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Trodelvy® (sacituzumab govitecan-hziy) Use in Combination With Pembrolizumab in Patients With 1L PD-L1+ mTNBC

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) and its use in combination with pembrolizumab (pembro) as first-line (1L) treatment in patients with programmed death ligand-1 positive (PD-L1+) metastatic triple-negative breast cancer (mTNBC).

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings for neutropenia and diarrhea are available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Summary

Relevant Product Labeling[1]

SG, in combination with pembro or pembro and berahyaluronidase alfa-pmph, is indicated for the 1L treatment of adult patients with unresectable locally advanced or mTNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-authorized test.

Clinical Data on SG Use in Combination With Pembro in 1L PD-L1+ mTNBC

ASCENT-04, is an ongoing, global, open-label, randomized, phase 3 study comparing the efficacy and safety of SG + pembro vs chemotherapy TPC (eg, gem + carbo, paclitaxel, or nab-paclitaxel) + pembro, as 1L treatment in patients with PD-L1+ (CPS ≥10), unresectable, locally advanced or mTNBC (n=443). Patients who experienced disease progression during treatment with TPC + pembro (as verified by BICR) could cross over to receive 2L SG monotherapy.[2]

- SG + pembro prolonged mPFS by BICR per RECIST v1.1 (primary endpoint) vs TPC + pembro (11.2 vs 7.8 mo; HR, 0.65; 95% CI: 0.51–0.84; *P*<0.001).[2]
  - A higher proportion of patients treated with SG + pembro vs TPC + pembro were alive and progression-free at 6 mo (72% [95% CI: 65–77%] vs 63% [95% CI: 56–69%], respectively) and at 12 mo (48% [95% CI: 41–56%] vs 33% [95% CI: 26–40%], respectively).
  - Median (range) follow-up at the time of the final PFS analysis was 14 (0.1–28.6) mo.
- Results for OS were immature (26% maturity rate) at the time of the final PFS analysis and further follow-up is ongoing; therefore, results are descriptive. A numerical trend in favor of SG + pembro vs TPC + pembro was observed (HR, 0.89; 95% CI: 0.62–1.29).[2]
- An ORR of 60% was observed in patients receiving SG + pembro vs 53% for TPC + pembro (OR, 1.3; 95% CI: 0.9–1.9). DOR (95% CI) with SG + pembro vs

TPC + pembro was 16.5 (12.7–19.5) mo vs 9.2 (7.6–11.3) mo, respectively. Formal statistical analyses of these results were not conducted at this time.[2]

- A total of 77 patients who progressed on TPC + pembro within the study crossed over to receive 2L SG monotherapy per protocol.[3]
- The safety profile of SG + pembro was consistent with the known safety profile of each agent, and no new safety concerns emerged.[2]
  - The most common any-grade TEAEs with SG + pembro vs TPC + pembro were diarrhea (70% vs 29%), nausea (68% vs 38%), and neutropenia (63% vs 59%).[2]
  - In the SG + pembro vs TPC + pembro arms, treatment-emergent SAEs were reported in 38% vs 31% of patients, respectively; of these, treatment-related SAEs were reported in 28% vs 19%.[2,4]
  - Incidence of TEAEs that led to treatment discontinuation was 12% with SG + pembro and 31% with TPC + pembro.[2]
  - TEAEs resulting in death occurred in 3% of patients in both treatment arms; 1% and <1% were deemed treatment-related with SG + pembro and TPC + pembro, respectively.[2,3]
- In an exploratory safety analysis, the overall any-grade EAIRs (95% CI) were 69.09 (60.26–78.85) and 36.68 (31.98–41.87) for the SG + pembro and TPC + pembro arms, respectively.[5]
  - Immune-mediated AEs were reported less frequently with SG + pembro vs TPC + pembro.
  - Time to onset of any-grade and Grade ≥3 neutropenia and diarrhea was generally shorter with SG + pembro than with TPC + pembro.
  - In the SG + pembro and TPC + pembro arms, neutropenia led to treatment discontinuation in 1% and 2% of patients, respectively.
  - In the SG + pembro and TPC + pembro arms, diarrhea led to treatment discontinuation in <1% of patients in the TPC + pembro arm.
  - Primary prophylaxis of G-CSF was associated with less frequent and less severe neutropenia in the SG + pembro arm than in the TPC + pembro arm.
- In a post hoc analysis, the median (95% CI) PFS2 was NR (NR–NR) in the SG + pembro arm (n=55) and 21 (16–NR) mo in the TPC + pembro arm (n=83).[6]
  - The median (95% CI) TFST was 17.3 (12.7–NR) mo in the SG + pembro arm and 9.8 (8.7–10.9) mo in the TPC + pembro arm. The most common 2L+ therapy was chemotherapy (88%) for the SG + pembro arm and SG (81%) for the TPC + pembro arm.
  - The median (95% CI) TSST was NR (22.9–NR) mo in the SG + pembro arm and 21 (16.6–NR) mo in the TPC + pembro arm.
- In subgroup analysis, mPFS was numerically longer with SG + pembro than with TPC + pembro, by both BICR and investigator assessments, across patients stratified by preselected TPC regimen, disease status, and presence of brain or visceral metastases at baseline. Safety data were not reported.[7]
- In an E-R analysis, no statistically significant relationship was observed between SG exposure and ORR (OR, 1.38; 90% CI: 0.58–3.26; *P*=0.536). Patients with $C_{min,D1,SG}$ exposures above Quartile 1 had a lower risk of disease progression or death than those with exposures at or below Quartile 1 (*P*<0.01); patients with baseline albumin levels above Quartile 1 also had a reduced risk of PFS events than those with levels at or below Quartile 1.[8]

