Sacituzumab Govitecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non–Small Cell Lung Cancer: The Randomized, Open-Label Phase III EVOKE-01 Study

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ABSTRACT

PURPOSE The open-label, phase III EVOKE-01 study evaluated sacituzumab govitecan (SG) versus standard-of-care docetaxel in metastatic non–small cell lung cancer (mNSCLC) with progression on/after platinum-based chemotherapy, anti–PD-(L)1, and targeted treatment for actionable genomic alterations (AGAs). Primary analysis is reported.

METHODS Patients were randomly assigned 1:1 (stratified by histology, best response to last anti–PD-(L)1–containing regimen, and AGA treatment received or not) to SG (one 10 mg/kg intravenous infusion on days 1 and 8) or docetaxel (one 75 mg/m^2 intravenous infusion on day 1) in 21-day cycles. Primary end point was overall survival (OS). Key secondary end points were investigator-assessed progression-free survival (PFS), objective response rate, patient-reported symptom assessment, and safety.

RESULTS In the intention-to-treat population (SG, n = 299; docetaxel, n = 304), 55.4% had one previous line of therapy. Median follow-up was 12.7 months (range, 6.0-24.0). The primary end point was not met. There was a numerical OS improvement for SG versus docetaxel (median, 11.1 *v* 9.8 months; hazard ratio [HR], 0.84 [95% CI, 0.68 to 1.04]; one-sided $P = .0534$), consistent across squamous and nonsquamous histologies. Median PFS was 4.1 versus 3.9 months (HR, 0.92 [95% CI, 0.77 to 1.11]). An OS benefit was observed for SG (n = 192) versus docetaxel (n = 191) in mNSCLC nonresponsive to last anti–PD-(L)1–containing regimen (3.5-month median OS increase; HR, 0.75 [95% CI, 0.58 to 0.97]); this was consistent across histologies. Among patients receiving SG and docetaxel, 6.8% and 14.2% discontinued because of treatment-related adverse events (TRAEs), respectively; 1.4% and 1.0%, respectively, had TRAEs leading to death.

CONCLUSION Although statistical significance was not met, OS numerically improved with SG versus docetaxel, which was consistent across histologies. Clinically meaningful improvement in OS was noted in mNSCLC nonresponsive to last anti–PD-(L)1–containing regimen. SG was better tolerated than docetaxel and consistent with its known safety profile, with no new safety signals.

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INTRODUCTION

Treatment for advanced or metastatic non–small cell lung cancer (NSCLC) progressing after platinum-based chemotherapy and/or immunotherapy, regardless of the presence of actionable genomic alterations (AGAs) and PD-L1 status, remains limited to chemotherapy.[1] However, survival outcomes are poor with current standard-of-care docetaxel and are accompanied by significant treatment-related adverse events (TRAEs) affecting patient quality of life (QoL).[2-5] Although targeted therapies and immunotherapies improve outcomes when used in first-line settings, resistance mechanisms promote disease progression in most patients,[6,7] and effective therapies for patients with disease progression on both immunotherapy and platinum-based chemotherapy are needed.

Sacituzumab govitecan (SG) is a first-in-class, trophoblast cell-surface antigen (Trop)-2–directed antibody-drug

CONTEXT

Key Objective

Docetaxel is standard treatment for advanced/metastatic non–small cell lung cancer progressing after platinum-based chemotherapy and/or immunotherapy but is associated with modest clinical outcomes and significant toxicity. This randomized, global phase III study evaluated the trophoblast cell-surface antigen 2–directed antibody-drug conjugate (ADC) sacituzumab govitecan (SG) versus docetaxel in this setting.

Knowledge Generated

SG demonstrated a numerical overall survival (OS) benefit over docetaxel (median, 11.1 *v* 9.8 months; hazard ratio, 0.84; one-sided $P = .0534$), which was consistent across histologies and clinically meaningful in patients nonresponsive to last anti–PD-(L)1–containing regimen. SG had fewer grade ≥3 adverse events (AEs) and AE-related discontinuations versus docetaxel.

Relevance *(T.E. Stinchcombe)*

SG did not demonstrate a statistically significant improvement in OS, and the results of this trial may have implications for other ADCs in development.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

conjugate (ADC) that selectively delivers topoisomerase I inhibitor SN-38, an active metabolite of irinotecan, to cancer cells and the surrounding tumor microenvironment.[8-10] Several ADCs targeting Trop-2 are being investigated in many solid tumors, including NSCLC.[11] SG is currently approved in multiple countries for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received ≥two previous therapies (≥one for metastatic disease) and hormone receptor–positive/human epidermal growth factor receptor 2–negative breast cancer after receipt of ≥two previous therapies, and in the United States to treat urothelial cancer after platinum-based and anti–PD-receptor-1 and/or PD-L1 (anti–PD-(L)1) therapy.

In a phase I/II basket study (IMMU-132-01), patients with heavily pretreated metastatic NSCLC derived durable clinical benefit from SG, with an objective response rate (ORR) of 16.7% (95% CI, 7.9 to 29.3) and median duration of response (DoR) of 6.0 months (95% CI, 2.5 to 21.0).[12] SG was well tolerated with no new safety findings. Here, we provide the primary results of EVOKE-01 (ClinicalTrials.gov identifier: NCT05089734), a global, randomized, open-label, phase III study of SG versus docetaxel in advanced or metastatic NSCLC that progressed on/after platinum-based chemotherapy and anti–PD-(L)1–containing regimen.

METHODS

Patients

Eligible patients were age 18 years and older with pathologically documented NSCLC and measurable stage IV disease[13] that progressed after platinum-based chemotherapy in combination or sequential with an anti–PD-(L)1–containing regimen. Patients with known AGAs must have received treatment with ≥one appropriate tyrosine kinase inhibitor (TKI), reflecting standard clinical practice. *EGFR*, *ALK*, and PD-L1 status were required before enrollment. Patients with stable, previously treated brain metastases (prednisone ≤10 mg maximum per day or equivalent and neurologic symptoms returned to baseline for ≥4 weeks) were also eligible. Additional details are provided in the Protocol (online only).

Study Design and Treatment

Patients were randomly assigned (1:1) with stratification by histology (squamous *v* nonsquamous), best response to last anti–PD-(L)1–containing regimen (investigator-assessed complete or partial response [CR/PR] *v* stable or progressive disease [SD/PD]), and receipt of previous therapy for AGAs (yes *v* no) to receive one 10 mg/kg intravenous infusion of SG on days 1 and 8 or one 75 mg/m^2 intravenous infusion of docetaxel on day 1 of every 21-day cycle. Palliative and/or supportive medications, including routine prophylactic use of growth factors for both groups, were administered per investigator's discretion and were compliant with national/institutional guidelines. Treatment continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met (see the Protocol for additional details).

This study was conducted in accordance with the International Council on Harmonisation Good Clinical Practice Guidelines, the Declaration of Helsinki, and any applicable local health authority and institutional review board/independent ethics committee requirements. All patients

provided written informed consent. The sponsor (Gilead Sciences) designed and conducted the trial and gathered data in collaboration with the study investigators.

