respectively

DIARRHEA

- Premedication or concomitant medicine was used in diarrhea management in 55% and 10% of patients in the SG and TPC arms, respectively (**Figure 5**)
  - Atropine use is recommended, if not contraindicated, for early diarrhea of any severity[10]
- No treatment discontinuations due to treatment-related diarrhea were observed in either treatment arm
- Dose reductions due to treatment-related diarrhea occurred in 5% and <1% of patients in the SG and TPC arms, respectively
- Dose interruptions due to treatment-related diarrhea occurred in 5% and 0% of patients in the SG and TPC arms, respectively

Figure 4. Neutropenia and Diarrhea



Assessed in the safety population.
G-CSF, granulocyte colony-stimulating factor; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related adverse event.

OUTCOMES BY DOSE REDUCTION/INTERRUPTION

- In total, 26% and 22% of patients in the SG and TPC arm, respectively, had a dose reduction and 61% and 33% had a dose interruption
- Objective response rates and clinical benefit rates were improved with SG vs TPC for patients with dose reduction or interruption (**Table 4**)
- Efficacy outcomes for patients with dose reduction or interruption in the SG arm were similar to those for the overall population (**Table 4**)[9]

Table 4. Efficacy Outcomes for Patients With Dose Reductions or Interruptions (BMNeg Population)

	Overall BMNeg Population§		Dose Reductions		No Dose Reductions		Dose Interruptions		No Dose Interruptions	
	SG (n=235)	TPC (n=233)	SG (n=62)	TPC (n=52)	SG (n=173)	TPC (n=181)	SG (n=144)	TPC (n=78)	SG (n=91)	TPC (n=155)
ORR (BICR)—no. (%)	82 (35)	11 (5)	29 (47)	7 (13)	53 (31)	4 (2)	56 (39)	5 (6)	26 (29)	6 (4)
CBR (BICR)—no. (%)	105 (45)	20 (9)	37 (60)	11 (21)	68 (39)	9 (5)	71 (49)	12 (15)	34 (37)	8 (5)
Best Overall Response										
CR	10 (4)	2 (1)	5 (8)	1 (2)	5 (3)	1 (1)	7 (5)	0 (0)	3 (3)	2 (1)
PR	72 (31)	9 (4)	24 (39)	6 (12)	48 (28)	3 (2)	49 (34)	5 (6)	23 (25)	4 (3)
Median PFS (BICR) —mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)	8.3 (5.4-10.3)	2.9 (2.7-4.3)	4.6 (3.5-5.7)	1.5 (1.4-1.7)	5.7 (4.3-7.0)	2.7 (1.7-3.0)	4.2 (2.9-6.8)	1.6 (1.5-2.2)

Assessed in brain metastases-negative population (SG, n=235; TPC, n=233).
BICR, blind independent central review; BMNeg, brain metastases–negative; CBR, clinical benefit rate; CR, complete response; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

TRAEs BY *UGT1A1* GENOTYPE

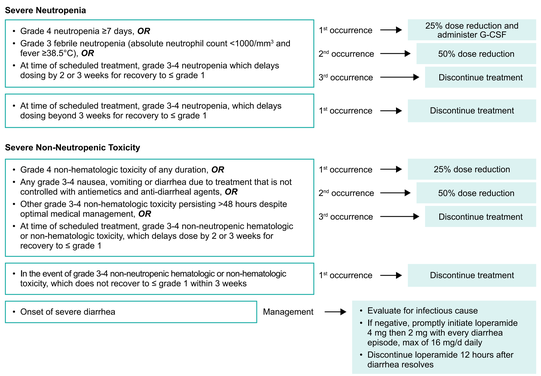
- In total, 250 patients in the SG arm (97%) had *UGT1A1* genotype data at baseline
  - *1/*1 (wild-type; normal enzymatic activity): 45%
  - *1/*28 (heterozygous; reduced enzymatic activity): 38%
  - *28/*28 (homozygous; diminished enzymatic activity): 14%
- Patients with *UGT1A1* *28/*28 had a higher incidence of grade ≥3 treatment-related AESIs vs *UGT1A1* *1/*1 and *1/*28, respectively (**Table 5**)
  - Neutropenia: 59% vs 53% and 47%
  - Febrile neutropenia: 18% vs 3% and 5%
  - Diarrhea: 15% vs 10% and 9%
- Treatment discontinuation due to TRAEs was higher for patients with *UGT1A1* *28/*28:
  - *1/*1: 2%
  - *1/*28: 1%
  - *28/*28: 6%

