Phase 2 Open-Label Study of Sacituzumab Govitecan as Second-Line Therapy in Patients With Extensive-Stage Small Cell Lung Cancer: Results From TROPiCS-03

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ORIGINAL ARTICLE

CONFIDENTIAL DRAFT

Phase 2 Open-Label Study of Sacituzumab Govitecan as Second-Line Therapy in Patients With Extensive-Stage Small Cell Lung Cancer: Results From TROPiCS-03

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Abstract (247/250 words)

Introduction: The phase 2 TROPiCS-03 study evaluated the efficacy/safety of sacituzumab govitecan (SG) as second-line treatment in patients with previously treated extensive-stage small cell lung cancer (ES-SCLC).

Methods: TROPiCS-03 (NCT03964727) is a multicohort, open-label, phase 2 basket study in solid tumors, including ES-SCLC. Adults with ES-SCLC that progressed after one prior line of platinum-based chemotherapy and anti-programmed death-(ligand) 1 (PD-[L]1) therapy received SG 10 mg/kg on days 1 and 8 of a 21-day cycle. The primary endpoint was investigator-assessed objective response rate (ORR), per RECIST v1.1. Key secondary endpoints included investigator-assessed duration of response (DOR) and progression-free survival (PFS); blinded independent central review (BICR)-assessed ORR, DOR, and PFS; overall survival (OS); and safety. Efficacy was evaluated in patients with platinum-resistant and platinum-sensitive disease.

Results: Among 43 patients (median follow-up, 12.3 [range, 8.1–20.1] months), investigator-assessed ORR was 41.9% (95% CI: 27.0%–57.9%), with 18 confirmed partial responses; median (95% CI) DOR, PFS, and OS were 4.73 (3.52–6.70), 4.40 (3.81–6.11), and 13.60 (6.57–14.78) months, respectively. Efficacy results by BICR assessment were similar. Investigator-assessed ORR (95% CI) was 35.0% (15.4%–59.2%) in patients with platinum-resistant disease (n=20) and 47.8% (26.8%–69.4%) with platinum-sensitive disease (n=23). Thirty-two (74.4%) patients experienced grade ≥3 treatment-emergent adverse events (TEAEs). No TEAE led to SG discontinuation; one treatment-related TEAE (neutropenic sepsis) led to death.

Conclusions: SG demonstrated promising efficacy in the second-line treatment of ES-SCLC, irrespective of platinum sensitivity. Safety was manageable and consistent with that observed in other SG studies.

Keywords (3–5): sacituzumab govitecan; antibody-drug conjugate; extensive-stage small cell lung cancer; platinum sensitivity; clinical trial

Article Classifications: SCLC, lung cancer, novel therapeutics

Introduction

Small cell lung cancer (SCLC) is an aggressive subtype of lung cancer, with the majority of cases attributable to smoking.[1,2] Over two thirds of patients present with extensive-stage (ES) disease, for which local radiation therapy is not a treatment option.[3-6] In these patients, standard-of-care frontline treatment consists of chemoimmunotherapy (with a platinum and an anti–programmed death-[ligand] 1 [PD-(L)1] compound).[7] Unfortunately, the prognosis is dismal, with 2-year survival rates of 14% and 22%, respectively,[8] and relapses occurring within 6 months in nearly all patients.[6] Outcomes are especially poor for patients with platinum-resistant disease (chemotherapy-free interval [CTFI] <90 days), as opposed to patients with platinum-sensitive disease (CTFI ≥90 days).[9]

Second-line treatment options for ES-SCLC are limited and have important efficacy and/or safety considerations. Approved in 1996, topotecan has been the standard of care for patients with ES-SCLC and is the only agent fully authorized in the second-line setting for the treatment of platinum-sensitive disease.[10,11] However, topotecan is associated with limited efficacy and high-grade hematologic toxicities, which may negatively impact adherence.[12-15] Another treatment option for relapsed disease is lurbinectedin, authorized by the US Food and Drug Administration under an accelerated approval pathway based on a single-arm, phase 2 study.[15-17] However, a subsequent confirmatory trial failed to show improved survival over physician's choice of chemotherapy, and future findings are expected from an ongoing phase 3 trial in relapsed SCLC.[18,19] Recently, tarlatamab, a bispecific T-cell engager, was also granted accelerated approval based on the results of a single-arm, phase 2 trial,[20,21] with further data awaited in the randomized setting. Despite recent developments in the second-line treatment of ES-SCLC, there remains a significant unmet need for therapeutic options that improve response and prolong survival in patients whose tumors have progressed on platinum-based chemotherapy and anti–PD-(L)1 therapy.

