Sacituzumab Govitecan as Second-Line Treatment in Patients With Extensive-Stage Small Cell Lung Cancer

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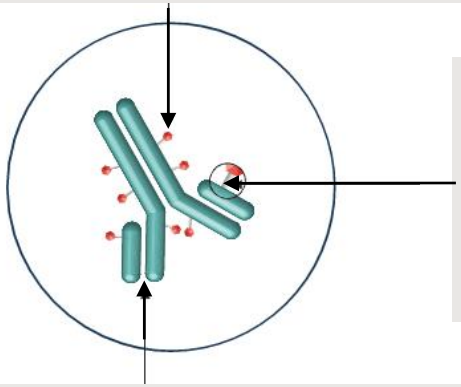
Background

- Treatment options for patients with relapsed SCLC are limited[1]
- Sacituzumab govitecan (SG) is a first-in-class Trop-2–directed ADC approved globally for 2L+ mTNBC and 2L+ HR+/HER2− mBC and approved in the US for 2L mUC via an accelerated approval program[2,3]

SN-38 payload

- SN-38 is more potent than the parent compound, irinotecan (Topo-1 inhibitor)
- SN-38 is rapidly internalized and efficiently released to the tumor with minimized effect on healthy tissues



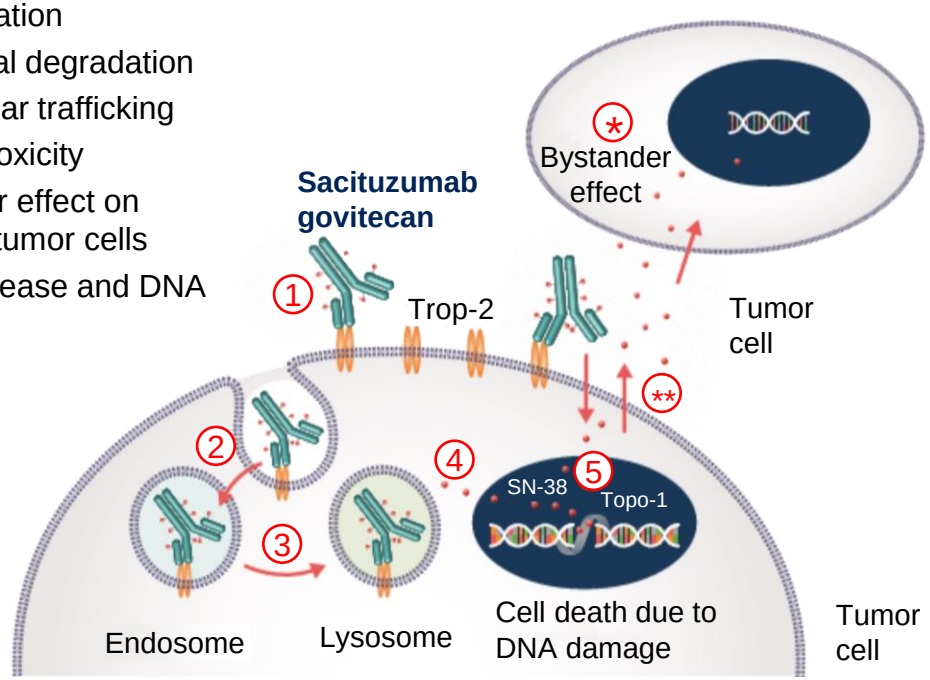
Linker for SN-38

- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)[4]

Humanized anti–Trop-2 antibody

- Binds with high (K_D = 0.3 nM) affinity to Trop-2, an epithelial antigen expressed on many solid tumors[5]

① Binding
② Internalization
③ Lysosomal degradation
④ Intracellular trafficking
⑤ Cell cytotoxicity
* Bystander effect on adjacent tumor cells
** SN-38 release and DNA damage



2L, second-line; **ADC**, antibody-drug conjugate; **HER2−**, human epidermal growth factor receptor 2-negative; **HR+,** hormone receptor-positive; **mBC**, metastatic breast cancer; **mTNBC**, metastatic triple-negative breast cancer; **mUC**, metastatic urothelial cancer; **SCLC**, small cell lung cancer; **Topo-1**, topoisomerase-1; **Trop-2**, trophoblast cell surface antigen 2; **US**, United States.

