

Exposure-Response Analysis of First-Line Sacituzumab Govitecan Plus Pembrolizumab for Participants With Metastatic Triple-Negative Breast Cancer From the ASCENT-04 Study

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Conclusions

- In the ASCENT-04 study, first-line (1L) sacituzumab govitecan (SG) + pembrolizumab significantly improved progression-free survival (PFS) vs chemotherapy + pembrolizumab in participants with previously untreated, programmed death ligand 1 (PD-L1)–positive metastatic triple-negative breast cancer (mTNBC)
- In the exposure-response (E-R) analysis, higher SG exposure during the first dose was associated with improved PFS in ASCENT-04; higher albumin levels were also associated with improved PFS
- No obvious trends were identified between objective response rate (ORR) and SG exposure in ASCENT-04
- The adverse events (AEs) observed in SG-treated participants in the pooled safety population are consistent with the known safety profile of SG and can be managed using established treatment guidelines
 - Higher SG exposure is associated with increased risk of neutropenia and diarrhea, although certain baseline factors also influenced these risks
- These findings support the favorable benefit-risk profile of the approved 1L SG dose of 10 mg/kg in PD-L1–positive mTNBC, regardless of patient characteristics. These participants had tested positive for a protein called programmed death ligand 1 (PD-L1)

Plain Language Summary

- In the ASCENT-04 study, sacituzumab govitecan (SG) plus pembrolizumab helped participants with metastatic triple-negative breast cancer (mTNBC) live longer without their disease worsening (called progression-free survival) compared with chemotherapy plus pembrolizumab. These participants had tested positive for a protein called programmed death ligand 1 (PD-L1)
- In this analysis, researchers evaluated whether progression-free survival and adverse events experienced by the participants were different based on SG levels in the blood
- Higher SG levels after the first treatment dose were associated with improved progression-free survival. Higher albumin levels (which may affect your body's ability to manage body fluids) were also linked to improved progression-free survival
- However, SG levels may not be linked to the chance of the tumor shrinking or disappearing
- Higher SG levels may increase the chance of adverse events such as neutropenia (low number of a type of white blood cell that fights infections) and diarrhea, although patient characteristics at the start of treatment also played a role
 - The adverse events seen in this study were expected based on previous experience with SG and can be managed using standard supportive care and treatment guidelines
- These results suggest that benefits of SG outweigh its risks across patients with different characteristics and support the approved dose of 10 mg per kilogram of body weight as a first treatment for people with PD-L1–positive mTNBC

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Introduction

- SG is a Trop-2–directed antibody-drug conjugate composed of the humanized anti–Trop-2 antibody hRS7 IgG1k linked by a proprietary hydrolysable linker to SN-38, the active metabolite of the topoisomerase I inhibitor irinotecan¹
- SG is approved for the treatment of unresectable locally advanced or mTNBC in the European Union, the United States, and other regions in the second-line or later setting as monotherapy and in 1L as monotherapy for PD-L1–ineligible patients and as a combination with pembrolizumab for patients whose tumors express PD-L1 (combined positive score [CPS] ≥ 10)^{2,3}
- In the ASCENT-04 study, 1L SG + pembrolizumab significantly improved PFS vs chemotherapy + pembrolizumab in participants with PD-L1–positive mTNBC (median, 11.2 vs 7.8 months; hazard ratio, 0.65 [95% CI, 0.51-0.84]; $P < .001$)⁴
- An integrated population pharmacokinetic (PK) model was developed to characterize the PK of SG, free SN-38, and total antibody (tAB) following SG administration (days 1 and 8 of 21-day cycles)
- E-R analyses were performed to evaluate relationships between exposure to SG, free SN-38, and tAB, and key efficacy and safety endpoints

Methods

- Efficacy endpoints from ASCENT-04 (PFS and ORR assessed by blinded independent central review) were evaluated at an SG dose of 10 mg/kg
- Safety endpoints (AEs and time to dose modifications) used pooled data from SG-treated participants in ASCENT-04, IMMU-132-01, IMMU-132-05, and IMMU-132-09, with SG starting doses of 8-18 mg/kg
- Exposure metrics including cycle 1 and steady-state minimum concentration (C_{min}), average concentration (C_{avg}), and maximum concentration (C_{max}) of SG; free SN-38; and tAB were tested using covariates shown in **Table 1**
- Logistic regression, parametric time-to-event models, and Cox proportional hazards model evaluated E-R relationships

Results

- Median age of participants was 57 (range, 23-88) years. Most participants were female (88%) and White (75%). Median baseline albumin was 39 g/L (**Table 1**)