Sacituzumab govitecan (SG) is a first-in-class trophoblast cell surface antigen 2 (Trop-2)–directed antibody-drug conjugate (ADC) consisting of a humanized monoclonal antibody linked to SN-38, the

active metabolite of the topoisomerase I inhibitor irinotecan.[22-25] SG is characterized by its nanomolar binding affinity for Trop-2, high drug-to-antibody ratio (7.6:1), hydrolysable linker that facilitates rapid internalization, and efficient delivery of SN-38 to Trop-2–expressing cancer cells and the surrounding tumor microenvironment (bystander effect).[22-25] SG is approved globally for patients with previously treated metastatic breast cancer that is either triple-negative or hormone receptor–positive, human epidermal growth factor receptor 2–negative.[26,27] Trop-2 is a transmembrane glycoprotein and calcium signaling transducer expressed in many epithelial cancers, including SCLC.[28,29] SG binds to Trop-2 on tumor cell membranes to deliver the cytotoxic payload into the tumor. High binding affinity, high drug-to-antibody ratio, along with a bystander effect and the potency of SN-38 may account for the efficacy of SG in tumors with low Trop-2 levels and provide a rationale for SG as a possible treatment for SCLC.[30-32] The well-characterized SN-38 payload of SG has proven efficacy in SCLC,[33,34] and SG monotherapy is well tolerated across different solid tumor types. In the phase 1/2 IMMU-132-01 basket study, SG demonstrated encouraging antitumor activity in patients with heavily pretreated SCLC, despite many trial patients having been previously exposed to standard-of-care topotecan.[34]

TROPiCS-03 (IMMU-132-11; NCT03964727) is an ongoing, multicohort, open-label, phase 2 study evaluating SG monotherapy in adult patients with previously treated metastatic solid tumors, including non-small cell lung cancer, head and neck squamous cell carcinoma, endometrial carcinoma, and ES-SCLC. Here, we report results from the fully enrolled ES-SCLC cohort of the proof-of-concept stage.

Materials and Methods

Study design and patients

Patients were enrolled in the ES-SCLC cohort of TROPiCS-03 between July 7, 2022, and July 6, 2023. Eligible patients had histologically confirmed ES-SCLC that progressed after no more than one prior line of platinum-based chemotherapy and anti–PD-(L)1 therapy, an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1, and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Key exclusion criteria included prior treatment with a topoisomerase I inhibitor (except for etoposide in combination with first-line platinum-based chemotherapy) and known active central nervous system (CNS) metastases or carcinomatous meningitis (patients with previously treated brain metastases with stable CNS disease for ≥4 weeks prior to first dose were eligible). Full eligibility criteria are described in the Study Protocol (**Supplemental Material 1**). A total of 79 patients with ES-SCLC were screened for eligibility, of whom 36 failed screening. The most common reason for screen failure was the presence of active CNS metastases and/or carcinomatous meningitis followed by receipt of >1 prior line of systemic treatment with platinum-based chemotherapy and anti–PD-(L)1 therapy (**Supplemental Figure 2**).

Procedures

SG was administered via intravenous infusion at 10 mg/kg on days 1 and 8 of each 21-day cycle. Treatment was continued until investigator-assessed progressive disease (PD) per RECIST v1.1, unacceptable toxicity, withdrawal, or death, whichever occurred first. Recommendations for dose reduction were according to the US prescribing information.[26] Treatment beyond PD was permitted if the investigator determined there was evidence of clinical benefit and the patient tolerated SG. Radiologic assessments (computed tomography or magnetic resonance imaging scans with IV contrast, if not contraindicated) of the chest, abdomen, pelvis, and any other involved disease sites (including brain, if appropriate) were performed at baseline, every 6 weeks in the 6 months after the first dose of study drug, and then every 9 weeks until radiologic PD per RECIST v1.1.

TROPiCS-03 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, Inc) designed and conducted the trial and gathered data in collaboration with the study investigators.

Endpoints

The primary endpoint was investigator-assessed objective response rate (ORR) (confirmed complete response [CR] or partial response [PR]) per RECIST v1.1. A confirmatory scan was required 4–6 weeks after initial documentation of CR or PR. Scans were also transferred to a central reader and analyzed by blinded independent central review (BICR). Key secondary endpoints were BICR-assessed ORR, duration of response (DOR; time from the date of the first response to first documented PD or death from any cause), clinical benefit rate (CBR; confirmed CR + PR + stable disease [SD] duration ≥6 months), and progression-free survival (PFS; time from the date of the first dose of study drug to first documented PD or death from any cause, whichever occurred first); investigator-assessed DOR, CBR, and PFS; overall survival (OS; time from the date of the first dose of SG to death from any cause); and the incidence of treatment-emergent adverse events (TEAEs; any adverse event with an onset date on or after the first study drug dose and no later than 30 days after the last study drug dose). Disease control rate (DCR), defined as the percentage of patients with confirmed CR + PR + SD, was also determined. Efficacy was also evaluated in the subgroups of patients with platinum-resistant (CTFI <90 days) and platinum-sensitive (CTFI ≥90 days) disease. TEAEs were classified per the Medical Dictionary for Regulatory Activities version 26.1 and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0.