End Points and Assessments

The primary end point was overall survival (OS). Secondary efficacy end points were investigator-assessed progression-free survival (PFS), ORR (percentage of patients with confirmed CR or PR), DoR, disease control rate (DCR; percentage of patients with confirmed SD, CR, or PR) as determined by RECIST version 1.1, and safety. Additional secondary end points included symptoms assessed by patient-reported time to deterioration (TTD) in the NSCLC Symptom Assessment Questionnaire (SAQ) shortness-of-breath domain (decline from baseline in one point on a five-point scale) and total score (decline from baseline in two points on a 20-point scale).[14]

Efficacy end points were evaluated by computed tomography or magnetic resonance imaging scans in all patients at screening and every 6 weeks for the first 12 months, and then every 9 weeks thereafter. For patients with known or suspected brain or bone metastases, additional imaging assessments were performed according to the protocol. Length of study follow-up was calculated as time from random assignment to data cutoff at final analysis for each patient in the intention-to-treat (ITT) population, regardless of death. TTD was assessed on day 1 of each cycle before other treatment procedures (Data Supplement, Methods, online only). Safety/tolerability was assessed in all treated patients by Medical Dictionary for Regulatory Activities version 26.1 with severity graded using National Cancer Institute—Common Terminology Criteria for Adverse Events version 5.[15]

Statistical Analyses

The sample size calculation was based on treatment group comparisons with OS as the primary end point. With an anticipated number of approximately 336 death events at final analysis, the study has 90% power to detect a hazard ratio (HR) of 0.7 for SG versus docetaxel at the one-sided alpha of .025.

There was one prespecified interim analysis, and a one-sided alpha of .0075 was spent on the basis of the actual number of death events. The independent data monitoring committee recommended the study continue as planned. The study team remained blinded to the results until final analysis was completed. At final analysis, 355 death events had occurred in the ITT population, and one-sided *P* value boundary for statistical significance of the primary end point was ≤.0223. All reported data are based on the final analysis.

The overall type I error rate was controlled at a one-sided alpha of .025 by implementing a graphical method–based hierarchical testing procedure[16]; secondary end point testing occurred only if the significance boundary was reached in the primary end point, in the order of OS, PFS, ORR, and TTD in shortness-of-breath domain and total score in NSCLC-SAQ. A Lan-DeMets alpha spending function that approximates an O'Brien-Fleming approach was used to account for multiplicity introduced by including an interim analysis for OS.

OS, PFS, and TTD were analyzed using the Kaplan-Meier method, with 95% CIs determined according to the Brookmeyer-Crowley method. Between-treatment group differences were assessed by stratified log-rank test. HRs and associated 95% CIs were estimated by a stratified Cox proportional hazards model. Response rates were compared between groups by the stratified Cochran-Mantel-Haenszel method. Stratification factors used for random assignment were applied to all stratified analyses. Safety was assessed in all patients who received ≥one dose of any study drug. Safety was summarized in each group using descriptive statistics for treatment-emergent AEs (TEAEs; defined as any AEs that began or worsened on/after study drug administration through 30 days after last dose of study drug) unless otherwise specified. Efficacy and TTD were assessed in the ITT population.

RESULTS

Patients and Treatments

Between November 17, 2021, and May 30, 2023, 603 patients with stage IV disease at study entry from 177 sites in 20 countries were randomly assigned to receive SG (n = 299) or docetaxel (n = 304; Fig 1). In total, 296 patients (99.0%) in the SG group and 288 (94.7%) in the docetaxel group received study treatment. Of the 19 patients randomly assigned but not treated, 12 withdrew consent (Fig 1).

Demographic and baseline disease characteristics were balanced between groups and generally consistent with this disease type (Table 1). Overall, patients in the SG and docetaxel groups had a median age of 65 years (range, 31-84), 68.0% were male, and 55.4% had received one previous line of therapy (Table 1). Most patients in both groups had nonsquamous histology (SG, 71.9%; docetaxel, 73.7%), and few (SG, 6.4%; docetaxel, 8.2%) received previous targeted therapy for an AGA because of the requirement of previous anti–PD-(L)1–containing regimen (AGAs summarized in the Data Supplement, Table S1). Patients who were nonresponsive to their last anti–PD-(L)1–containing regimen (investigator-assessed best response of SD/PD) constituted 63.5% of the study population (SG, 64.2%; docetaxel, 62.8%).

With a median study follow-up of 12.7 months (range, 6.0-24.0), the median duration of exposure was 3.45 months (range, 0.03-18.69) for SG (33.4% received SG ≥6 months) and 2.33 months (range, 0.03-19.75) for docetaxel (17.4% received docetaxel ≥6 months). Median relative dose

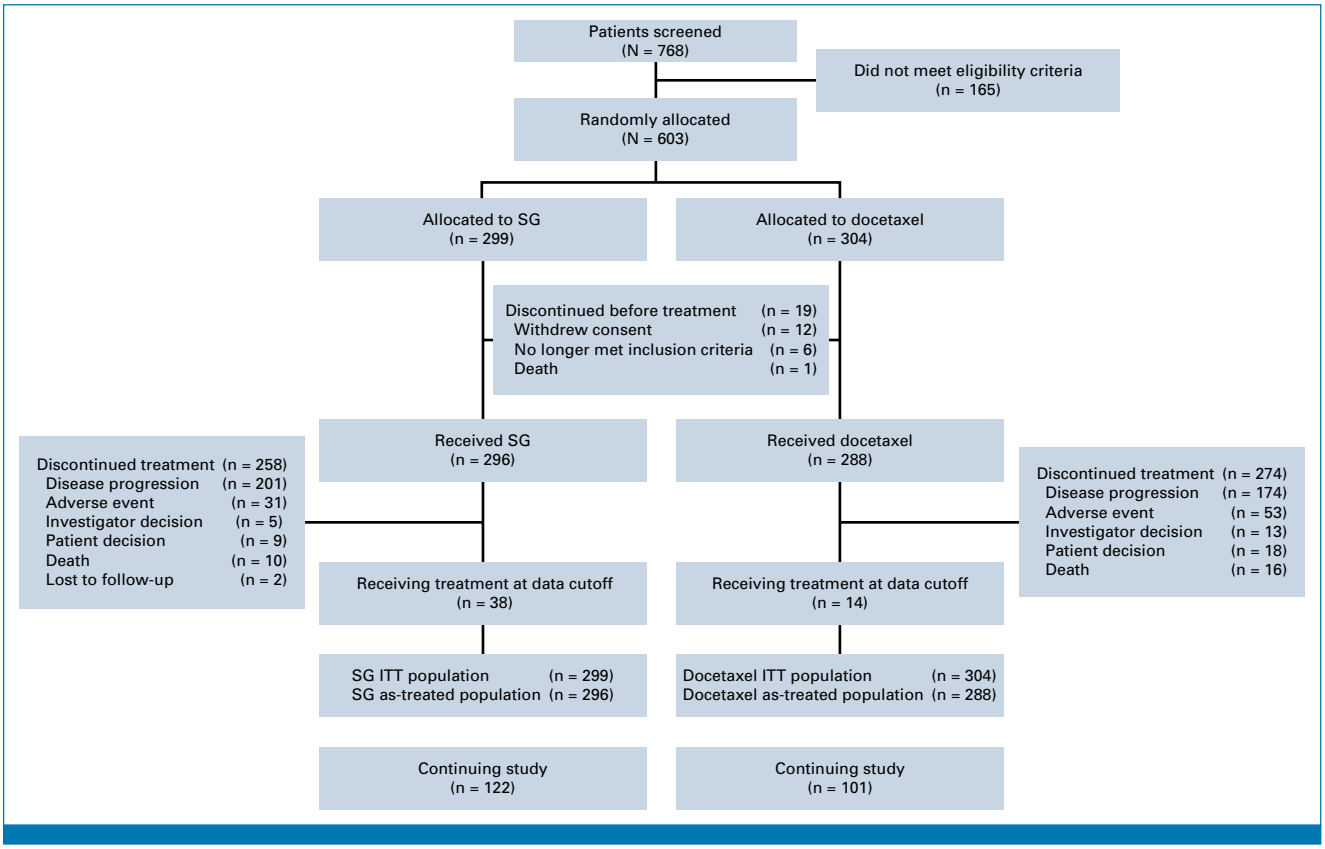


FIG 1. Patient disposition: CONSORT diagram. ITT, intention-to-treat; SG, sacituzumab govitecan.