1. Dingemans AC, et al. *Ann Oncol.* 2021;32:839-53. 2. TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc; April 2024. 3. TRODELVY® (sacituzumab govitecan-hziy) [summary of product characteristics]. Carrigtwohill, Ireland: Gilead Sciences Ireland UC; July 2023. 4. Goldenberg DM, et al. *Oncotarget.* 2015;6:22496-512. 5. Agatsuma T, et al, inventors; Daiichi Sankyo, assignee. US patent: US 9850312 B2. 2017.

TROPiCS-03 Study Design

- The ongoing, open-label, multicohort, phase 2 TROPiCS-03 study (NCT03964727) is evaluating SG in patients with metastatic or locally advanced solid tumors
  - A preliminary analysis showed SG has promising antitumor activity and a manageable safety profile in an extensive-stage small cell lung cancer (ES-SCLC) cohort[1]
  - Here, we report updated results with additional patients and longer follow-up from the ES-SCLC cohort

Key eligibility criteria
- Histologically confirmed ES-SCLC
- Disease progression after no more than 1 prior line of platinum-based chemo and anti–PD-(L)-1 therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0–1
- Stable, treated brain metastases allowed[a]

→ **ES-SCLC cohort** (N = 43)

→ **SG 10 mg/kg** IV on D1 and D8 21-day cycles (until PD or unacceptable toxicity)

→ **Survival follow-up**

Primary end points
- ORR (INV[b])

Secondary end points
- DOR, CBR, PFS (INV[b])
- ORR, DOR, CBR, PFS (BICR[b])
- OS
- Safety

- At data cutoff (8 March 2024), median follow-up was 12.3 (range, 8.1–20.1) months

[a]Patients with stable CNS disease for ≥4 weeks prior to the first study dose and all neurologic symptoms returned to baseline may be included in the study. All patients with carcinomatous meningitis are excluded from the study, regardless of clinical stability. [b]Per RECIST v1.1.
BICR, blinded independent central review; **CBR**, clinical benefit rate; **chemo**, chemotherapy; **CNS**, central nervous system; **D**, day; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES-SCLC**, extensive-stage small cell lung cancer; **INV**, investigator-assessed; **IV**, intravenous; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PD-(L)1**, programmed death (ligand) 1; **PFS**, progression-free survival; **RECIST v1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SG**, sacituzumab govitecan.
1. Dowlati A, et al. Oral presentation ESMO 2023. Abstract #1099MO.

Patient Exposure and Disposition

Patient exposure and disposition	ES-SCLC (N = 43)
Median duration of treatment, months (range)	4.4 (0.03–18.04)
Median number of cycles received, cycles (range)	7 (1–25)
Discontinued study drug, n (%)	36 (83.7)
Ongoing study drug, n (%)	7 (16.3)

- Disease progression was the most common reason for treatment discontinuation in 31 (72.1%) patients
- No patients discontinued treatment because of an adverse event

ES-SCLC, extensive-stage small cell lung cancer.

Patient Baseline Characteristics and Disease History

Characteristics	ES-SCLC[a] (N = 43)
Median age, years (range)	67 (48–83)
Male, n (%)	20 (46.5)
Race, n (%)	
White	36 (83.7)
Black or African American	2 (4.7)
Asian	2 (4.7)
Other/not specified/not reported	3 (7.0)
Current or former smoker, n (%)	42 (97.7)
ECOG PS 1, n (%)	35 (81.4)
Chemotherapy-free interval, n (%)[b]	
<90 days (platinum-resistant)	20 (46.5)
≥90 days (platinum-sensitive)	23 (53.5)

Disease history	ES-SCLC[a] (N = 43)
Stage IV at initial diagnosis, n (%)[c]	40 (93.0)
Metastatic disease sites, n (%)	
Liver	13 (30.2)
Brain	5 (11.6)
Prior anticancer therapy, n (%)	
Platinum-based chemotherapy/ Immune checkpoint inhibitors	43 (100.0)
Best response to last prior anti-cancer therapy, n (%)[d]	
CR/PR	24 (55.8)
SD/PD	16 (37.2)

[a]All patients had extensive-stage disease and no more than 1 prior line of platinum-based chemotherapy and anti–PD-(L)-1 therapy at study entry. [b]Chemotherapy-free interval was defined as time from the last dose of first-line platinum-containing chemotherapy to the occurrence of progressive disease. [c]Stage III at initial diagnosis (n = 2). [d]Not available/reported (n = 3).
CR, complete response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES-SCLC**, extensive-stage small cell lung cancer; **PD**, progressive disease; **PD-(L)1**, programmed death (ligand) 1; **PR**, partial response; **SD**, stable disease.