Statistics

The sample size was not based on a formal power calculation but was used to ensure accuracy in the estimation of ORR. Assuming that the true ORR is 25%, a sample size of approximately 40 patients would ensure that the half-width of the 95% confidence interval (CI) is ≤13.4%. All patients who received

SG were analyzed. Two-sided exact 95% CIs for ORR and CBR were calculated using the Clopper-Pearson method. For time-to-event endpoints, the Kaplan-Meier method was used to estimate medians, and the 95% CIs for the medians were calculated using the Brookmeyer-Crowley method. Only patients with confirmed CR or PR were included in the DOR analysis. For the analysis of PFS, patients not known to have progressed or died were censored on the date of last tumor assessment. For the analysis of OS, patients not known to have died were censored on the date they were last known to be alive. The frequency and severity of TEAEs were summarized descriptively.

The data cutoff date for these analyses was March 8, 2024. All statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Patients

Among the 43 patients with ES-SCLC treated with SG in TROPiCS-03, the median age was 67 (range, 48–83) years (**Table 1**). Most patients had an ECOG PS score of 1 (81.4%) and were former or current tobacco users (97.7%). All patients had metastatic disease at study enrollment, and all had received prior platinum-based chemotherapy and anti–PD-(L)1 therapy as first line of therapy. Twenty (46.5%) patients had platinum-resistant disease, and 23 (53.5%) had platinum-sensitive disease. At enrollment, liver and brain metastases were present in 13 (30.2%) and 5 (11.6%) patients, respectively.

The median duration of study follow-up was 12.3 (range, 8.1–20.1) months, and 7 (16.3%) patients were still receiving treatment. The median duration of exposure to SG was 4.4 (range, 0.03–18.04) months, and the median number of treatment cycles received was 7 (range, 1–25). Thirty-six (83.7%) patients discontinued SG, most commonly due to disease progression (72.1%).

Efficacy

ORR was 41.9% (95% CI: 27.0%–57.9%) in the intent-to-treat population per investigator assessment, with all responses being confirmed PRs (**Table 2**). The median time to response was 1.43 (range, 1.15–4.17) months. The median DOR was 4.73 (95% CI: 3.52–6.70) months, and the 6-month DOR rate was

48.2% (95% CI: 23.9%–68.9%) (**Table 2**). SD was observed in an additional 18 (41.9%) patients, of whom 3 had SD duration ≥6 months. The DCR was 83.7% (95% CI: 69.3%–93.2%), and the CBR was 48.8% (95% CI: 33.3%–64.5%) (**Table 2**). Only 4 (9.3%) patients had PD as best response. A spider plot of tumor response by week is shown in **Figure 1A**. Tumor shrinkage was observed in 76.7% of patients (33/43), with 48.8% (21/43) having a reduction of >30% (**Figure 1B**). Median PFS and OS were 4.40 (95% CI: 3.81–6.11) and 13.60 (95% CI: 6.57–14.78) months, respectively (**Table 2** and **Figure 2**). On the basis of BICR assessment, the ORR was 44.2%, with 2 (4.7%) confirmed CRs and 17 (39.5%) PRs confirmed (**Supplemental Table 1**). Moreover, 81.4% (35/43) of patients experienced tumor shrinkage, with 53.5% (23/43) having a reduction of >30% (**Supplemental Figure 1**).

When analyzing outcomes in patients with platinum-resistant and platinum-sensitive disease, investigator-assessed ORR was 35.0% (95% CI: 15.4%–59.2%) and 47.8% (95% CI: 26.8%–69.4%), respectively (**Table 2**). Tumor shrinkage was observed in 48.8% of patients (21/43) with platinum sensitive disease and 27.9% of patients (12/43) with platinum-resistant disease (**Figure 1B**). Similar tumor shrinkage was observed when these patient subgroups were evaluated by BICR (**Supplemental Figure 1**). Median PFS was 3.81 (95% CI: 1.38–7.56) months in those with platinum-resistant disease and 4.98 (95% CI: 4.07–7.43) months in those with platinum-sensitive disease, while median OS was 6.57 (95% CI, 4.73–17.71) and 14.72 (95% CI: 7.72–not reached) months, respectively. Similar outcomes were observed when these patient subgroups were evaluated by BICR (**Supplemental Table 1**).

