Safety Analysis of Phase 3 ASCENT-04 Study of Sacituzumab Govitecan + Pembrolizumab vs Chemotherapy + Pembrolizumab for Previously Untreated PD-L1+ Metastatic Triple-Negative Breast Cancer

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Poster #PS5-02-28

San Antonio Breast Cancer Symposium®-December 9-12, 2025

Conclusions

- The overall safety profile with sacituzumab govitecan (SG) + pembrolizumab (pembro) was consistent with that of each agent with no exacerbation of immune-mediated adverse events (imAEs), supporting a favorable benefit/risk profile for SG + pembro vs chemotherapy (chemo) + pembro in participants with previously untreated programmed death-ligand 1-positive (PD-L1+) metastatic triple-negative breast cancer (mTNBC)
- After adjusting for longer duration of treatment with SG + pembro vs chemo + pembro (exposure adjusted incidence rate [EAIR]), rates of treatment-emergent adverse events (TEAEs) leading to dose reduction and treatment discontinuation and rates of anemia, thrombocytopenia, pneumonitis, and neuropathy peripheral favored SG + pembro, while rates of diarrhea and colitis favored chemo + pembro
  - These results are consistent with previously reported rates of TEAEs leading to treatment discontinuation (12% with SG + pembro vs 31% with chemo + pembro) and dose reduction (35% vs 44%)[5]
- The rates of most imAEs (including hypothyroidism, pneumonitis, and infusion reactions) were lower with SG + pembro vs chemo + pembro
- Time to onset of diarrhea was shorter for SG + pembro vs chemo + pembro; time to onset of neutropenia and duration of both TEAEs was similar between treatment groups, and both were manageable with supportive care

Plain Language Summary

In the ASCENT-04/KEYNOTE-D19 clinical study, participants received either sacituzumab govitecan (SG) + pembrolizumab (pembro) or chemotherapy (chemo) + pembro to see which combination was more effective as initial treatment for metastatic triple-negative breast cancer tumors that express a protein called PD-L1. Pembro specifically targets tumors that express PD-L1. Here, the researchers performed a more in-depth analysis of safety from the study. When accounting for the amount of drug that participants received over time, those who received SG + pembro experienced fewer adverse events leading to dose reduction and treatment discontinuation compared with those who received chemo + pembro. Neutropenia and diarrhea, 2 common adverse events during SG + pembro treatment, generally resolved quickly using existing management guidelines. Along with previously reported data, these results support SG + pembro as an effective treatment with manageable adverse events for people with metastatic triple-negative breast cancer that expresses PD-L1.

References: **1.** Goldenberg DM, et al. *Oncotarget*. 2015;6:22496-512. **2.** Bardia A, et al. *N Engl J Med*. 2021;384:1529-41. **3.** TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; 2025. **4.** TRODELVY® (sacituzumab govitecan-hziy) [summary of product characteristics]. County Cork, Ireland: Gilead Sciences Ireland UC; 2025. **5.**Tolaney SM, et al. Oral presentation at ASCO; May 30-June 3, 2025; Chicago, IL, USA. Abstract LBA109. **6.** de Azambuja E, et al. Oral presentation at ESMO; October 17-21, 2025; Berlin, Germany. Abstract LBA22.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators. This study was funded by Gilead Sciences, Inc. Medical writing and editorial support was provided by Ben Labbe, PhD, of Parexel, and funded by Gilead Sciences, Inc.

Disclosures: **KK** reports grants or contracts from AstraZeneca, bioTheranostics, Daiichi Sankyo, Genentech/Roche, Gilead Sciences, Inc., Lilly, Menarini, Merck, Mersana, Myovant Sciences, Novartis, Pfizer, ProteinQure, Puma Biotechnology, Regor, Relay Therapeutics, and Seattle Genetics; and other financial interests with ADC Therapeutics and EQRX.

Introduction

- SG is an antibody-drug conjugate, directed to Trop-2,[1] that has been approved in multiple countries for the treatment of mTNBC in patients who have received ≥ 2 prior systemic therapies, with ≥ 1 for metastatic disease[2-4]
- In the phase 3, randomized ASCENT-04/KEYNOTE-D19 study, treatment with SG + pembro resulted in statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared with chemo + pembro, along with higher objective response rate (ORR) and longer duration of response (DOR) for participants with previously untreated mTNBC[5]; quality of life was also generally maintained with SG + pembro, with reduced symptom burden and improved functioning in multiple domains[6]
- We report the first in-depth safety analysis from ASCENT-04/KEYNOTE-D19

Methods

- Participants with previously untreated, locally advanced, unresectable PD-L1+ mTNBC were randomized to receive SG (10 mg/kg intravenously, days 1 and 8 of 21-day cycle) + pembro (200 mg day 1 of 21-day cycle) or pembro + chemo (paclitaxel, nab-paclitaxel, or gemcitabine + carboplatin) until disease progression or unacceptable toxicity as previously described[5]
- The primary end point was PFS by blinded independent central review (BICR); key secondary end points included overall survival, ORR and DOR by BICR, safety, and participant-reported outcomes
- Exploratory analysis was performed for EAIRs, defined as number of participants with ≥ 1 specified TEAE per patient-year of exposure (PYE)
  - EAIR was calculated as number of participants with a specific event divided by total PYE in each group; PYE was defined as the sum of each patient's time at risk (exposure duration) within the study
- Incidence, severity, time to onset, duration, and impact of adverse event management were assessed for select TEAEs for SG and/or pembro