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Clinical Data on SG Use in Combination With Pembro in 1L PD-L1+ mTNBC

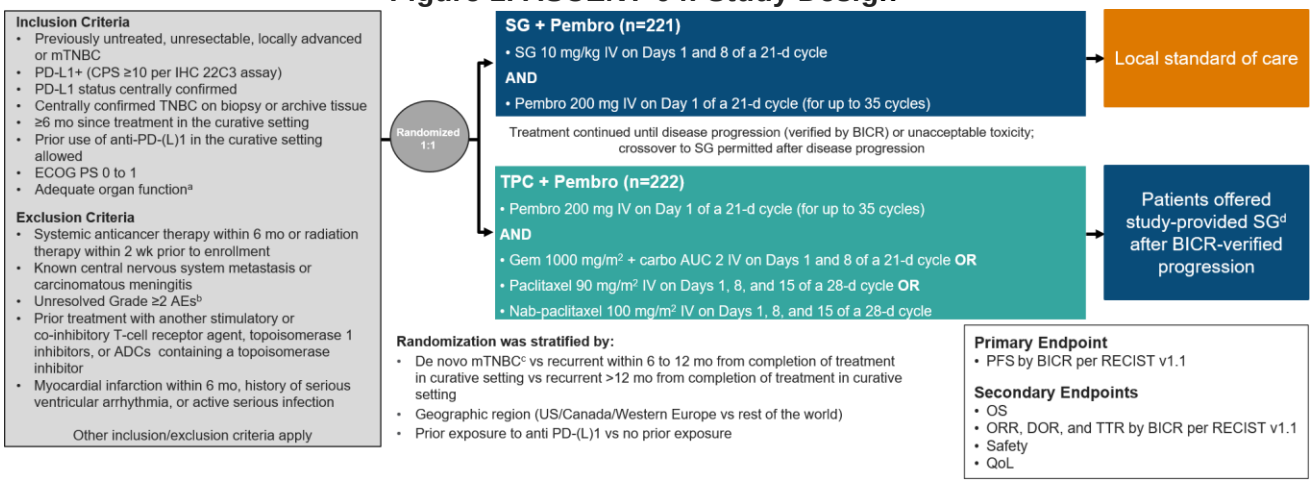
ASCENT-04 Study

Study design and demographics[2]

ASCENT-04 is an ongoing, global, open-label, randomized, phase 3 study comparing the efficacy and safety of SG + pembro vs TPC + pembro as 1L treatment in patients with PD-L1+ (CPS ≥10), unresectable, locally advanced or mTNBC (Figure 1).

A total of 443 female patients were enrolled. Patients who experienced disease progression during treatment with TPC + pembro (as verified by BICR) could cross over to receive 2L SG monotherapy.

Figure 1. ASCENT-04: Study Design[2,9]



Abbreviations: AUC=area under the curve; IHC=immunohistochemistry; QOL=quality of life; TNBC=triple-negative breast cancer; ULN=upper limit of normal; TTR=time to response.
[a]Hgb ≥9 g/dL, absolute neutrophil count ≥1500/mm^3, platelets ≥100,000/mcL, bilirubin ≤1.5 × ULN, AST/ALT ≤2.5 × ULN or ≤5 × ULN with known liver metastases, serum albumin >3 g/dL, and CrCl ≥30 mL/min.
[b]Unresolved Grade ≤2 neuropathy, endocrine-related AEs, and any-grade alopecia were allowed.
[c]Up to 35% of patients with de novo mTNBC were eligible.
[d]Patients could have also received commercial SG in any line, and other subsequent treatments per local practice were also permitted.

See Table 1 for select baseline demographics and disease characteristics.

Table 1. ASCENT-04: Baseline Demographics and Disease Characteristics[2]

Select Demographics and Characteristics		SG + Pembro (n=221)	TPC + Pembro (n=222)
Age, median (range), y		54 (23–88)	55 (27–82)
≥65 y, n (%)		58 (26)	57 (26)
Race or ethnic group,[a] n (%)	White/Black/Asian	139 (63)/13 (6)/43 (19)	118 (53)/11 (5)/63 (28)
	Other or not specified	26 (12)	30 (14)
Geography, n (%)	US, Canada, and Western Europe	85 (38)	85 (38)
	Rest of the world[b]	136 (62)	137 (62)
ECOG PS,[c] n (%)	0/1	156 (71)/65 (29)	154 (69)/67 (30)

Select Demographics and Characteristics			SG + Pembro (n=221)	TPC + Pembro (n=222)
Curative treatment-free interval, n (%)	De novo		75 (34)	75 (34)
	Recurrent within 6–12 mo		40 (18)	40 (18)
	Recurrent >12 mo		106 (48)	107 (48)
Metastatic sites, n (%)	Lymph node		159 (72)	154 (69)
	Lung		111 (50)	95 (43)
	Bone		61 (28)	45 (20)
	Liver		55 (25)	57 (26)
	Brain		8 (4)	6 (3)
	Other[d]		81 (37)	71 (32)
Chemotherapy selected prior to randomization,[e] n (%)		Taxane	116 (52)	114 (51)
		Gem/carbo	105 (48)	108 (49)
Prior anti-PD-(L)1 therapy,[f] n (%)			9 (4)	11 (5)