intensity (percentage of total amount of study drug administered relative to the total amount of study drug expected to be administered while on treatment) was 98.4% for SG and 98.3% for docetaxel. At data cutoff, 122 (40.8%) and 101 (33.2%) patients in the SG and docetaxel groups, respectively, remained on study. Among the 52 patients (8.6%) who remained on study drug, more remained in the SG group (12.7% *v* docetaxel, 4.6%; Fig 1). The most common reason for discontinuation of study treatment was PD in both groups (SG, 201 [67.2%]; docetaxel, 174 [57.2%]; Fig 1).

Efficacy

Efficacy in the ITT Population

At the protocol-specified primary analysis, the study did not meet statistical significance for the primary end point of OS. A numerical improvement in median OS was observed with SG (11.1 months [95% CI, 9.4 to 12.3]) versus docetaxel (9.8 months [95% CI, 8.1 to 10.6]), with a 16% reduction in risk of death numerically favoring SG versus docetaxel (HR, 0.84 [95% CI, 0.68 to 1.04]; one-sided $P = .0534$; Fig 2A and Table 2). The 12-month OS rate was 46.59% (95% CI, 40.45 to 52.50) and 36.72% (95% CI, 30.88 to 42.57) for SG and docetaxel groups, respectively. OS results were consistent in most predefined subgroups (Fig 2B), including squamous (HR, 0.83 [95% CI, 0.56 to 1.22]) and nonsquamous (HR, 0.87 [95% CI, 0.68 to 1.11]) histologies. In the ITT population, 37.8% of patients in the SG group received subsequent anticancer therapy (most commonly docetaxel), and 31.3% in the docetaxel group received subsequent anticancer therapy (most commonly single-agent gemcitabine or vinorelbine; Data Supplement, Table S2).

Median PFS was 4.1 months (95% CI, 3.0 to 4.4) with SG and 3.9 months (95% CI, 3.1 to 4.2) with docetaxel (HR, 0.92 [95% CI, 0.77 to 1.11]; Fig 3A and Table 2). Median PFS with SG was similar among patients with squamous (3.8 months [95% CI, 2.8 to 5.4]) and nonsquamous (4.1 months [95% CI, 2.9 to 5.3]) histologies (Data Supplement, Fig S1). The 6-month PFS rate was 33.71% (95% CI, 28.21 to 39.28) in the SG group and 31.39% (95% CI, 25.75 to 37.17) in the docetaxel group.

ORR was 13.7% (95% CI, 10.0 to 18.1) with SG and 18.1% (95% CI, 13.9 to 22.9) with docetaxel (difference of −4.3% [95% CI, −10.1 to 1.5]; Table 2). Median DoR was 6.7 months (95% CI, 4.4 to 9.8) with SG and 5.8 months (95% CI, 4.1 to 8.3) with docetaxel (Table 2). DCR was 67.6% (95% CI, 61.9 to 72.8) in the SG group and 67.1% (95% CI, 61.5 to 72.4) in the docetaxel group (Table 2).

Efficacy on the Basis of Best Response to Last Anti–PD-(L)1–Containing Regimen

A clinically meaningful improvement in OS was observed in patients who were nonresponsive (SD/PD) to their last

TABLE 1. Patient Baseline Characteristics and Demographics

Characteristic	SG (n = 299)	Docetaxel (n = 304)
Age, years, median (range)	66 (31-84)	64 (32-83)
<65, No. (%)	136 (45.5)	161 (53.0)
≥65, No. (%)	163 (54.5)	143 (47.0)
Sex, No. (%)		
Male	194 (64.9)	216 (71.1)
Female	105 (35.1)	88 (28.9)
Race or ethnic group, No. (%)		
White	229 (76.6)	216 (71.1)
Black	6 (2.0)	7 (2.3)
Asian	17 (5.7)	26 (8.6)
Other/not specified[a]	47 (15.7)	55 (18.1)
ECOG PS,[b] No. (%)		
0	101 (33.8)	89 (29.3)
1	198 (66.2)	212 (69.7)
2[c]	0	1 (0.3)
Histology, No. (%)		
Nonsquamous[d]	215 (71.9)	224 (73.7)
Squamous	84 (28.1)	80 (26.3)
Disease stage at diagnosis,[e] No. (%)		
Stage I-III	76 (25.4)	102 (33.6)
Stage IV	219 (73.2)	202 (66.4)
Patients with brain metastasis, No. (%)	35 (11.7)	39 (12.8)
Previous lines of therapy, No. (%)		
1	167 (55.9)	167 (54.9)
2	103 (34.4)	101 (33.2)
≥3	29 (9.7)	36 (11.8)
Best response to last anti–PD-(L)1–containing regimen,[f] No. (%)		
Responder (CR/PR)	106 (35.5)	113 (37.2)
Nonresponder (SD/PD)	192 (64.2)	191 (62.8)
Not available	1 (0.3)	0
Previous therapy for AGA, No. (%)		
Yes	19 (6.4)	25 (8.2)
EGFR alteration[g]	6 (2.0)	13 (4.3)
ALK alteration[g]	1 (0.3)	1 (0.3)
No	280 (93.6)	279 (91.8)

Abbreviations: AGA, actionable genomic alteration; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan.

[a]Other races included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and other.

[b]ECOG PS was missing for two patients in the docetaxel group.

[c]ECOG PS = 2 for one patient in the docetaxel group on cycle 1, day 1.

[d]Histologies not otherwise specified were included in the nonsquamous subgroup.

[e]Disease stage at diagnosis was missing for four patients in the SG group.

[f]Response to previous anti–PD-(L)1–containing regimen was per investigator assessment.

[g]Patients with multiple types of AGA were counted once for each type; more genes shown in the Data Supplement (Table S1).

anti–PD-(L)1–containing regimen. Median OS was 11.8 months (95% CI, 9.6 to 12.5) with SG and 8.3 months (95% CI, 7.0 to 10.6) with docetaxel (HR, 0.75 [95% CI, 0.58 to 0.97]; Fig 2C). In patients who were responsive to previous anti–PD-(L)1–containing regimen (CR/PR), the OS HR was 1.09 (95% CI, 0.76 to 1.56; Fig 2D). Baseline demographics and characteristics and use of subsequent therapy were similar between groups (Data Supplement, Tables S2 and S3). Results were consistent across histologies (squamous: HR, 0.62 [95% CI, 0.38 to 1.02]; nonsquamous: HR, 0.79 [95% CI, 0.59 to 1.07]; Figs 3B and 3C).

Patient-Reported Disease-Related Symptoms

NSCLC-SAQ TTD in shortness-of-breath and total score were key secondary end points. The NSCLC-SAQ completion rate was ≥88.4% in SG and ≥93.7% in docetaxel through week 25 and was generally comparable across treatment groups. Median TTD was longer for SG versus docetaxel for NSCLC-SAQ shortness-of-breath domain (2.8 *v* 2.1 months; HR, 0.75 [95% CI, 0.61 to 0.91]; Data Supplement, Fig S2A) and total score (3.1 *v* 2.7 months; HR, 0.80 [95% CI, 0.66 to 0.97]; Data Supplement, Fig S2B), and this difference was sustained over the observed time period.