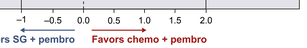
Results

- As previously described, participant demographics and baseline characteristics were well balanced between the treatment groups, and all participants were female; in the chemo + pembro group, 51% of participants received taxane and 49% received gemcitabine + carboplatin[5]
- The TEAEs observed were consistent with the known safety profiles of SG and chemo: most common were diarrhea, nausea, and neutropenia with SG + pembro and neutropenia, fatigue, and anemia with chemo + pembro
- Median duration of treatment was 8.9 months for SG and 8.5 months for pembro in the SG + pembro group and was 6.2 months for chemo and 6.4 months for pembro in the chemo + pembro group
- Any-grade TEAEs occurred in 220 (> 99%) of participants who received SG + pembro and 219 (> 99%) who received chemo + pembro
  - Any-grade EAIR for SG + pembro was 69.09 (95% CI, 60.26, 78.85); for chemo + pembro, it was 36.68 (95% CI, 31.98, 41.87)
- Additional EAIR data are shown in **Figure 1**
- imAEs occurred in 30% of participants treated with SG + pembro and 40% of participants treated with chemo + pembro; hypothyroidism was the most common TEAE of special interest in both treatment groups (**Table 1**)

Results

Figure 1. Exposure-Adjusted Incidence Rates

TEAEs	SG + Pembro (n = 221) n (%)	SG + Pembro (n = 221) EAIR (95% CI)	Chemo + Pembro (n = 220) n (%)	Chemo + Pembro (n = 220) EAIR (95% CI)	EAIR Difference (95% CI)
Grade ≥ 3	158 (71)	2.19 (1.86, 2.56)	154 (70)	2.13 (1.81, 2.49)	0.06 (−0.43, 0.55)
Serious	84 (38)	0.59 (0.47, 0.73)	68 (31)	0.52 (0.41, 0.66)	0.06 (−0.12, 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, 0.75)
Led to SG/chemo dose reduction	78 (35)	0.62 (0.49, 0.78)	96 (44)	0.94 (0.76, 1.14)	−0.31 (−0.56, −0.08)
Led to any treatment discontinuation	26 (12)	0.15 (0.10, 0.21)	68 (31)	0.53 (0.41, 0.67)	−0.38 (−0.53, −0.25)
Treatment-related, grade ≥ 3	149 (67)	1.95 (1.65, 2.29)	141 (64)	1.76 (1.48, 2.07)	0.20 (−0.24, 0.64)
Treatment-related, serious	61 (28)	0.41 (0.31, 0.52)	42 (19)	0.29 (0.21, 0.40)	0.11 (−0.03, 0.25)
Neutropenia[a]	143 (65)	2.13 (1.79, 2.51)	132 (60)	1.77 (1.48, 2.10)	0.36 (−0.11, 0.84)
Anemia[b]	81 (37)	0.62 (0.49, 0.77)	112 (51)	1.21 (0.99, 1.45)	−0.59 (−0.86, −0.33)
Thrombocytopenia[c]	10 (5)	0.06 (0.03, 0.10)	63 (29)	0.49 (0.38, 0.63)	−0.44 (−0.58, −0.31)
Diarrhea	155 (70)	2.05 (1.74, 2.40)	63 (29)	0.53 (0.41, 0.68)	1.52 (1.18, 1.89)
Colitis[d]	13 (6)	0.07 (0.04, 0.13)	3 (1)	0.02 (0.00, 0.06)	0.05 (0.00, 0.11)
Nausea	150 (68)	1.94 (1.64, 2.28)	83 (38)	0.78 (0.62, 0.97)	1.16 (0.81, 1.53)
Pneumonitis[e]	6 (3)	0.03 (0.01, 0.07)	17 (8)	0.11 (0.06, 0.18)	−0.08 (−0.15, −0.02)
Fatigue[f]	129 (58)	1.51 (1.26, 1.79)	123 (56)	1.55 (1.29, 1.85)	−0.04 (−0.43, 0.35)
Peripheral neuropathy	15 (7)	0.09 (0.05, 0.14)	46 (21)	0.35 (0.26, 0.47)	−0.26 (−0.39, −0.15)



[a]Neutropenia includes preferred terms of neutropenia and febrile neutropenia. [b]Anemia includes preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased. [c]Thrombocytopenia includes preferred terms of thrombocytopenia and platelet count decreased. [d]Colitis includes preferred terms of colitis, enterocolitis, and autoimmune colitis. [e]Pneumonitis includes preferred terms of pneumonitis, interstitial lung disease, and immune-mediated lung disease. [f]Fatigue includes preferred terms of fatigue and asthenia. Chemo, chemotherapy; EAIR, exposure-adjusted incidence rate; pembro, pembrolizumab; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