Table 5. TRAEs by *UGT1A1* Genotype (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=250)†					
		*1/*1 Wild-Type (n=113)		*1/*28 Heterozygous (n=96)		*28/*28 Homozygous (n=34)	
	TRAE‡	All Grade, %	Grade ≥3, %	All Grade, %	Grade ≥3, %	All Grade, %	Grade ≥3, %
Hematologic	Neutropenia§	76 (67)	60 (53)	55 (57)	45 (47)	24 (71)	20 (59)
	Anemia†	37 (33)	5 (4)	29 (30)	6 (6)	16 (47)	5 (15)
	Leukopenia**	18 (16)	10 (9)	13 (14)	9 (9)	8 (24)	5 (15)
	Lymphopenia¶	10 (9)	1 (1)	5 (5)	1 (1)	4 (12)	2 (6)
	Febrile neutropenia	3 (3)	3 (3)	5 (5)	5 (5)	6 (18)	6 (18)
	Thrombocytopenia†	3 (3)	0	6 (6)	0	4 (12)	4 (12)
Gastrointestinal	Diarrhea	65 (58)	11 (10)	57 (59)	9 (9)	21 (62)	5 (15)

Assessed in the safety population of patients with *UGT1A1* genotype. Shown are key TRAEs significantly impacted by the *UGT1A1* *28/*28 genotype. Other TRAEs like nausea, vomiting, constipation, fatigue, alopecia, and decrease appetite were not significantly impacted. †Seven patients had *UGT1A1* genotypes not listed in the table. ‡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 and according to severity by NCI CTCAE v4.03. §Combined preferred terms of 'neutropenia' and 'decreased neutrophil count.' ¶Combined preferred terms of 'anemia,' 'hemoglobin decreased,' and 'red blood cell count decreased.' **Combined preferred terms of 'leukopenia' and 'decreased white blood cell count.' ††Combined preferred terms of 'lymphopenia' and 'decreased lymphocyte count.' ‡‡Combined preferred terms of 'thrombocytopenia' and 'decreased platelet count.'
MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE v4.03, National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03; SG, sacituzumab govitecan; TRAE, treatment-related adverse event; UGT, uridine diphosphate glucuronosyltransferase.

Figure 5. AE Management Strategies[10]



AE, adverse event; G-CSF, granulocyte colony-stimulating factor; TRAE, treatment-related adverse event.

ALOPECIA

- SG is an anti–Trop-2 monoclonal antibody conjugated to SN-38 (an active metabolite of irinotecan)
- Irinotecan is among the chemotherapy agents that can cause hair loss
- SG is associated with grade 2 alopecia in 41% of patients, but this may be under-reported

NAUSEA AND VOMITING

- Nausea and vomiting with SG can typically occur up to 3 weeks after initiation of treatment, which should be considered when managing treatment-associated symptoms
- Premedication or concomitant medication in management of nausea and vomiting was used in 86% and 63% of patients in the SG and TPC arms, respectively

CONCLUSIONS

- SG was generally well tolerated, with a manageable safety profile, consistent with previous reports[9]
  - No severe cardiovascular toxicity, no grade >2 neuropathy or >3 interstitial lung disease
  - No treatment-related deaths reported
  - AEs leading to treatment discontinuation were low (4.7% safety population); no patients discontinued due to treatment-related neutropenia or diarrhea
- Individuals with *UGT1A1* homozygous *28/*28 genotype were at modestly higher risk for neutropenia and diarrhea with SG and should be monitored closely
  - The frequency of homozygous mutation was low; thus, the ability to discern additional differences was limited
  - These data suggest that *UGT1A1* status does not alter recommendations for treatment or management
- Active monitoring and early intervention with routine AE management strategies (ie, dose reductions/concomitant medication usage) for patients with pretreated metastatic TNBC allow optimal therapeutic exposure
  - Initial dosing at 10 mg/kg is recommended, with dose reductions as needed for toxicity
  - Dose reductions to manage toxicity do not appear to impact efficacy
  - Atropine is recommended to manage cholinergic reactions
  - Effective antiemetic therapy is important and prevents discontinuation of therapy
  - The efficacy of scalp cooling for prevention of SG-induced alopecia is unknown

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