Safety

In the safety analysis set, any-grade TEAEs occurred in 295/296 patients (99.7%) in the SG group and 282/288 patients (97.9%) in the docetaxel group (Table 3). The incidence of grade ≥3 TEAEs was lower with SG than docetaxel (66.6% *v* 75.7%). TEAEs reported by a higher proportion (≥5% difference) of patients in the SG versus docetaxel group were diarrhea, alopecia, nausea, anemia, constipation, vomiting, pruritus, and abdominal pain; only diarrhea, nausea, and abdominal pain (n = 1 each) led to SG discontinuation. TEAEs reported by a higher proportion (≥5% difference) of patients in the docetaxel group were neutropenia, stomatitis, leukopenia, peripheral edema, dysgeusia, and peripheral neuropathy; neutropenia (n = 3), peripheral edema (n = 2), and peripheral neuropathy (n = 1) led to docetaxel discontinuation.

TEAEs leading to dose reductions occurred in 87 (29.4%) patients in the SG group and 112 (38.9%) in the docetaxel group. The proportion of patients with TEAEs leading to study treatment discontinuation was lower with SG (n = 29, 9.8%) than docetaxel (n = 48, 16.7%). TRAEs leading to treatment discontinuation occurred in 20 (6.8%) and 41 (14.2%) patients in the SG and docetaxel groups, respectively. There were seven deaths from TEAEs that were considered treatment-related by investigators: four SG patients (one each: febrile neutropenia, neutropenic colitis, sepsis, and septic shock) and three docetaxel patients (one each: unknown cause, pneumonia, and pneumonitis).

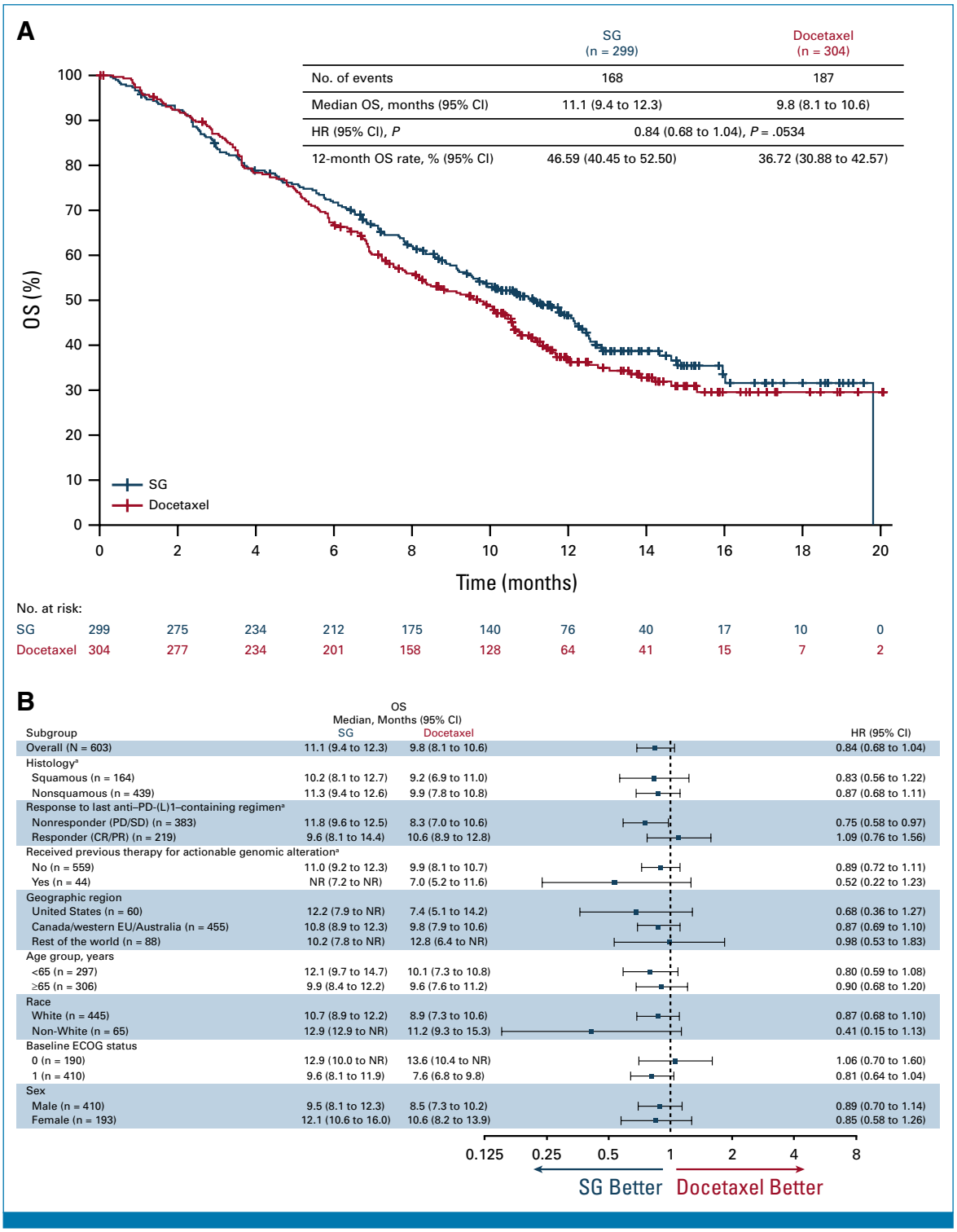


FIG 2. OS. (A) OS in the intention-to-treat population (all randomly assigned patients). The HR and 95% CIs were calculated using the Cox proportional hazards model, adjusted for randomization stratification factors of histology and best response to last anti–PD-(L)1–containing regimen received. One-sided *P* value derived from the stratified log-rank test. (B) Subgroup analysis of OS. HR and 95% CIs for subgroup analysis are calculated using the unstratified Cox proportional hazards model without adjustment. Not otherwise specified histology is combined with nonsquamous. (C) OS in patients nonresponsive (SD/PD) to last anti–PD-(L)1–containing regimen. (D) OS in patients responsive (CR/PR) to last previous anti–PD-(L)1–containing regimen. The HRs and 95% CIs for the subgroup analyses were calculated using the unstratified Cox proportional hazards model without any adjustment. [a]Randomization stratification factors. CR, complete response; ECOG, Eastern Cooperative Oncology Group; EU, European Union; HR, hazard ratio; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan. (continued on following page)