[a]As reported by patients; "Other" includes American Indian or Alaska Native and not permitted.
[b]Includes Argentina, Australia, Brazil, Chile, Czech Republic, Hong Kong, Hungary, Israel, Japan, Malaysia, Mexico, Poland, Singapore, South Africa, South Korea, Taiwan, and Turkey.
[c]One patient in the TPC + pembro arm had an ECOG PS ≥2.
[d]Other metastatic sites include pleura, pleural effusion, skin, soft tissue, chest wall, and muscle.
[e]Actual chemotherapy received was consistent with what was selected prior to randomization; however, 2 patients underwent randomization but did not receive treatment.
[f]While 20 patients were included in the stratified subgroup of prior exposure to anti-PD-(L)1 therapy (yes) per the interactive response technology system, only 6 patients received prior treatment with anti-PD-(L)1 agents per the clinical database.

Efficacy

Primary endpoint[2]

SG + pembro significantly improved mPFS vs TPC + pembro with a 35% reduction in the risk of disease progression or death and a numerically higher proportion of patients alive and progression-free at the 6- and 12-mo timepoints (Table 2). The median (range) duration of follow-up at the time of the final PFS analysis was 14 (0.1–28.6) mo. At the data cutoff date, 43% of patients (n=95) in the SG + pembro arm and 23% of patients (n=52) in the TPC + pembro arm remained on study treatment.

Table 2. ASCENT-04: PFS by BICR and Investigator Assessment[2,4]

			SG + Pembro (n=221)	TPC + Pembro (n=222)
BICR analysis	Number of PFS events		109	140
	mPFS (95% CI), mo		11.2 (9.3–16.7)	7.8 (7.3–9.3)
	Stratified HR (95% CI); log-rank *P*-value[a]		0.65 (0.51–0.84); <0.001	
	PFS rate, % (95% CI)	6-mo	72 (65–77)	63 (56–69)
		12-mo	48 (41–56)	33 (26–40)
Investigator assessment	Number of PFS events		111	142
	mPFS (95% CI), mo		11.3 (9.2–14.6)	8.3 (7.3–9.3)
	Stratified HR (95% CI)		0.67 (0.52–0.87)	
	PFS rate, % (95% CI)	6-mo	75 (68–80)	61 (54–68)
		12-mo	48 (41–55)	36 (29–42)

[a]Two-sided *P*-value from stratified log-rank test.

Secondary endpoints

At the data cutoff for the final PFS analysis, results for OS were immature (26% maturity rate); therefore, results for OS are descriptive. A numerical trend in favor of SG + pembro was observed (HR, 0.89; 95% CI: 0.62–1.29).[2,4]

A total of 77 patients who progressed on TPC + pembro crossed over to receive 2L SG monotherapy per protocol.[3]

Statistical testing was not conducted for subsequent endpoints in the statistical hierarchy, as the statistical boundary for OS was not crossed; therefore, results of these endpoints can only be presented descriptively. The ORR (95% CI) was 60% (52.9–66.3%) with SG + pembro and 53% (46.4–59.9%) with TPC + pembro (OR, 1.3; 95% CI: 0.9–1.9). The median DOR (95% CI), in patients with a CR or PR, was 16.5 (12.7–19.5) mo vs 9.2 (7.6–11.3) mo with SG + pembro vs TPC + pembro, respectively.[2]

Safety[2]

The median duration (range) of treatment was 8.9 (<0.1–27.1) mo for SG and 8.5 (<0.1–26.8) mo for pembro in the SG + pembro arm. The median duration (range) of treatment was 6.2 (<0.1–26.3) mo for TPC and 6.4 (<0.1–25.6) mo for pembro in the TPC + pembro arm.

Overall, the safety profile of SG + pembro was consistent with the known safety profile for each agent, with no additive toxicity observed. The rate of SAEs was higher with SG + pembro vs TPC + pembro; however, the rate of TEAEs that led to treatment discontinuation was lower (Table 3).

TEAEs that led to death occurred in 7 patients in the SG + pembro arm (3 were deemed treatment related [pneumonia, neutropenic sepsis, pulmonary embolism]) and in 6 patients in the TPC + pembro arm (1 was deemed treatment related [pneumonia]; Table 3). TEAEs that led to death with SG + pembro were pneumonia, sepsis, neutropenic sepsis, pulmonary embolism, and suicide (each, n=1); there were 2 deaths of unknown cause. TEAEs that led to death with TPC + pembro were cardiac arrest, large intestine perforation, pneumonia, sepsis, post-procedural complication, and death of unknown cause (each, n=1).

Table 3. ASCENT-04: Safety Summary[2,4]

AEs, n (%)	SG + Pembro (n=221)	TPC + Pembro (n=220)
Any TEAE	220 (>99)	219 (>99)
Grade ≥3	158 (71)	154 (70)
Treatment-emergent SAEs	84 (38)	68 (31)
Treatment-related	61 (28)	42 (19)
TEAEs that led to treatment discontinuation[a]	26 (12)	68 (31)
TEAEs that led lead to dose interruption	171 (77)	162 (74)
TEAEs that led to dose reduction[b]	78 (35)	96 (44)
TEAEs that led to death	7 (3)	6 (3)
Treatment-related	3 (1)	1 (<1)

[a]The most common any-grade TEAEs that led to treatment discontinuation were pneumonitis (1%) for SG + pembro and peripheral neuropathy (5%), pneumonitis (3%), and thrombocytopenia (3%) for TPC + pembro.
[b]There was no dose reduction for pembro per the protocol.