Table 1. Baseline Covariates in the Pooled E-R Safety Dataset

Median (Range)	n	SG	n (%)	SG (n = 1012)
Age, years	1012	57 (23-88)	Female	895 (88)
Body weight, kg	1011	69 (37-140)	Race*	
Tumor size, mm	709	58 (10-348)	White	761 (75)
Albumin, g/L	1010	39 (19-51)	Black	58 (6)
LDH, U/L	998	254 (60-5930)	Asian	65 (6)
Absolute neutrophil count, 10 ³ cells/μL	1009	4 (1-20)	Other	56 (6)
eGFR, mL/min/1.73 m ²	1012	88 (16-316)	ECOG PS	
			0	457 (45)
			1-2	555 (55)
			UGT1A1 genotype ^b	
			*1/*28	404 (40)
			*1/*1	391 (39)
			*28/*28	104 (10)
			*1/*6	9 (1)
			*6/*6	2 (< 1)
			Other	21 (2)
			Hepatic impairment	
			Normal	713 (70)
			Mild-moderate	299 (30)
			eGFR, mL/min/1.73 m ²	
			< 60	91 (9)
			60-90	453 (45)
			> 90	468 (46)

*Missing race, n = 72 (7%). *Missing UGT1A1 genotype, n = 81 (8%). ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; E-R, exposure response; LDH, lactate dehydrogenase; SG, sacituzumab govitecan.

Results

- Summary of exposure metrics in the efficacy population are shown in **Table 2**. SG and tAB metrics were highly correlated with each other, whereas correlations between free SN-38 and SG/tAB exposures were comparatively weaker

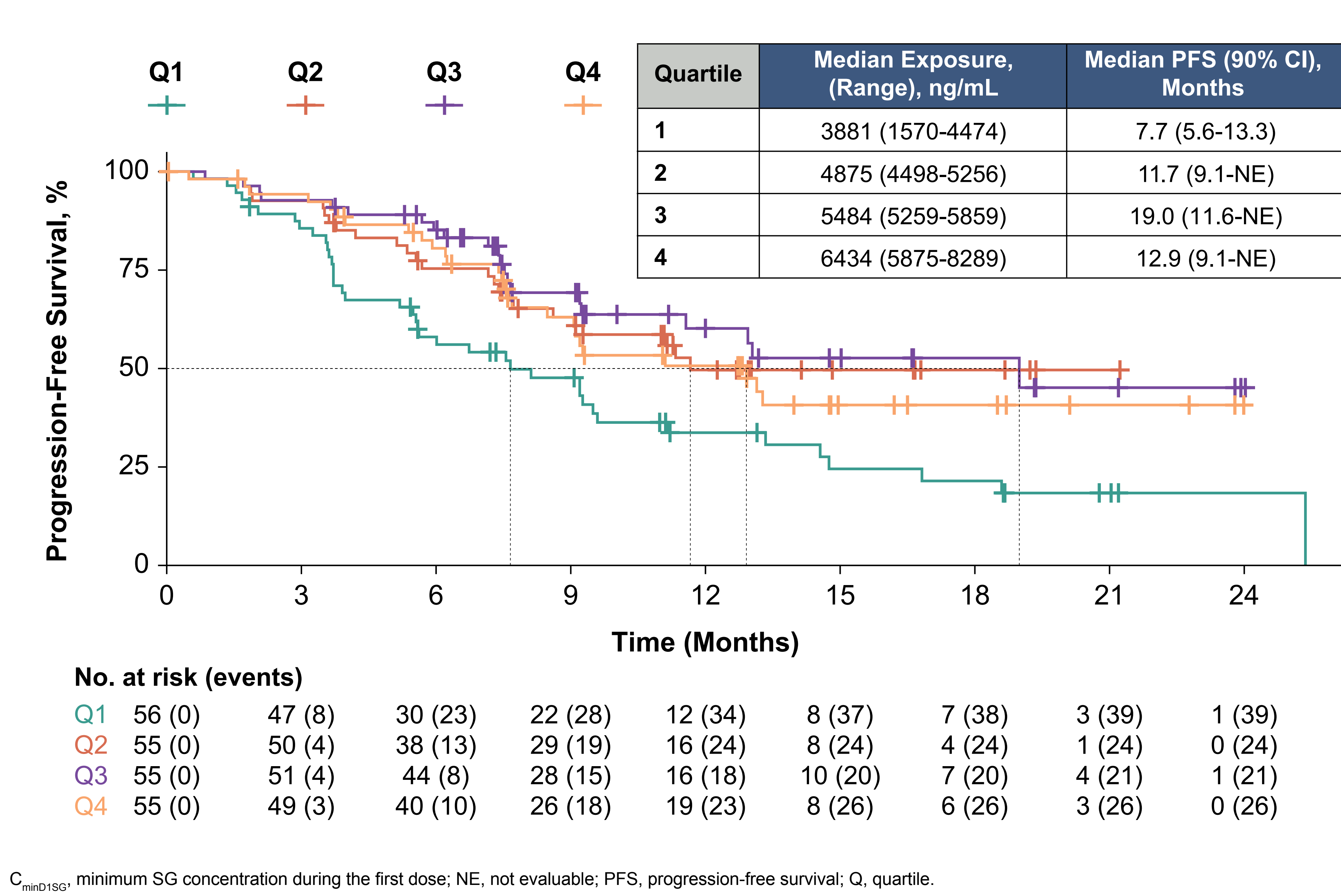
Table 2. PK Metrics at Dose 1 in the Efficacy Analysis (ASCENT-04)