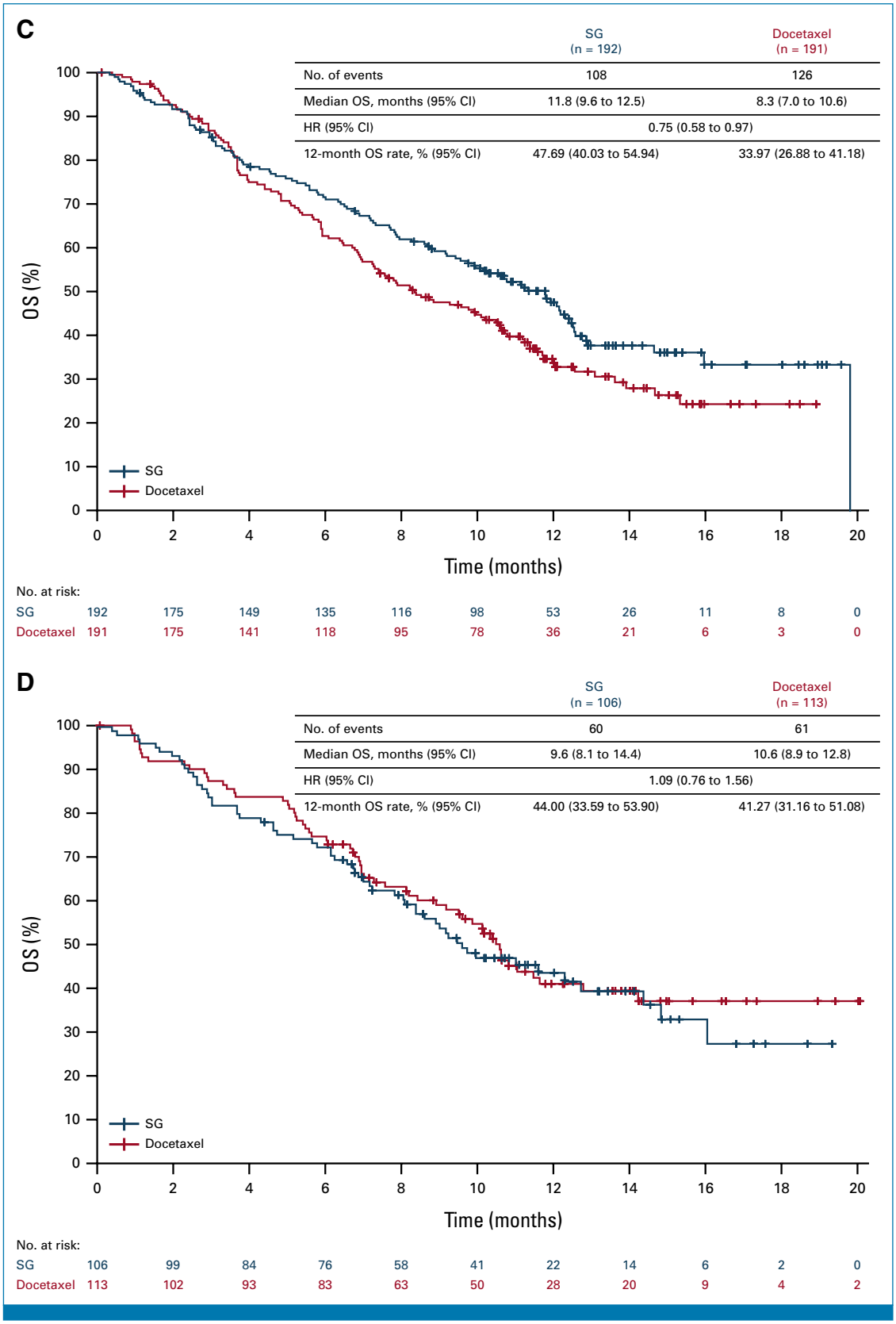


FIG 2. (Continued).

TABLE 2. Summary of Treatment Efficacy

Variable	SG (n = 299)	Docetaxel (n = 304)
OS, months, median (95% CI)	11.1 (9.4 to 12.3)	9.8 (8.1 to 10.6)
HR for death (95% CI), one-sided *P*[a]	0.84 (0.68 to 1.04), .0534	
OS in patients nonresponsive (SD/PD) to last anti–PD-(L)1 regimen, months, median (95% CI)	11.8 (9.6 to 12.5)	8.3 (7.0 to 10.6)
HR for death (95% CI)	0.75 (0.58 to 0.97)	
OS in patients responsive (CR/PR) to last anti–PD-(L)1 regimen, months, median (95% CI)	9.6 (8.1 to 14.4)	10.6 (8.9 to 12.8)
HR for death (95% CI)	1.09 (0.76 to 1.56)	
PFS (95% CI), months, median (95% CI)	4.1 (3.0 to 4.4)	3.9 (3.1 to 4.2)
HR for disease progression[b] or death (95% CI)	0.92 (0.77 to 1.11)	
ORR,[b,c] No. (%)	41 (13.7)	55 (18.1)
CR	0	3 (1.0)
PR	41 (13.7)	52 (17.1)
SD	161 (53.8)	149 (49.0)
PD	66 (22.1)	64 (21.1)
Not evaluable/not assessed	31 (10.4)	36 (11.8)
DCR,[d] No. (%)	202 (67.6)	204 (67.1)
DoR,[e] months, median (95% CI)	6.7 (4.4 to 9.8)	5.8 (4.1 to 8.3)
DoR rate at 6 months[e,f]	52.5 (35.6 to 66.9)	46.5 (31.9 to 59.8)

Abbreviations: CR, complete response; DCR, disease control rate; DoR, duration of response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; v1.1, version 1.1.

[a]On the basis of stratified log-rank test (two-sided $P = .1068$).

[b]Investigator-assessed per RECIST v1.1.

[c]Patients without tumor assessment (SG, n = 28; docetaxel, n = 35), response defined as best overall response of confirmed CR + PR; not formally tested.

[d]Disease control defined best overall response of confirmed CR, PR, or SD as assessed by the investigator per RECIST v1.1.

[e]Evaluated in patients with confirmed CR or PR.

[f]On the basis of Kaplan-Meier estimates.

DISCUSSION

There is an unmet medical need for safe and effective treatment options that prolong survival in patients with metastatic NSCLC who progressed on/after platinum-based chemotherapy and combination/sequential anti–PD-(L)1–containing regimen. EVOKE-01 is one of the first ADC studies in this setting. Although the study did not meet protocol-specified statistical significance for the primary end point of OS, SG treatment resulted in a 16% reduction in risk of death versus docetaxel in the ITT population and was associated with a numerically higher OS rate at all prespecified landmark time points. OS is an objective end point less subject to assessment bias than PFS.[17] There were fewer high-grade TEAEs and TEAEs leading to dose reduction and/or discontinuation with SG than docetaxel; more patients remained on SG than docetaxel at final analysis. Importantly, patients reported longer TTD in NSCLC-SAQ symptoms with SG treatment.

Despite recent advances with immune checkpoint inhibitors for earlier-line NSCLC, most patients have disease that eventually progresses. Docetaxel with/without nintedanib/ramucirumab have been investigated in this setting, but both are associated with modest efficacy and significant AEs affecting patient QoL.[18-20] In the REVEL study, ramucirumab plus docetaxel improved OS versus docetaxel monotherapy in patients previously treated with platinum doublet chemotherapy but not anti–PD-(L)1.[20] With the modest OS improvement from addition of ramucirumab to docetaxel (median, 10.5 months) versus docetaxel (median, 9.1 months; HR, 0.86 [95% CI, 0.75 to 0.98]; $P = .023$), docetaxel monotherapy is the globally accepted comparator for NSCLC studies in this setting.[20] In EVOKE-01, docetaxel performed as expected. However, a delayed separation between OS Kaplan-Meier curves was observed, starting at approximately 4 months and thereafter favoring SG over docetaxel. At 12 months, the OS rate for patients with SG was approximately 10% higher than with docetaxel. Subsequent therapies were consistent with the standard of care in both treatment groups, and the OS benefit in the SG group was maintained in a sensitivity analysis censoring patients who received subsequent docetaxel. Other underlying biologic factors pertaining to this observation remain to be determined.