The most common any-grade and Grade ≥3 AEs are presented in Table 4.

Table 4. ASCENT-04: Most Common Any-Grade (20%) and Grade ≥3 (≥5%) TEAEs[2a]

TEAEs, n (%)	SG + Pembro (n=221)		TPC + Pembro (n=220)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	155 (70)	22 (10)	63 (29)	5 (2)
Nausea	150 (68)	7 (3)	83 (38)	4 (2)
Neutropenia	139 (63)	95 (43)	130 (59)	98 (45)

TEAEs, n (%)	SG + Pembro (n=221)		TPC + Pembro (n=220)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	129 (58)	18 (8)	123 (56)	7 (3)
Alopecia	114 (52)	N/A	71 (32)	N/A
Constipation	90 (41)	1 (<1)	76 (35)	1 (<1)
Anemia	81 (37)	16 (7)	112 (51)	35 (16)
Vomiting	65 (29)	2 (1)	31 (14)	4 (2)
Headache	55 (25)	1 (<1)	38 (17)	0
Rash	47 (21)	2 (1)	44 (20)	3 (1)
ALT increased	44 (20)	8 (4)	66 (30)	13 (6)
Leukopenia	42 (19)	7 (3)	46 (21)	19 (9)
AST increased	35 (16)	7 (3)	56 (25)	8 (4)
Febrile neutropenia	17 (8)	17 (8)	4 (2)	4 (2)
Peripheral neuropathy	15 (7)	1 (<1)	46 (21)	7 (3)
Thrombocytopenia	10 (5)	1 (<1)	63 (29)	30 (14)

[a]Data for all patients who received trial treatment are included. Shown are AEs that began on or after the date of the first dose of study drug up to 30 d (or 90 d for SAEs) after the date of the last dose of study drug, or 1 d before the initiation of subsequent anticancer therapy (including crossover treatment if applicable), whichever occurred first.

Note: Combined preferred terms of neutropenia include neutrophil count decreased; leukopenia includes WBC count decreased; anemia includes Hgb decreased and RBC count decreased; thrombocytopenia includes platelet count decreased; and fatigue includes asthenia.

AESIs are presented in Table 5; these events were consistent with the known safety profiles of each agent. No new safety concerns were observed.

Table 5. ASCENT-04: AESIs[4]

AESIs,[a] n (%)		SG + Pembro (n=221)		TPC + Pembro (n=220)	
		Any Grade	Grade ≥3	Any Grade	Grade ≥3
SG AESIs	Neutropenia	143 (65)	104 (47)	132 (60)	100 (45)
	Hypersensitivity	43 (19)	4 (2)	51 (23)	5 (2)
	Serious infections secondary to neutropenia	6 (3)	5 (2)	3 (1)	3 (1)
	Grade ≥3 diarrhea	N/A	22 (10)	N/A	5 (2)
Pembro AESIs	Hypothyroidism	16 (7)	1 (<1)	35 (16)	0
	Colitis	13 (6)	4 (2)	3 (1)	1 (<1)
	Infusion reactions (not immune mediated)[a]	11 (5)	3 (1)	19 (9)	5 (2)
	Gastritis	10 (5)	0	7 (3)	0
	Hyperthyroidism	8 (4)	0	14 (6)	0
	Pneumonitis	6 (3)	4 (2)	17 (8)	3 (1)
	Severe skin reactions	6 (3)	3 (1)	8 (4)	5 (2)
	Adrenal insufficiency	3 (1)	0	4 (2)	2 (1)
	Hypophysitis	2 (1)	0	2 (1)	0
	Type 1 diabetes mellitus	1(<1)	1 (<1)	1 (<1)	1 (<1)
	Encephalitis	1 (<1)	1 (<1)	0	0
	Pericarditis	1 (<1)	1 (<1)	0	0
	Hepatitis	1 (<1)	0	4 (2)	3 (1)
	Pancreatitis	0	0	4 (2)	2 (1)
	Thyroiditis	0	0	2 (1)	0
	Myelitis	0	0	1 (<1)	1 (<1)
	Exocrine pancreatic insufficiency	0	0	1 (<1)	0
	Nephritis	0	0	1 (<1)	0

[a]AESI were included in a list of terms specified by the sponsor and were assessed regardless of attribution to the trial regimen. AESI observed in ≥1 patient in either group.

Exploratory safety analysis[5]

EAIRs (defined as the number of patients with ≥1 specified TEAE per PYE) were calculated as the number of patients with a specific TEAE divided by the total PYE in each group; PYE was defined as the sum of each patient's time at risk (exposure duration) within the study. Due to the exploratory nature of this post hoc analysis, all results presented in Table 6 should be considered nominal.

The overall EAIRs for any-grade TEAEs (95% CI) were 69.09 (60.26–78.85) and 36.68 (31.98–41.87) for the SG + pembro and TPC + pembro arms, respectively.