Efficacy

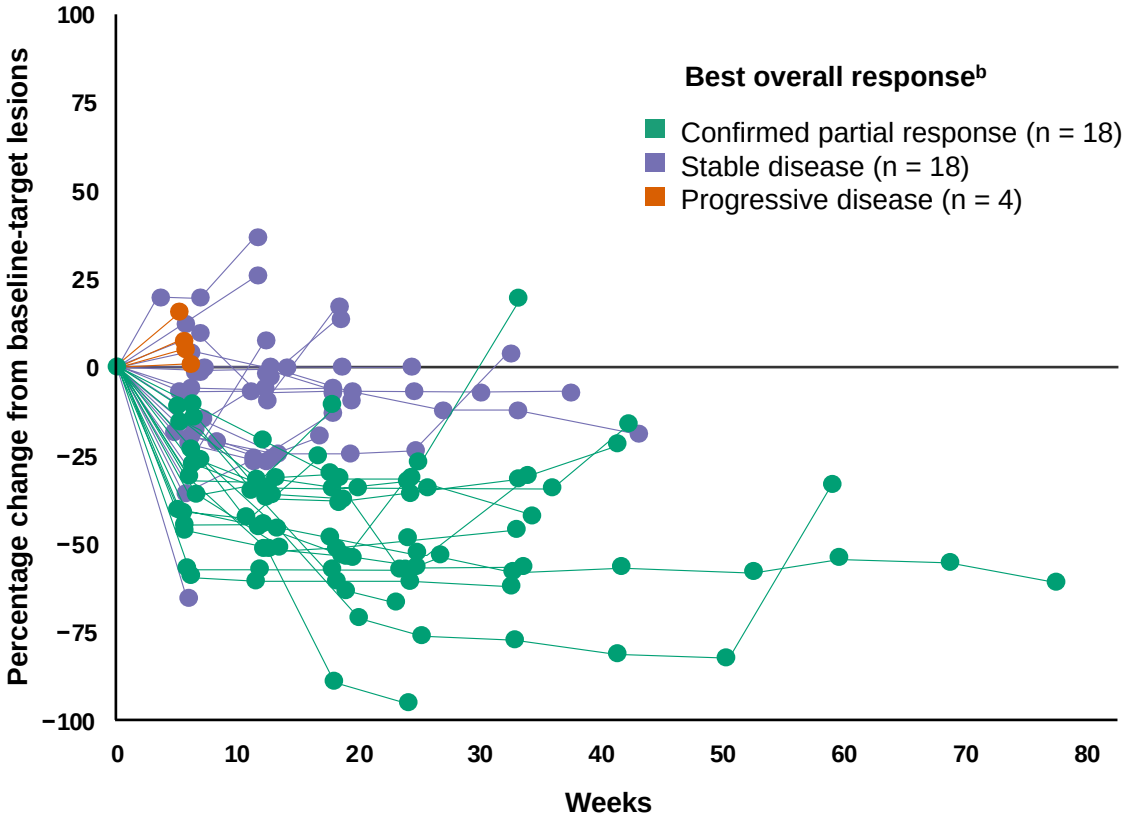
Efficacy[a]	All patients (N = 43)
ORR, % (95% CI)	41.9 (27.0–57.9)
BOR, n (%)	
Confirmed PR	18 (41.9)
SD	18 (41.9)
PD	4 (9.3)
Not assessed[b]	3 (7.0)
DCR (confirmed PR + SD), % (95% CI)	83.7 (69.3–93.2)
CBR (confirmed PR + SD for ≥6 months), % (95% CI)	48.8 (33.3–64.5)
Median DOR, months (95% CI)[c,d]	4.7 (3.5–6.7)
DOR rate at 6 months, % (95% CI)[c]	48.2 (23.9–68.9)