Median (Range) (n = 221)			
Variable (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 (0.08-5.00)	85.1 (26.3-206.0)	14.3 (3.78-38.2)

C_{avg} , average concentration; C_{max} , maximum concentration; C_{min} , minimum concentration; PK, pharmacokinetics; SG, sacituzumab govitecan; tAB, total SG antibody.

- There was a flat E-R relationship for ORR across the range of SG exposures at the 10 mg/kg dose (n = 221). The estimated exposure slope was not statistically significant (odds ratio, 1.38 [90% CI, 0.58-3.26]; $P = .536$)
- Participants with $C_{min,D1,SG}$ exposures in quartiles 2-4 (Q2-Q4) had a lower risk of PFS events compared with Q1 (disease progression or death; $P < .01$; **Figure 1**)
- No E-R trend was observed across Q2–Q4 $C_{min,D1,SG}$ exposure quartiles for PFS events (**Figure 1**)

Figure 1. Kaplan-Meier Curves of PFS Stratified by Quartiles of $C_{min,D1,SG}$



- Participants with baseline albumin levels above Q1 had a reduced risk of PFS events. No clear trend in PFS was observed among participants in Q2-Q4 (**Figure 2**). Baseline serum albumin was a significant covariate ($P < .01$)
- Median PFS was 7.7 months in Q1 compared with 13-17 months across Q2-Q4 (**Figure 2**)
- Summary of exposure metrics for the safety population are presented in **Table 3**. PK metrics for SG and tAB were highly correlated, while free SN-38 was moderately correlated with SG/tAB exposure