Table 6. ASCENT-04 Exploratory Analysis: EAIRs[5]

TEAEs	SG + Pembro (n=221)		TPC + Pembro (n=220)		EAIR Difference (95% CI)
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	
Grade ≥3	158 (71)	2.19 (1.86–2.56)	154 (70)	2.13 (1.81–2.49)	0.06 (-0.43 to 0.55)
Treatment related	149 (67)	1.95 (1.65–2.29)	141 (64)	1.76 (1.48–2.07)	0.2 (-0.24 to 0.64)
Serious TEAEs	84 (38)	0.59 (0.47–0.73)	68 (31)	0.52 (0.41–0.66)	0.06 (-0.12 to 0.25)
Treatment related	61 (28)	0.41 (0.31–0.52)	42 (19)	0.29 (0.21–0.4)	0.11 (-0.03 to 0.25)
Led to any dose interruption	171 (77)	2.75 (2.35–3.19)	162 (74)	2.59 (2.21–3.02)	0.16 (-0.43 to 0.75)
Led to SG/TPC dose reduction	78 (35)	0.62 (0.49–0.78)	96 (44)	0.94 (0.76–1.14)	-0.31 (-0.56 to -0.08)
Led to any treatment discontinuation	26 (12)	0.15 (0.1–0.21)	68 (31)	0.53 (0.41–0.67)	-0.38 (-0.53 to -0.25)
TEAEs[a]					
Diarrhea	155 (70)	0.13 (0.08–0.19)	63 (29)	0.03 (0.01–0.07)	0.09 (0.03–0.16)
Nausea	150 (68)	1.94 (1.64–2.28)	83 (38)	0.78 (0.62–0.97)	1.16 (0.81–1.53)
Neutropenia	143 (65)	2.13 (1.79–2.51)	132 (60)	1.77 (1.48–2.1)	0.36 (-0.11 to 0.84)
Fatigue	129 (58)	151 (1.26–1.79)	123 (56)	1.55 (1.29–1.85)	-0.04 (-0.43 to 0.35)
Anemia	81 (37)	0.62 (0.49–0.77)	112 (51)	1.21 (0.99–1.45)	-0.59 (-0.86 to -0.33)
Neuropathy peripheral	15 (7)	0.09 (0.05–0.14)	46 (21)	0.35 (0.26–0.47)	-0.26 (-0.39 to -0.15)
Colitis	12 (5)	0.07 (0.04–0.13)	2 (1)	0.02 (0–0.06)	0.05 (0–0.11)
Thrombocytopenia	10 (5)	0.06 (0.03–0.1)	63 (29)	0.49 (0.38–0.63)	-0.44 (-0.58 to -0.31)
Pneumonitis	6 (3)	0.03 (0.01–0.07)	17 (8)	0.11 (0.06–0.18)	-0.08 (-0.15 to -0.02)

[a]Combined preferred terms of TEAEs were as follows: neutropenia includes neutropenia and febrile neutropenia; fatigue includes fatigue and asthenia; anemia includes anemia, Hgb decreased, and RBC count decreased; colitis includes colitis, enterocolitis, and autoimmune colitis; thrombocytopenia includes thrombocytopenia and platelet count decreased; pneumonitis includes pneumonitis, interstitial lung disease, and immune-mediated lung disease.

Note: EAIR values <0 indicate a difference that favors SG + pembro, and values >0 indicate a difference that favors TPC + pembro.

Pembro-related TEAEs of special interest (≥5% in either arm) are shown in Table 7. Overall, 30% and 40% of patients in the SG + pembro and TPC + pembro arms, respectively, reported an immune-mediated AE.

Table 7. ASCENT-04: Pembro TEAEs of Special Interest[5]

TEAE of Special Interest, n (%)	SG + Pembro (n=221)		TPC + Pembro (n=220)	
	Any-Grade	Grade ≥3	Any Grade	Grade ≥3
Hypothyroidism	16 (7)	1 (<1)	35 (16)	0
Colitis	13 (6)	4 (2)	3 (1)	1 (<1)
Infusion reactions	11 (5)	3 (1)	19 (9)	5 (2)
Hyperthyroidism	8 (4)	0	14 (6)	0

TEAE of Special Interest, n (%)	SG + Pembro (n=221)		TPC + Pembro (n=220)	
	Any-Grade	Grade ≥3	Any Grade	Grade ≥3
Pneumonitis	6 (3)	4 (2)	17 (8)	3 (1)

Note: TEAEs were recorded if they occurred with or after the first dose of study drug through 30 d after the last study drug dose (up to 90 d after SAEs) or 1 d before the start of the subsequent chemotherapy agent (including crossover treatment if pursued); whichever date the first of either occurred was the end of the evaluation period.

Time to onset and duration of neutropenia and diarrhea

Neutropenia and diarrhea (any grade and Grade ≥3) generally occurred earlier in treatment vs later with SG + pembro. Median times to onset of any-grade and Grade ≥3 neutropenia and diarrhea were generally shorter with SG + pembro vs TPC + pembro (Table 8). Median duration of diarrhea and neutropenia was generally comparable between treatment arms. These results should be interpreted with caution due to small sample sizes in the TPC + pembro arm for the time to onset and the duration of any-grade and Grade ≥3 diarrhea, and due to the small sample size in the SG + pembro arm for the time to onset and the duration of Grade ≥3 diarrhea.