- Median time to response was 1.4 months (range, 1.2–4.2)
- Similar results were seen by blinded independent central review, with 2 patients having confirmed CR

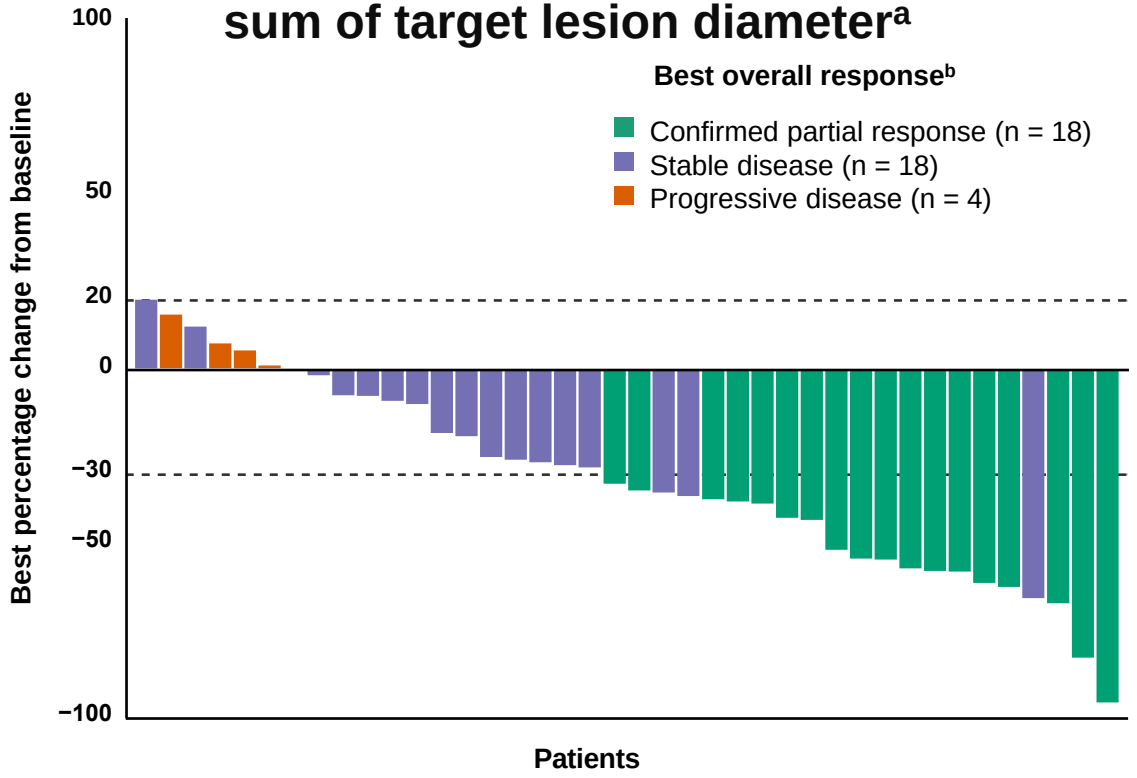
SD duration was defined as the time from the date of first dose of study drug to the first documentation of PD or death from any cause.
[a]By investigator assessment [b]Patients without any post-baseline assessments were counted as not assessed. [c]Based on Kaplan-Meier estimates. [d]Calculated for patients with confirmed PR.
BICR, blinded independent central review; **BOR**, best overall response; **CBR**, clinical benefit rate; **CR**, complete response; **DCR**, disease control rate; **DOR**, duration of response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease.

Efficacy Analyses

Tumor response over time[a]