As response to anti–PD-(L)1 treatment has prognostic impact on OS,[21] best response to last anti–PD-(L)1–containing regimen was selected as a stratification factor. Treatment of patients progressing on anti–PD-(L)1 therapy remains

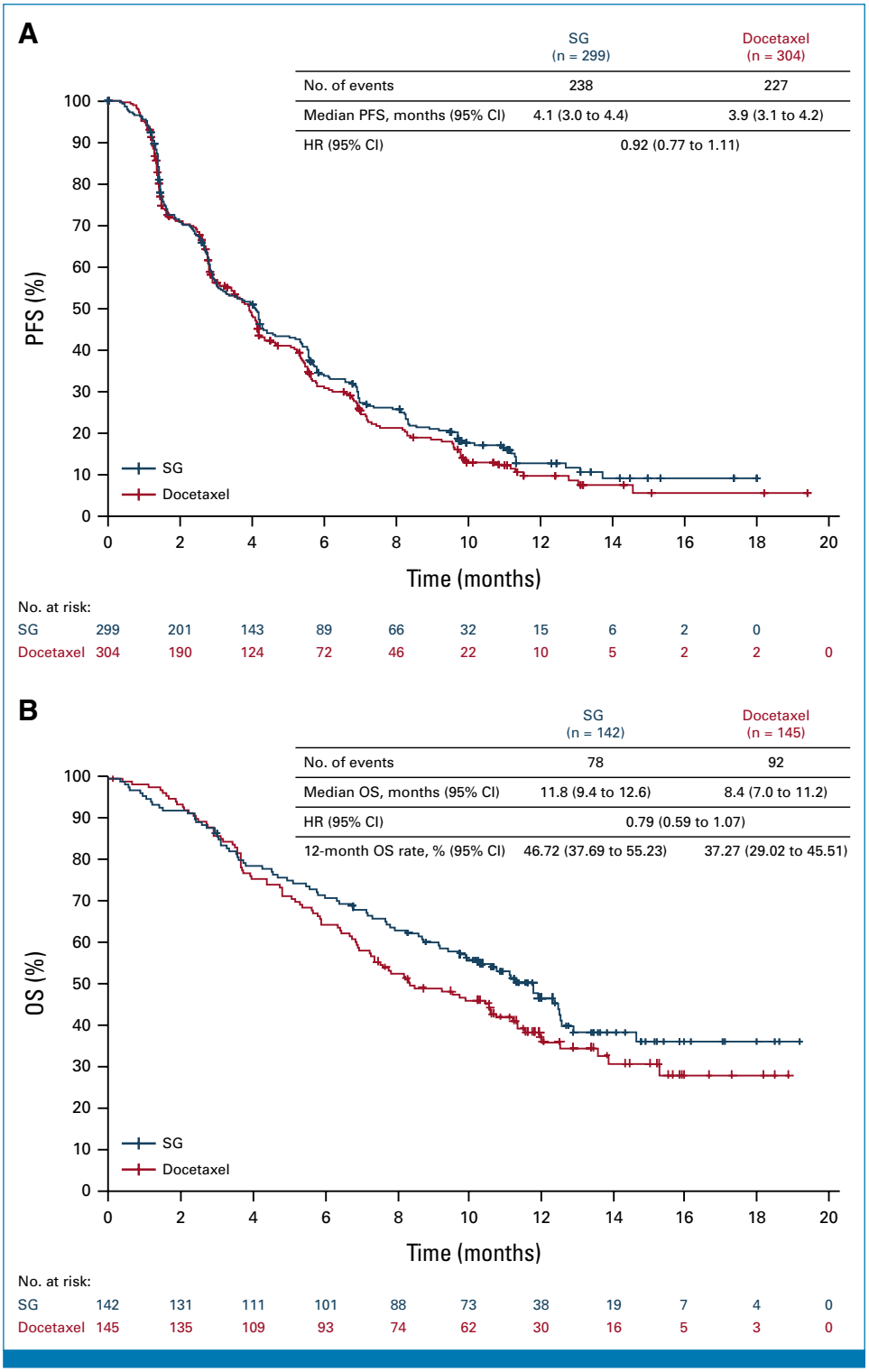


FIG 3. PFS in the ITT population and OS in patients with SD/PD to last anti–PD-(L)1–containing regimen by histology. (A) PFS in the ITT population (all randomly assigned patients). The HR and 95% CIs for PFS were calculated using the Cox proportional hazards model, adjusted for randomization stratification factors of histology and best response to last anti–PD-(L)1–containing regimen received. (B) OS in patients with SD/PD to last anti–PD-(L)1–containing regimen and nonsquamous NSCLC. (C) OS in patients with SD/PD to last anti–PD-(L)1–containing regimen and squamous NSCLC. The HR and 95% CIs for subgroup analyses were calculated using the unstratified Cox proportional hazards model without any adjustment. Histology not otherwise specified is combined with nonsquamous. HR, hazard ratio; ITT, intention-to-treat; NSCLC, non–small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; SD, stable disease; SG, sacituzumab govitecan. (continued on following page)

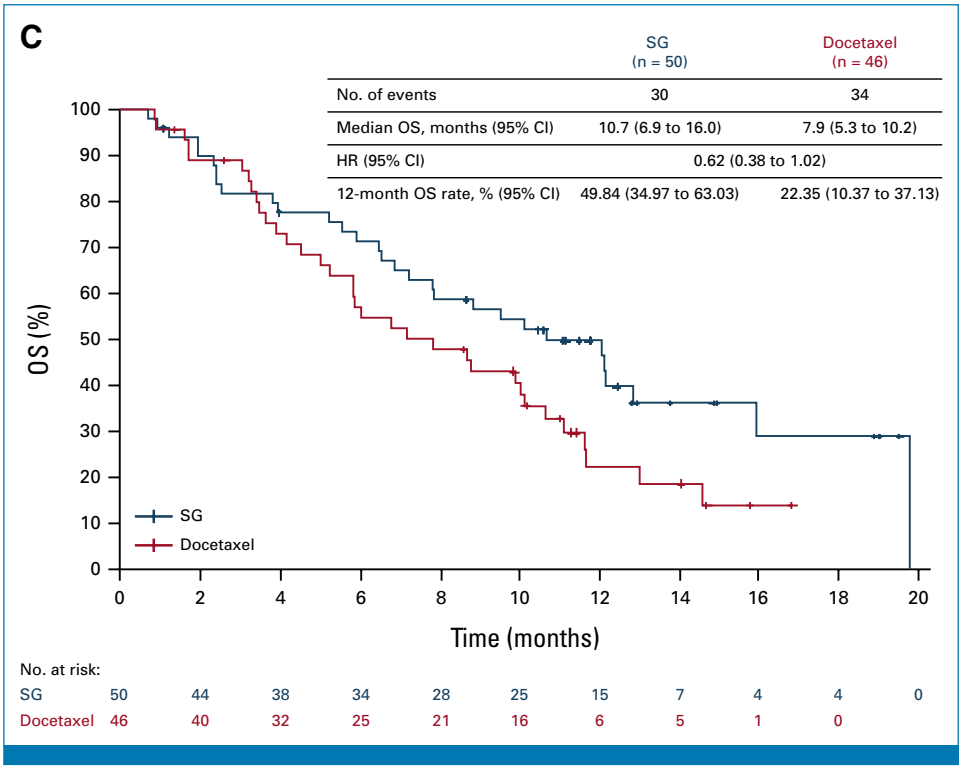


FIG 3. (Continued).

challenging, and multiple recent studies involving novel immunomodulatory agents, such as canakinumab, and studies with multitargeted TKIs with continued anti–PD-(L)1 therapy have failed to improve OS over docetaxel.[4,22] These failures largely stem from the heterogeneity of patient populations and that the mechanism of innate and acquired resistance to anti–PD-(L)1–containing therapy is not well understood. In the first-line setting, only about 30% to 60% of patients achieve objective response to immune therapy alone or combined with chemotherapy.[23-26] Herein, a clinically meaningful 3.5-month OS improvement was observed favoring SG over docetaxel, with 25% reduction in risk of death in patients who were nonresponsive to their last anti–PD-(L)1–containing regimen. Best response to previous anti–PD-(L)1–containing regimen was investigator-assessed. These patients represent a population with the highest unmet medical need, and the OS improvement observed suggests that SG is a potential treatment option in this population. Importantly, the OS difference in this subgroup was consistent across squamous and nonsquamous histologies.