Table 8. ASCENT-04: Time to Onset and Duration of Neutropenia and Diarrhea[5]

		SG + Pembro (n=221)				TPC + Pembro (n=220)			
		Any Grade		Grade ≥3		Any Grade		Grade ≥3	
		n[a]	Median (Range), D	n	Median (Range), D	n	Median (Range), D	n	Median (Range), D
Time to onset[b]	Neutropenia[c]	143	19 (6–624)	104	21 (7–624)	132	27 (7–366)	100	29 (7–378)
	Diarrhea	155	14 (1–462)	22	17 (1–715)	63	64 (1–496)	5	299 (202–513)
Duration[d]	Neutropenia[c]	140	9 (2–72)	102	8 (1–22)	131	12 (2–61)	100	8 (1–21)
	Diarrhea	140	7 (1–709)	22	8 (1–98)	57	6 (1–117)	5	4 (1–11)

[a]The n for time to onset and duration may differ, as some events had no recorded end date or were ongoing.
[b]The time to onset of the first event of neutropenia or diarrhea was calculated as follows: onset date or first event – first dose date of any study drug.
[c]Neutropenia includes preferred terms for neutrophil count decreased, neutropenia, and febrile neutropenia.
[d]The duration of the first event (of multiple any-grade or Grade ≥3 events) of neutropenia or diarrhea was calculated as follows: end date of the event – onset date of the event + 1 d (per episode).

Management of neutropenia

In the SG + pembro and TPC + pembro arms, neutropenia led to dose reduction in 19% and 18% of patients, respectively, and to treatment discontinuation in 1% and 2% of patients.

The use of G-CSF as primary prophylaxis in the SG + pembro arm resulted in fewer cases of and less severe neutropenia than in the TPC + pembro arm (Table 9).

Table 9. ASCENT-04: Management of Neutropenia[5]

Neutropenia, n (%)	SG + Pembro (n=221)		TPC + Pembro (n=220)	
Primary Prophylaxis	**Yes (n=43)**	**No (n=178)**	**Yes (n=20)**	**No (n=200)**
Any grade	20 (47)	123 (69)	13 (65)	119 (60)
Grade ≥3	15 (35)	89 (50)	10 (50)	90 (45)
Secondary Prophylaxis[a]	**Yes (n=75)**	**No (n=47)**	**Yes (n=37)**	**No (n=81)**
Any grade	55 (73)	30 (64)	20 (54)	49 (60)
Grade ≥3	34 (45)	16 (34)	11 (30)	36 (44)

[a]Excluded patients who received G-CSF for primary prophylaxis and included patients eligible for G-CSF.

Management of diarrhea

Most instances of diarrhea were Grade 1 (SG + pembro, 37%; TPC + pembro, 17%) or Grade 2 (SG + pembro, 24%; TPC + pembro, 10%); the incidence rate of severe diarrhea in this study was similar to that observed in earlier studies of SG. In the SG + pembro and TPC + pembro arms, diarrhea led to dose reduction in 5% and 1% of patients, respectively, and to treatment discontinuation in <1% of patients in the TPC + pembro arm. Nine of the 13 cases of colitis were non-severe, and 1 patient discontinued SG + pembro due to colitis.

Of the patients who received treatment for diarrhea, 90% and 77% of patients in the SG + pembro and TPC + pembro arms, respectively, received loperamide; 12% and 3% received atropine. Cases of colitis were managed per the pembro product labeling.

Post hoc analysis: PFS2 and subsequent therapies[6]

A post hoc analysis assessed PFS2 (defined as time from randomization to first documented progression on next-line therapy per investigator assessment or death due to any cause, whichever occurred first), TFST, and TSST.

The PFS2 was longer in the SG + pembro arm than in the TPC + pembro arm, with a 33% risk reduction of a PFS2 event with SG + pembro (Table 10).

Table 10. ASCENT-04 Post Hoc Analysis: PFS2[6]

PFS2		SG + Pembro (n=221)	TPC + Pembro (n=222)
PFS2 events		55	83
PFS2, median (95% CI), mo		NR (NR–NR)	21 (16–NR)
Stratified HR (95% CI)		0.67 (0.48–0.95)	
PFS2 rate, % (95% CI)	18-mo	71.9 (64.5–78)	53 (44.5–60.8)
	24-mo	63.7 (51.1–73.9)	45.6 (35.6–55.1)

At data cutoff, 125 patients (57%) in the SG + pembro arm and 170 (77%) in the TPC + pembro arm had discontinued treatment; 84 (67%) and 138 (81%), respectively, discontinued due to progressive disease. Among patients who discontinued treatment, 69 (55%) and 119 (70%), respectively, received 2L+ therapy (Table 11 and Table 12). The most common 2L+ therapy was chemotherapy (88%) for the SG + pembro arm and SG (81%) for the TPC + pembro arm.