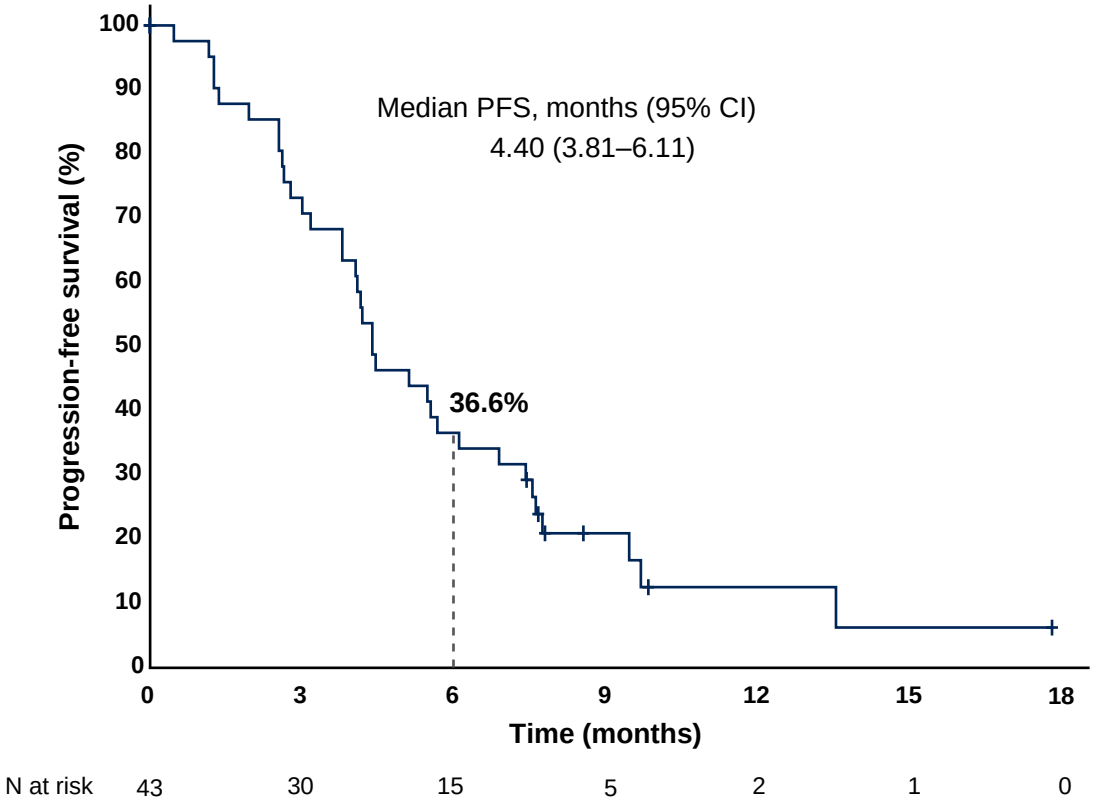
Best percentage change from baseline in total sum of target lesion diameter[a]