Trop-2 is highly expressed in both squamous and nonsquamous NSCLC,[27] making it a good target for safe and effective delivery of cytotoxic payloads. Despite an identical target, the individual constructs of Trop-2–directed ADCs, including the linker and payload, determine the therapeutic index and individual safety and efficacy of each. Recently, datopotamab deruxtecan, another Trop-2–directed ADC, demonstrated PFS improvement versus docetaxel in patients with previously treated metastatic NSCLC; however, no OS improvement has been reported to date as a final analysis has yet to be reported.[5,28] The benefit of datopotamab deruxtecan seems to be limited to patients with nonsquamous histology.[5] By contrast, in EVOKE-01, the numerical improvement in OS with SG over docetaxel was observed in all clinically relevant subgroups, including squamous and nonsquamous histologies. The numerical improvement in OS with SG in both histologies was more pronounced in patients who were nonresponsive to their last anti–PD-(L)1–containing regimen. Studies of Trop-2 as a possible biomarker are ongoing and will be reported.

In EVOKE-01, SG was better tolerated than docetaxel. The incidence of high-grade TEAEs and TEAEs leading to discontinuation were lower with SG than docetaxel, and median duration of exposure to SG was longer. SG demonstrated a manageable safety profile, consistent with what is known,[12,29,30] with no new safety signals. The incidence of high-grade fatigue and diarrhea was higher with SG, while the incidence of high-grade neutropenia, dyspnea, stomatitis, and leukopenia was higher with docetaxel. SG-associated risks were adequately managed through monitoring and dose modification guidance per prescribing information.[31] This is further supported by improvements in patient-reported TTD of NSCLC-related symptoms, which are reflective of tolerability and better disease control.

TABLE 3. Summary of Treatment-Emergent Adverse Events in All Treated Patients

	SG (n = 296), No. (%)		Docetaxel (n = 288), No. (%)	
Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TEAEs[a,b]	295 (99.7)	197 (66.6)	282 (97.9)	218 (75.7)
TEAEs reported in ≥10% in either group[c]				
Fatigue	168 (56.8)	37 (12.5)	161 (55.9)	28 (9.7)
Diarrhea	156 (52.7)	31 (10.5)	97 (33.7)	11 (3.8)
Alopecia	128 (43.2)	2 (0.7)	86 (29.9)	2 (0.7)
Nausea	123 (41.6)	5 (1.7)	75 (26.0)	3 (1.0)
Anemia	119 (40.2)	19 (6.4)	89 (30.9)	17 (5.9)
Neutropenia	111 (37.5)	73 (24.7)	123 (42.7)	106 (36.8)
Constipation	86 (29.1)	0	49 (17.0)	1 (0.3)
Decreased appetite	78 (26.4)	7 (2.4)	69 (24.0)	6 (2.1)
Vomiting	62 (20.9)	7 (2.4)	43 (14.9)	6 (2.1)
Cough	46 (15.5)	0	45 (15.6)	1 (0.3)
Dyspnea	42 (14.2)	4 (1.4)	51 (17.7)	13 (4.5)
Stomatitis	39 (13.2)	3 (1.0)	58 (20.1)	7 (2.4)
Leukopenia	38 (12.8)	15 (5.1)	63 (21.9)	50 (17.4)
Pruritus	37 (12.5)	1 (0.3)	11 (3.8)	0
Pyrexia	37 (12.5)	2 (0.7)	34 (11.8)	2 (0.7)
Back pain	33 (11.1)	2 (0.7)	19 (6.6)	2 (0.7)
Abdominal pain	31 (10.5)	3 (1.0)	14 (4.9)	0
Arthralgia	30 (10.1)	2 (0.7)	29 (10.1)	1 (0.3)
Rash	30 (10.1)	0	19 (6.6)	0
Febrile neutropenia	23 (7.8)	23 (7.8)	29 (10.1)	27 (9.4)
Lymphopenia	23 (7.8)	9 (3.0)	31 (10.8)	12 (4.2)
Peripheral edema	16 (5.4)	0	35 (12.2)	4 (1.4)
Dysgeusia	14 (4.7)	0	30 (10.4)	0
Peripheral neuropathy	11 (3.7)	0	38 (13.2)	2 (0.7)
Treatment-related[c]	279 (94.3)	156 (52.7)	262 (91.0)	173 (60.1)
TEAEs leading to discontinuation	29 (9.8)		48 (16.7)	
Treatment-related[c]	20 (6.8)		41 (14.2)	
TEAEs leading to death	10 (3.4)		13 (4.5)	
Treatment-related[d]	4 (1.4)		3 (1.0)	
TEAEs leading to dose reduction	87 (29.4)		112 (38.9)	
TEAEs leading to treatment interruption	171 (57.8)		81 (28.1)	

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

[a]TEAE is any AE with an onset date on or after the study drug start date and no later than 30 days after last dose of study drug.

[b]Coded according to MedDRA version 26.1 and AE severity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Multiple AEs were counted only once per participant for the highest severity grade for each preferred term.

[c]Determined by investigator.

[d]Treatment-related TEAEs that led to death, investigator-assessed, included cardiac failure, cerebrovascular accident, death, febrile neutropenia, hematemesis, ischemic stroke, myocardial ischemia, neutropenic colitis, sepsis, and septic shock (one each) in the SG group and death (n = 4), pneumonia (n = 3), cardiac failure, acute respiratory failure, cardiorespiratory arrest, intestinal obstruction, pneumonitis, and respiratory failure (one each) in the docetaxel group.

Although EVOKE-01 did not meet statistical significance for the primary end point, SG is an active therapeutic agent in metastatic NSCLC that conferred modest numerical OS benefit over docetaxel in the ITT population. A numerical OS benefit was also observed in the subgroup of patients who were nonresponsive to last anti–PD-(L)1–containing regimen. Patients with metastatic NSCLC still need novel treatment options, and these data support further investigation of SG in this patient population. A phase II study evaluating SG with

pembrolizumab with/without platinum-based chemotherapy in previously untreated metastatic NSCLC lacking AGAs (EVOKE-02; ClinicalTrials.gov identifier: NCT05186974) and a phase III study evaluating SG plus pembrolizumab versus pembrolizumab monotherapy in first-line PD-L1–high metastatic NSCLC (EVOKE-03; ClinicalTrials.gov identifier: NCT05609968) are underway.[32,33]

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DATA SHARING STATEMENT

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers on the basis of submitted curriculum vitae and reflecting no conflict of interest. The requested proposal must also include a statistician. Approval of such requests is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Sacituzumab Govitecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non–Small Cell Lung Cancer: The Randomized, Open-Label Phase III EVOKE-01 Study

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Consulting or Advisory Role: Bristol Myers Squibb, MSD, AstraZeneca, Novartis, Takeda, Roche, Sanofi, Celgene, Daiichi Sankyo, Pfizer, Seagen, Lilly, GlaxoSmithKline, Bayer, Blueprint Medicines, Janssen, Regeneron, AbbVie, Mirati Therapeutics, Merck, Boehringer Ingelheim, Abion, Gilead Sciences
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Travel, Accommodations, Expenses: Pfizer, Roche, AstraZeneca, Merck
Uncompensated Relationships: Merck

No other potential conflicts of interest were reported.