Table 11. ASCENT-04 Post Hoc Analysis: Subsequent Therapies in the 2L Setting[6]

	SG + Pembro (n=221)	TPC + Pembro (n=222)
Any subsequent therapy, n	69	119
Any subsequent therapy in 2L, n (%)	68 (99)[a]	119 (100)
Taxanes	23 (33)	8 (7)
Platinum agents	18 (26)	3 (3)
ADC	7 (10)	94 (79)
T-DXd	5 (7)	2 (2)
SG	2 (3)	92 (77)[b]
PD-(L)1 inhibitor	6 (9)	7 (6)
Anthracyclines	4 (6)	5 (4)
PARPi	3 (1)	1 (1)
Other[c]	40 (58)	14 (12)

	SG + Pembro (n=221)	TPC + Pembro (n=222)
TFST, median (95% CI), mo	17.3 (12.7–NR)	9.8 (8.7–10.9)
Stratified HR (95% CI)	0.59 (0.46–0.76)	

[a]One patient did not have the line of therapy documented and was excluded from 2L- and 3L-specific analyses.
[b]Included both patients who received SG in the commercial 2L setting (n=15) and patients who crossed over to SG on study (n=77).
[c]Included cape (n=20), gem and bevacizumab (each, n=7), cyclophosphamide (n=3), eribulin (n=2), eribulin mesylate, etoposide, gem hydrochloride, investigational agent, letrozole, ribociclib, trastuzumab, and vinorelbine (each, n=1) in the SG + pembro arm and cyclophosphamide (n=6), cape (n=4), gem (n=2), bevacizumab and eribulin mesylate (each, n=1) in the TPC + pembro arm.

Table 12. ASCENT-04 Post Hoc Analysis: Subsequent Therapies in the 3L Setting[6]

	SG + Pembro (n=221)	TPC + Pembro (n=222)
Any subsequent therapy, n	69	119
Any subsequent therapy in 3L, n (%)	18 (26)[a]	29 (24)
Taxanes	5 (7)	3 (3)
Anthracyclines	4 (6)	2 (2)
Platinum agents	3 (4)	5 (4)
ADC	2 (3)	6 (5)
T-DXd	2 (3)	3 (3)
SG	0	3 (3)[b]
PD-(L)1 inhibitor	1 (1)	2 (2)
PARPi	0	1 (1)
Other[c]	11 (16)	18 (15)
TSST, median (95% CI), mo	NR (22.9–NR)	21 (16.6–NR)
Stratified HR (95% CI)	0.82 (0.59–1.14)	
Stratified log-rank nominal *P*-value	0.229	

[a]One patient did not have the line of therapy documented and was excluded from 2L- and 3L-specific analyses.
[b]One patient in the TPC + pembro arm received SG beyond 3L.
[c]Included cyclophosphamide (n=3), cape and bevacizumab (each, n=2), and eribulin, gem, vinorelbine, eribulin mesylate, fluorouracil, pertuzumab/trastuzumab, and investigational drug (each, n=1) in the SG + pembro arm and cape and eribulin (each, n=4), gem and cyclophosphamide (each, n=2), and bevacizumab, vinorelbine, Bt 8009, gem hydrochloride, letrozole, regorafenib, and investigational agent (each, n=1) in the TPC + pembro arm.

Subgroup analysis: mPFS by preselected TPC regimen, disease status, and presence of baseline brain or visceral metastases[7]

A subgroup analysis evaluated outcomes by preselected TPC regimen, disease status, and presence of BrM at baseline. A separate post hoc analysis also evaluated outcomes according to the presence of visceral metastases at baseline. The statistical analysis was not powered to detect differences between subgroups. Baseline characteristics were generally well balanced between the SG + pembro and TPC + pembro arms within each subgroup.

By BICR and investigator assessments, mPFS was numerically longer with SG + pembro vs TPC + pembro across all subgroups (Table 13). The incidence of new lesions at the time of progression was lower with SG + pembro vs TPC + pembro (24% vs 34%, respectively). In addition, fewer patients treated with SG + pembro vs TPC + pembro developed new visceral lesions (13% vs 18%, respectively).

Table 13. ASCENT-04 Subgroup Analysis: mPFS by BICR and Investigator Assessments (ITT Population)[7]

		SG + Pembro (n=221)		TPC + Pembro (n=222)		Unstratified HR (95% CI)
		n	mPFS (95% CI), mo	n	mPFS (95% CI), mo	
By BICR						
Preselected TPC regimen	Taxane	116	11.1 (8.6–16.7)	114	9.2 (7.2–12.9)	0.82 (0.58–1.17)
	Gem + carbo	105	11.3 (9.2–21.2)	108	7.4 (6.9–9)	0.52 (0.36–0.75)
Disease status	De novo metastatic	75	8.1 (7.3–18.6)	75	7.7 (6.1–11.9)	0.89 (0.59–1.34)
	Recurrent (6–12 mo)	40	9.9 (5.7–16.8)	40	7.2 (4.4–9.1)	0.62 (0.36–1.08)
	Recurrent (>12 mo)	106	16.6 (11–NR)	107	8.7 (7.3–10.8)	0.52 (0.35–0.76)
BrM	Yes[a]	8	5.7 (0.5–NR)	6	3.7 (1.3–NR)	0.64 (0.19–2.14)
	No	213	11.7 (9.3–16.8)	216	8.4 (7.4–9.3)	0.65 (0.5–0.84)
Visceral metastases	Yes	147	9.3 (7.7–11.7)	140	7 (5.6–7.5)	0.64 (0.47–0.85)
	No	74	16.8 (12.9–NR)	82	9.9 (9–12.9)	0.64 (0.39–1.05)
Investigator Assessment						
Preselected TPC regimen	Taxane	116	11.1 (9.2–13.3)	114	9.2 (7.3–12.4)	0.83 (0.59–1.18)
	Gem + carbo	105	13.3 (8.6–NR)	108	7.5 (6–9)	0.53 (0.37–0.76)
Disease status	De novo metastatic	75	9.2 (7.5–13.3)	75	8.9 (6.1–10.5)	0.77 (0.51–1.16)
	Recurrent (6–12 mo)	40	7.7 (5.6–12.9)	40	7.4 (5.6–9.3)	0.89 (0.52–1.54)
	Recurrent (>12 mo)	106	NR (9.6–NR)	107	8.4 (6.9–10.8)	0.5 (0.34–0.75)
BrM	Yes	8	5.5 (0.5–9.3)	6	5.4 (1.5–NR)	0.65 (0.19–2.3)
	No	213	11.7 (9.2–14.8)	216	8.4 (7.3–9.3)	0.65 (0.51–0.84)
Visceral metastases	Yes	147	9.5 (9.1–13)	140	7.2 (5.7–8.4)	0.64 (0.47–0.85)
	No	74	16.8 (8.6–NR)	82	9.3 (8.3–15.4)	0.69 (0.43–1.1)