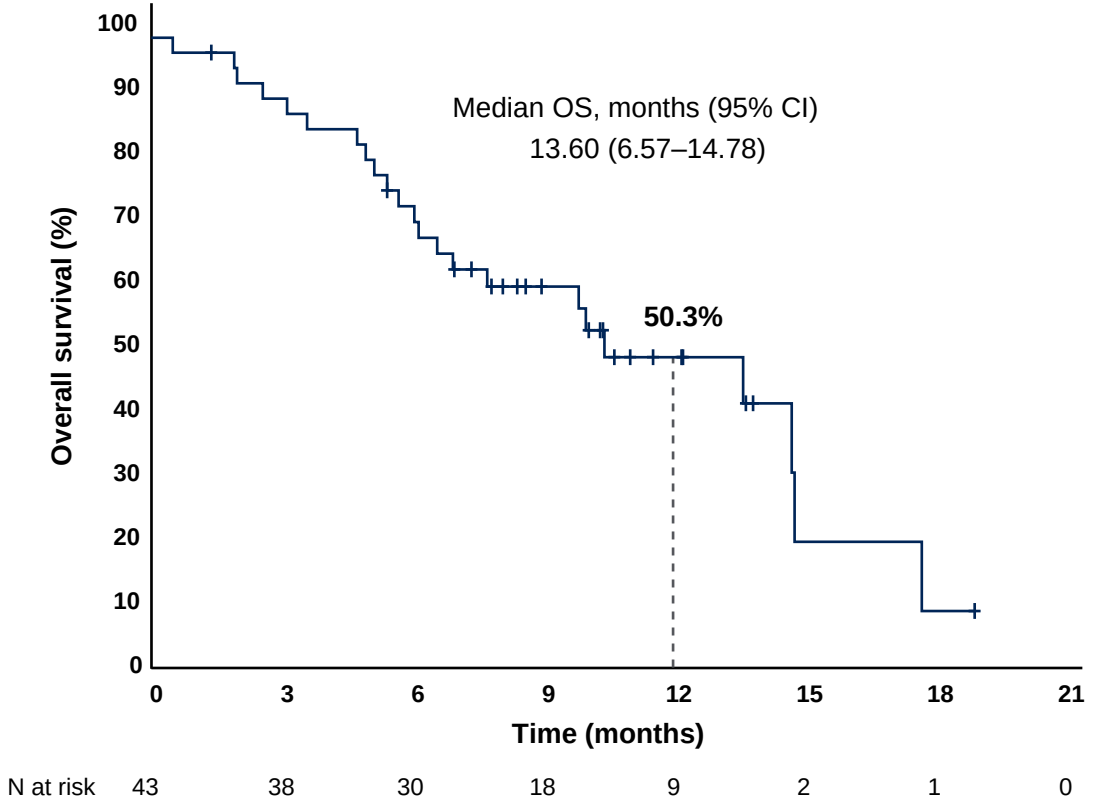


- 76.7% (33/43) of patients had tumor shrinkage
- 48.8% (21/43) of patients had a reduction of >30% in target lesion diameter

[a]By investigator assessment. [b]Three patients without any post-baseline assessments were counted as not assessed for response.

Progression-Free Survival[a] and Overall Survival





[a]By investigator assessment.
OS, overall survival; **PFS**, progression-free survival.