Table 1. Pembrolizumab TEAEs of Special Interest[a]

AEOSI Category, n (%)	SG + Pembro (n = 221) Any grade	SG + Pembro (n = 221) Grade ≥ 3	Chemo + Pembro (n = 220) Any grade	Chemo + Pembro (n = 220) 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
Pneumonitis	6 (3)	4 (2)	17 (8)	3 (1)

TEAEs began on or after first dose of study drug up to 30 days (up to 90 days after serious AEs) after last dose date of study drug or the day prior to the initiation of subsequent anticancer therapy (including crossover treatment if applicable), whichever came first. AEs were coded using Medical Dictionary for Regulatory Activities, v27.1.
[a]AEOSIs were those included in a list of terms specified by the sponsor and were assessed regardless of attribution to trial regimen. Any-grade AEOSIs that occurred in ≥ 5% of participants in either treatment group are included. AE, adverse event; AEOSI, adverse event of special interest; chemo, chemotherapy; pembro, pembrolizumab; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

- Median time to onset of diarrhea (any grade and grade ≥ 3) was notably shorter for participants treated with SG + pembro compared with chemo + pembro (**Table 2**)
- Median duration of diarrhea and neutropenia was comparable between the treatment groups

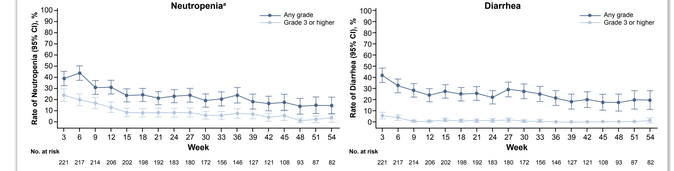
Table 2. Time to Onset and Duration of Neutropenia and Diarrhea

	SG + Pembro (n = 221) Any grade n[a]	SG + Pembro (n = 221) Any grade Days (range)	SG + Pembro (n = 221) Grade ≥ 3 n[a]	SG + Pembro (n = 221) Grade ≥ 3 Days (range)	Chemo + Pembro (n = 220) Any grade n[a]	Chemo + Pembro (n = 220) Any grade Days (range)	Chemo + Pembro (n = 220) Grade ≥ 3 n[a]	Chemo + Pembro (n = 220) Grade ≥ 3 Days (range)
Median 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)
Median 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]Number of participants may differ between time to onset and duration data due to events with no recorded end date or ongoing events. [b]Time to onset of first event is calculated as time from the first dose date of any study drug to the onset date of first event. [c]Neutropenia includes preferred terms of neutrophil count decreased, neutropenia, and febrile neutropenia. [d]Duration is the median duration among multiple episodes of any grade or among multiple episodes of grade ≥ 3 (the end date of event of interest – the onset date of event of interest + 1 day for each episode). Chemo, chemotherapy; pembro, pembrolizumab; SG, sacituzumab govitecan.

- Frequencies of neutropenia and diarrhea with SG + pembro were highest early in treatment (**Figure 2**)

Figure 2. Neutropenia and Diarrhea Over Time With SG + Pembro



Rate of neutropenia and diarrhea was calculated for every 3-week interval and defined as the number of participants who experienced the event in the interval divided by the number of participants at risk in the interval. [a]Neutropenia includes preferred terms of neutrophil count decreased, neutropenia, and febrile neutropenia. SG, sacituzumab govitecan.

- The use of primary prophylactic granulocyte colony-stimulating factor (G-CSF) was associated with less frequent and less severe neutropenia in the SG + pembro group (**Table 3**)
  - Neutropenia led to dose reduction in 19% and 18% of participants and to treatment discontinuation in 1% and 2% in the SG + pembro and chemo + pembro groups, respectively
- Most diarrhea was grade 1 (SG + pembro, 37% vs chemo + pembro, 17%) or grade 2 (24% vs 10%; overall 60% vs 26% grade 1/2); severe diarrhea rates were comparable with prior SG studies
  - Diarrhea led to dose reduction in 5% and 1% of participants in the SG + pembro and chemo + pembro groups, respectively, and to treatment discontinuation in < 1% in the chemo + pembro group
  - Among participants who received antidiarrheals, diarrhea was managed mostly with loperamide in both treatment groups (SG + pembro, 90%; chemo + pembro, 77%); atropine was more commonly used in the SG + pembro group (12%) vs the chemo + pembro group (3%)
- Most cases of colitis were nonsevere (9 of 13) and 1 case led to treatment discontinuation in the SG + pembro group; colitis was managed according to pembro prescribing information

Table 3. Management of Neutropenia

Neutropenia, n (%)	SG + Pembro (n = 221)		Chemo + Pembro (n = 220)	
Primary G-CSF 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 G-CSF 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]Includes participants eligible for secondary prophylactic G-CSF use and excludes participants who received primary G-CSF prophylaxis. Chemo, chemotherapy; G-CSF, granulocyte colony-stimulating factor; pembro, pembrolizumab; SG, sacituzumab govitecan.