Safety data were not reported.

E-R analysis with SG[8]

An E-R analysis evaluated the association of SG exposure with PFS and ORR. A safety analysis specific to ASCENT-04 was not performed. At Dose 1 in the efficacy analysis, the PK variables for SG and its metabolites are shown in Table 14.

Table 14. ASCENT-04 E-R Analysis: PK Metrics at Dose 1 of SG in the Efficacy Analysis[8]

Variables, Median (Range), ng/mL	C_{min}	C_{max}	C_{avg}
SG	5260 (1570–8290)	255,000 (128,000–547,000)	70,200 (35,500–150,000)
tAB	70,800 (9320–142,000)	227,000 (114,000–485,000)	131,000 (64,200–275,000)
Free SN-38	0.35 (0.08–5)	85.1 (26.3–206)	14.3 (3.78–38.2)

Abbreviations: C_{avg}=average concentration; C_{max}=maximum concentration; C_{min}=minimum concentration; SN-38=active metabolite of SG; tAB=total SG antibody.

No statistically significant relationship was observed between SG exposure and ORR (OR, 1.38; 90% CI: 0.58–3.26; *P*=0.536). Patients with $C_{min,D1,SG}$ exposures above Quartile 1 had

a lower risk of disease progression or death than those with exposures at or below Quartile 1 (*P*<0.01); however, no trend of E-R with PFS was noted for Quartiles 2 to 4. Baseline albumin levels above Quartile 1 were associated with a reduced risk of PFS events than levels at or below Quartile 1 (Table 15). Baseline serum albumin was a significant covariate (n=1010; baseline median [range], 39 [19–51] g/dL; *P*<0.01).

Table 15. ASCENT-04 E-R Analysis: mPFS at Month 24 Stratified by Quartiles of SG C_{min} and Baseline Albumin Levels[8]

		SG + Pembro (n=221)		
		Exposure, Median (Range)	**Events Through to Month 24, n**	**mPFS (90% CI), mo**
PFS Stratified by Quartiles of $C_{min,D1,SG}$				
Quartile	1	3881 (1570–4474)	39	7.7 (5.6–13.3)
	2	4875 (4498–5256)	24	11.7 (9.1–NE)
	3	5484 (5259–5859)	21	19 (11.6–NE)
	4	6434 (5875–8289)	26	12.9 (9.1–NE)
		Baseline Albumin Level, Median (Range), g/dL	**Events Through to Month 24, n**	**mPFS (90% CI), mo**
PFS Stratified by Quartiles of Baseline Albumin Level				
Quartile	1	36 (24–38)	39	7.7 (6.7–11.1)
	2	40 (38–42)	25	12.9 (9.2–NE)
	3	43 (42–44)	24	14.6 (7.7–NE)
	4	45 (44–48)	22	16.8 (11.3–NE)

Abbreviation: NE=not evaluable.

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Abbreviations

1L/2L/3L=first-/second-/third-line
2L+=second-line or later
ADC=antibody-drug conjugation
AE=adverse event
AESI=adverse events of special interest
BICR=blinded independent central review
BrM=brain metastases
cape=capecitabine
carbo=carboplatin
$C_{min,D1,SG}$=minimum SG concentration during the first dose
CPS=combined positive score
EAIR=exposure-adjusted incidence rate
ECOG PS=Eastern Cooperative Oncology Group Performance Status
E-R=exposure-response
DOR=duration of response
G-CSF=granulocyte colony-stimulating factor
gem=gemcitabine
HR=hazard ratio
mPFS=median progression-free survival
mTNBC=metastatic triple-negative breast cancer
NR=not reached
OR=odds ratio
ORR=objective response rate
OS=overall survival
PARPi=poly (ADP-ribose) polymerase inhibitor
PD=progressive disease
PD-(L)1=programmed death (ligand) 1
pembro=pembrolizumab
PFS=progression-free survival
PFS2=progression-free survival after next line of treatment
PK=pharmacokinetic(s)
PYE=patient-years of exposure
RECIST=Response Evaluation Criteria in Solid Tumors
SAE=serious adverse event
SG=sacituzumab govitecan-hziy
TEAE=treatment-emergent adverse event
TFST=time to first subsequent therapy
TPC=treatment of physicians' choice
TSST=time to second subsequent therapy
T-DXd=trastuzumab deruxtecan

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