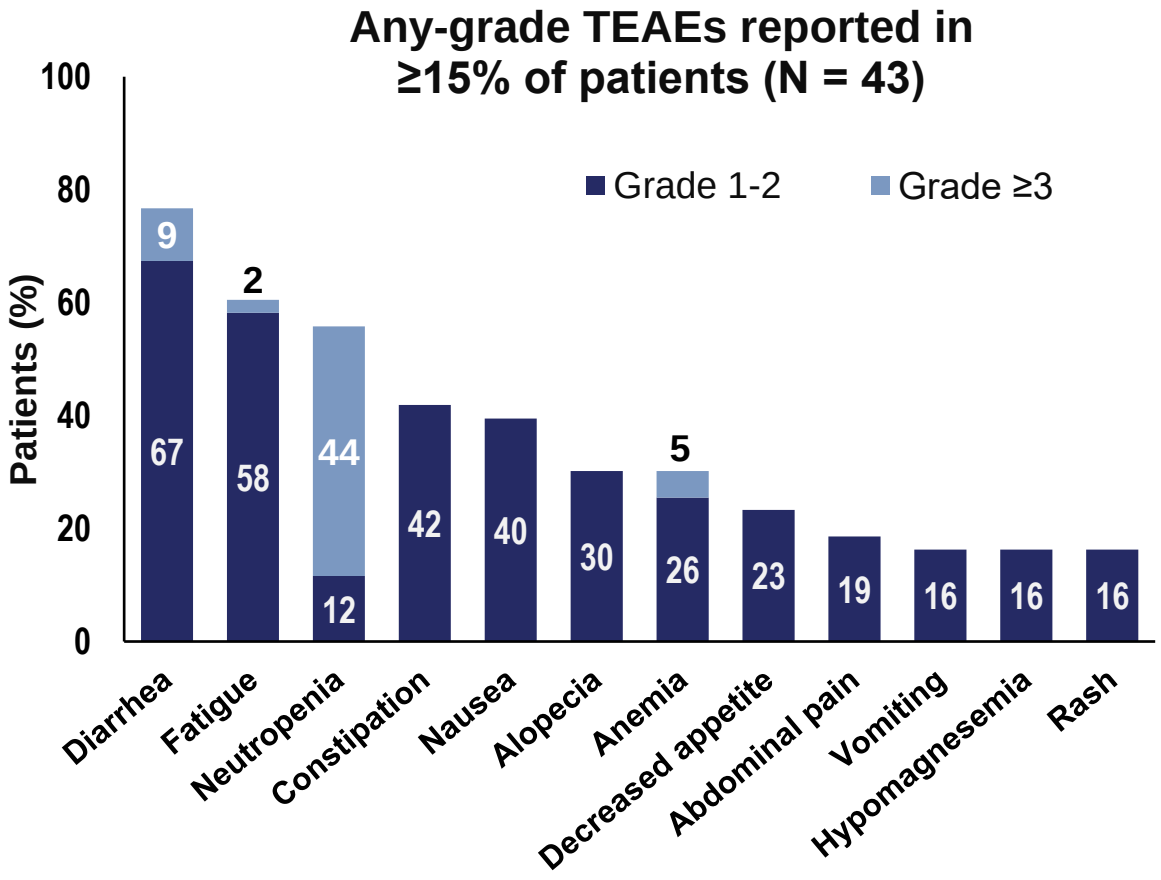
Efficacy Outcomes in Subgroups

Efficacy[a]	Platinum resistant (CTFI <90 days) (n = 20)	Platinum sensitive (CTFI ≥90 days) (n = 23)
ORR, % (95% CI)	**35.0 (15.4–59.2)**	**47.8 (26.8–69.4)**
BOR, n (%)		
Confirmed PR	7 (35.0)	11 (47.8)
SD	7 (35.0)	11 (47.8)
PD	4 (20.0)	0
Not assessed[b]	2 (10.0)	1 (4.3)
DCR (confirmed PR + SD), % (95% CI)	70.0 (45.7–88.1)	95.7 (78.1–99.9)
CBR (confirmed PR + SD for ≥6 months), % (95% CI)	40.0 (19.1–63.9)	56.5 (34.5–76.8)
Median DOR, months (95% CI)[c,d]	6.3 (1.5–6.9)	4.4 (3.0–NR)
DOR rate at 6 months, % (95% CI)[c]	57.1 (17.2–83.7)	41.6 (13.1–68.4)
Median PFS, months (95% CI)[c]	3.8 (1.4–7.6)	5.0 (4.1–7.4)
Median OS, months (95% CI)[c]	6.6 (4.7–17.7)	14.7 (7.7–NR)

SD duration was defined as the time from the date of first dose of study drug to the first documentation of PD or death from any cause.
[a]By investigator assessment. [b]Patients without any post-baseline assessments were counted as not assessed. [c]Based on Kaplan-Meier estimates. [d]Calculated for patients with confirmed PR.
BOR, best overall response; **CBR**, clinical benefit rate; **CTFI**, chemotherapy-free interval; **DCR**, disease control rate; **DOR**, duration of response; **NR**, not reached; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PR**, partial response; **SD**, stable disease.

Safety Summary

Event, n (%)	ES-SCLC (N = 43)
Any-grade TEAEs	43 (100.0)
Grade ≥3 TEAEs	32 (74.4)
Serious TEAEs	22 (51.2)
TEAEs leading to dose reduction[a]	16 (37.2)
TEAEs leading to discontinuation	0
TEAEs leading to death[b]	3 (7.0)
Related to study drug[c]	1 (2.3)



TEAE was defined as any adverse event with an onset date on or after the study treatment start date and no later than 30 days after the last dose of study treatment.
[a]The most frequent reasons for dose reduction were neutropenia (16.3%) and diarrhea (7.0%). [b]One death each from neutropenic sepsis, pneumonia, and sepsis. [c]Death from neutropenic sepsis.
ES-SCLC, extensive-stage small cell lung cancer; **TEAE**, treatment-emergent adverse event.

Conclusions

- SG showed promising efficacy as a second-line treatment for patients with ES-SCLC
  - — ORR was 41.9% (95% CI, 27.0–57.9); DOR rate at 6 months was 48.2% (95% CI, 23.9–68.9)
  - — Median PFS was 4.40 months (95% CI, 3.81–6.11) and median OS was 13.60 months (95% CI, 6.57–14.78)
  - — Efficacy by BICR was consistent
- SG demonstrated antitumor activity in patients with both platinum-resistant (ORR, 35.0%; 95% CI, 15.4–59.2) and platinum-sensitive (ORR, 47.8%; 95% CI, 26.8–69.4) disease
- The safety profile of SG was consistent with that observed in other SG studies
  - — Most common grade ≥3 TEAEs were neutropenia and diarrhea
- These encouraging data warrant further investigation of SG in ES-SCLC in a randomized phase 3 study

BICR, blinded independent central review; **DOR**, duration of response; **ES-SCLC**, extensive-stage small cell lung cancer; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **SG**, sacituzumab govitecan; **TEAE**, treatment-emergent adverse event.

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