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APPENDIX

TABLE A1. List of EVOKE-01 Study Principal Investigators

Country	Study Investigator
Australia	Elizabeth Ahern
Australia	Venessa Chin
Australia	Stephen Della-Fiorentina
Australia	Kevin Jasas
Australia	Christos Karapetis
Australia	Jeremy Long
Australia	Louise Nott
Australia	Kenneth O'Byrne
Australia	Craig Underhill
Austria	Richard Greil
Austria	Maximilian Hochmair
Austria	Andreas Pircher
Belgium	Wim Demey
Belgium	Paul Germonpré
Belgium	Elke Govaerts
Belgium	Thierry Pieters
Belgium	Reinier Wener
Brazil	Alan Azambuja
Brazil	Giuliano Borges
Brazil	Gilberto Castro
Brazil	Suellen Castro
Brazil	Felipe Cruz
Brazil	Fábio Franke
Brazil	Eduardo Silva
Canada	Parneet Cheema
Canada	Robert El-Maraghi
Canada	Swati Kulkarni
Canada	Rami Nassabein
Canada	Scott Owen
France	Clarisse Audigier Valette
France	Jaafar Bennouna
France	Christos Chouaid
France	Alexis Cortot
France	Sebastien Couraud
France	Didier Debieuvre
France	Fabrice Denis
France	Patrick Dumont
France	Radj Gervais
France	Nicolas Girard
France	Etienne Giroux Leprieur
France	Florian Guisier
France	Sandrine Hiret
France	Henri Janicot
France	Corinne Lamour
France	Jeannick Madelaine

(continued in next column)

TABLE A1. List of EVOKE-01 Study Principal Investigators (continued)

Country	Study Investigator
France	Marie Marcq
France	Emilie Pluquet
France	Jean Louis Pujol
France	Magali Ravoire
France	Marielle Sabatini
France	Alain Vergnenegre
Germany	Sabine Bohnet
Germany	Martin Faehling
Germany	Melanie Janning
Germany	Eckart Laack
Germany	Niels Reinmuth
Germany	Achim Rittmeyer
Germany	Claas Wesseler
Greece	Sofia Baka
Greece	George Fountzilas
Greece	Panagiotis Katsaounis
Greece	Athanasios Kotsakis
Greece	Ioannis (Giannis) Mountzios
Greece	Konstantinos Syrigos
Israel	Julia Dudnik
Israel	Carmel Fink
Israel	Ofer Merimsky
Israel	Hovav Nechushtan
Israel	Julia Sobolev
Italy	Franceso Agustoni
Italy	Anna Cecilia Bettini
Italy	Matteo Brighenti
Italy	Giulio Cerea
Italy	Filippo De Marinis
Italy	Salvatore Grisanti
Italy	Francesco Grossi
Italy	Andrea Luciani
Italy	Evaristo Maiello
Italy	Hector Soto Parra
Italy	Pierfrancesco Tassone
Italy	Giuseppe Tonini
Japan	Yoko Agemi
Japan	Koichi Azuma
Japan	Tomohisa Baba
Japan	Yuka Fujita
Japan	Eiki Ichihara
Japan	Takashi Kasai
Japan	Terufumi Kato
Japan	Haruki Kobayashi
Japan	Shoichi Kuyama

(continued on following page)

TABLE A1. List of EVOKE-01 Study Principal Investigators (continued)

Country	Study Investigator
Japan	Kazumi Nishino
Japan	Masahide Oki
Japan	Kyoichi Okishio
Japan	Tomohiro Sakamoto
Japan	Yuki Sato
Japan	Yuki Shinno
Japan	Takayuki Takahama
Japan	Koichi Takayama
Japan	Yasutaka Watanabe
Japan	Noriko Yanagitani
Japan	Yoshitaka Zenke
Mexico	Daniel Motola Kuba
Mexico	Tomas Daniel Pineda Razo
The Netherlands	Robin Cornelissen
The Netherlands	Lizza Hendriks
The Netherlands	Jeroen Kloover
The Netherlands	Klaar Maas
The Netherlands	Cor van der Leest
Poland	Lubomir Bodnar
Poland	Boguslawa Karaszewska
Poland	Andrzej Mruk
Portugal	Paula Alves
Portugal	Antonio Araujo
Portugal	Isabel Domingues
Portugal	Ana da Conceicao Fernandes Rodrigues
Portugal	Nuno Gil
Portugal	Helena Magalhaes
Portugal	Barbara Parente
Puerto Rico	Marcia Correa
Puerto Rico	Hector Velez-Cortes
Spain	Andres Aguilar Hernandez
Spain	Ruben Alonso Calderon
Spain	Joaquim Barrera
Spain	David Baz
Spain	Antonio Calles
Spain	Maria Campelo
Spain	Francisco Carpeno
Spain	Enric Costa
Spain	Manuel Dols
Spain	Manuel Domine Gomez
Spain	Miguel Fernandez de Sanmamed
Spain	Enriqueta Felip Font
Spain	Jose Fuentes
Spain	Maria Pilar Garrido Lopez
Spain	Oscar Juan Vidal
Spain	Jose Larriba
Spain	Laia Martinez
Spain	Ramon Palmero Sanchez
Spain	Luis Paz-Ares
Spain	Silverio Ros Martinez
Spain	Jon Zugazagoitia Fraile
Turkey	Ahmet Bilici
Turkey	Irfan Cicin
Turkey	Umut Demirci
Turkey	Yesim Eralp
Turkey	Mahmut Gumus
Turkey	Ozan Yazici
The United Kingdom	Shobhit Baijal
The United Kingdom	Katy Clarke
The United Kingdom	Farah Lim
The United Kingdom	Dakshinamoorthy Muthukumar
The United Kingdom	Nicola Steele
The United Kingdom	Yvonne Summers
The United States of America	Ahmed Abdelaziz
The United States of America	Eric Avery
The United States of America	Firas Badin
The United States of America	Charles Connor
The United States of America	Davey Daniel
The United States of America	Amir Faridi
The United States of America	January Fields-Meehan
The United States of America	Marina Garassino
The United States of America	Todd Gersten
The United States of America	Daniel Haggstrom
The United States of America	David Hakimian
The United States of America	William Houck
The United States of America	Henrik Illum
The United States of America	Roger Keresztes
The United States of America	Charles Kurkul
The United States of America	Charles Kuzma
The United States of America	Rachel Lerner
The United States of America	Steven Liu
The United States of America	Smitha Menon
The United States of America	Rami Owera
The United States of America	Vipul Patel
The United States of America	Ivor Percent
The United States of America	Andrew Piper
The United States of America	Sucharu Prakash
The United States of America	Douglas Reznick
The United States of America	Jorge Rios-Perez
The United States of America	Jun Sun
The United States of America	Restituto Tibayan
The United States of America	Anne Traynor
The United States of America	William Walsh
The United States of America	Donald Wender

(continued in next column)

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