Figure 2. Kaplan-Meier Curves of PFS Stratified by Quartiles of Baseline Albumin

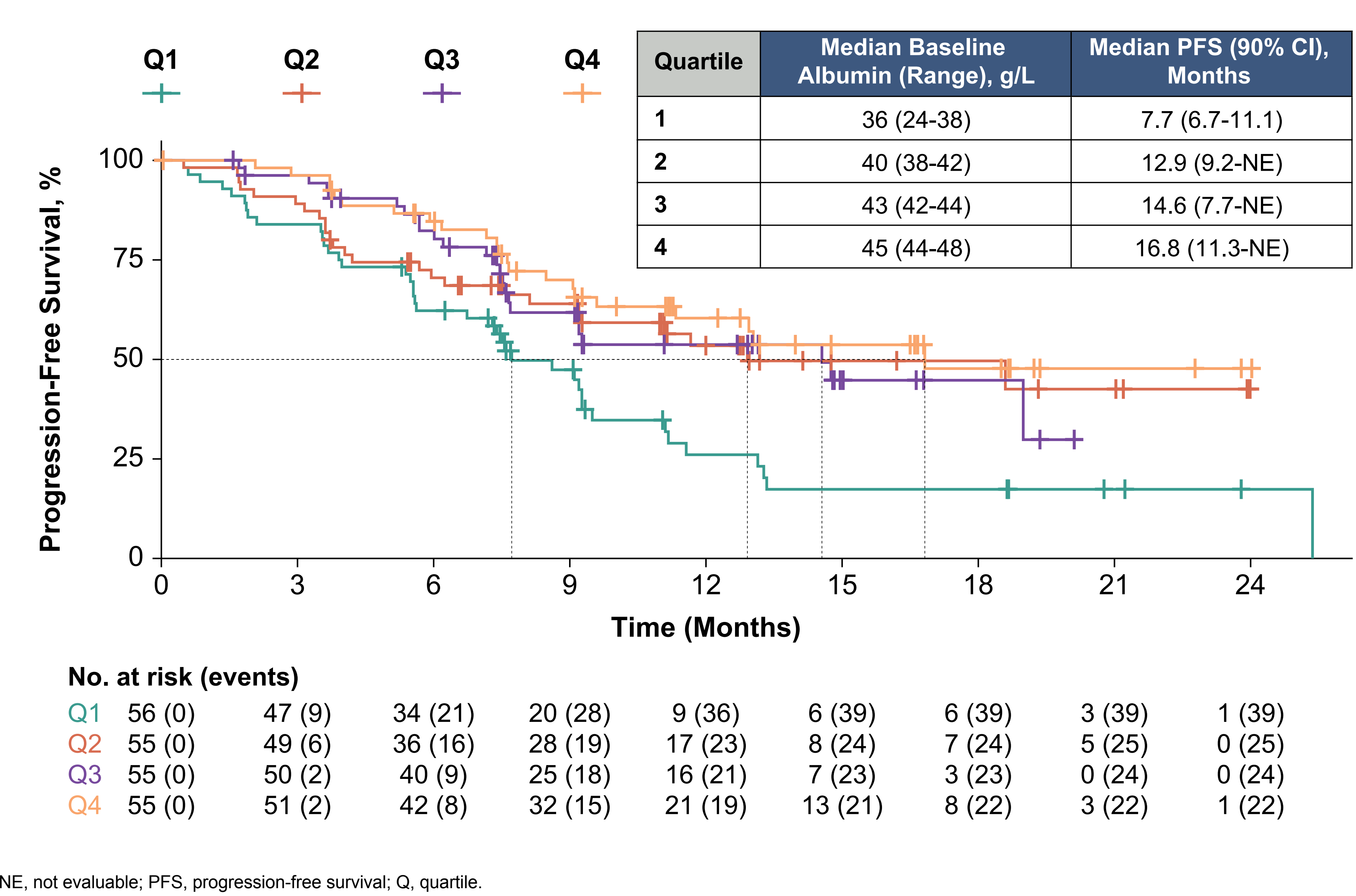


Table 3. PK Metrics at Dose 1 in the Safety Analysis (All Data)

Median (Range) (n = 1012)			
Variable (ng/mL)	C_{min}	C_{max}	C_{avg}
SG	5230 (467-12,100)	250,000 (91,300-547,000)	69,900 (24,800-156,000)
tAB	73,800 (320-208,000)	222,000 (82,200-485,000)	132,000 (44,100-309,000)
Free SN-38	0.45 (0.07-94.60)	93.3 (9.9-436.0)	16.4 (2.54-126.0)

C_{avg} , average concentration; C_{max} , maximum concentration; C_{min} , minimum concentration; PK, pharmacokinetics; SG, sacituzumab govitecan; tAB, total SG antibody.

- In the exposure-safety analysis (n = 1012), maximum SG concentration during the first dose ($C_{max,D1,SG}$) was significantly associated with any-grade and grade ≥ 3 neutropenia, febrile neutropenia, diarrhea, and time to AEs leading to dose reductions
- The following covariate effects reflect exposure-adjusted associations identified by the E-R models and are intended to characterize variability in model-predicted outcomes. These findings should not be interpreted as an independent safety risk assessment or evidence of causality
 - Higher model-predicted rates of any-grade/grade ≥ 3 neutropenia-related AEs were associated with *UGT1A1* *28/*28 or *1/*28 genotype, lower baseline absolute neutrophil count or albumin, higher body weight or body mass index, and mild-to-moderate hepatic impairment; febrile neutropenia was additionally associated with reduced renal function (estimated glomerular filtration rate [eGFR] 60-90 mL/min/1.73 m²)
 - Only 5 participants had moderate hepatic impairment; therefore, mild and moderate hepatic impairment were combined for model estimation. No conclusions should be drawn for these subpopulations
 - Higher body weight was the only covariate associated with model-predicted rates of any-grade/grade ≥ 3 diarrhea
 - UGT1A1* *1/*28 or *28/*28 genotype and reduced renal function (eGFR < 90 mL/min/1.73 m²) were each associated with the probability of dose reductions due to AEs
 - A previous population-based PK study showed that *UGT1A1* genotype did not have a clinically relevant impact on SG exposure,⁵ suggesting that genotype-based dose reduction is not needed despite the AE-related dose reductions observed in the current analysis
- No statistically significant exposure relationships were observed for nausea, vomiting, infections, hypersensitivity, or time to AEs leading to dose delays