Regarding age and gender, efficacy (ORR, PFS, OS) was observed in elderly (≥65 years) and younger patients (<65 years) as well as in both males and females (**Supplemental Table 2**).

Safety

All patients experienced ≥1 TEAE of any grade, most commonly diarrhea (76.7%), fatigue (60.5%), and neutropenia (55.8%) (**Table 3**). Grade ≥3 TEAEs were observed in 32 (74.4%) patients, with neutropenia (44.2%) and diarrhea (9.3%) being the most frequent. Overall, 26 (60.5%) patients experienced a grade

≥3 treatment-related TEAE. Serious TEAEs occurred in 22 (51.2%) patients; febrile neutropenia was the most common serious TEAE (7.0%).

TEAEs leading to dose reduction occurred in 16 (37.2%) patients, with neutropenia (16.3%) and diarrhea (7.0%) being the most frequent. No patient discontinued SG because of a TEAE. TEAEs leading to death occurred for 3 patients (pneumonia, neutropenic sepsis, and sepsis). Only the death due to neutropenic sepsis was considered related to SG by the investigator.

Discussion

The results from this phase 2 study indicate that patients with ES-SCLC benefit from SG treatment, with an ORR of 41.9% and a median DOR of 4.73 months per investigator assessment. Importantly, SG demonstrated promising antitumor activity in patients with platinum-resistant and platinum-sensitive disease, which is noteworthy given the poor outcomes and lack of approved treatment options in the former setting.

Currently, topotecan is the only agent fully authorized by global regulatory agencies for the second-line treatment of ES-SCLC.[9-11,35] More recently, therapies using novel mechanisms of action—such as lurbinectedin, an alkylating agent, and tarlatamab, a bispecific T-cell engager—became available in the US, under an accelerated approval pathway.[16,21] However, randomized phase 3 trials are ongoing for both agents, with pending results.[19] The ORR observed with SG in TROPiCS-03 (41.9%) appears more promising than that with topotecan (18%–25%) on the basis of historical controls[12-15,18] and is in line with that achieved with lurbinectedin (35.2%)[17] and tarlatamab (40%).[20,21] Nevertheless, results with SG stand out from those with other compounds for several reasons. First, patients with platinum-sensitive and platinum-resistant ES-SCLC treated with SG achieved ORRs of 48% and 35%, respectively. In contrast, ORR with oral or intravenous topotecan was lower in patients with platinum-sensitive and platinum-resistant disease.[12,14,15,36] Second, in contrast to other trials, TROPiCS-03 enrolled a patient population previously treated with the current front-line standard of care (platinum-based chemotherapy and anti–PD-[L]1 therapy). Licensure trials of topotecan and lurbinectedin recruited patients with either extensive-stage or limited-stage disease, with the former having a worse prognosis than the latter,[37] and only

required prior treatment with chemotherapy. In a phase 2 study of tarlatamab, patients with ES-SCLC were not required to have been previously exposed to anti–PD-(L)1 immunotherapy, and only 73% had received it.[20] The recruitment of patient populations with less aggressive or less pretreated disease, or both, has the potential to inflate efficacy outcomes.

Other investigational drugs with targeted mechanisms of action evaluated for their potential in treating patients with relapsed advanced/metastatic SCLC (second-line or later) include HPN328 (a trispecific T-cell engager) and the B7-homolog 3–directed ADCs ifinatamab deruxtecan and HS-20093.[38-42] In a phase 2 study of ifinatamab deruxtecan in ES-SCLC, ORR rates of 55% and 26% were observed in patients receiving 12 mg/kg (n=42) and 8 mg/kg (n=46) doses, respectively.[39] Common treatment-related TEAEs with this agent were nausea (50% and 28%), decreased appetite (43% and 17%), and anemia (36% and 13%).[39] Treatment-related interstitial lung disease events occurred in 4 and 5 patients treated with 8 and 12 mg/kg, respectively.[39] In a phase 1 study, patients with ES-SCLC were treated with either 8 (n=31) or 10 mg/kg (n=22) HS-20093 ADC.[40] ORR was 61% and 50% and median PFS was 5.9 months and 7.3 months, respectively.[40] Overall, top 3 treatment-related TEAEs with HS-20093 were anemia (86%), leukopenia (80%), and neutropenia (68%).[40] SHR-A1921, a humanized Trop-2 targeting monoclonal antibody attached to a topoisomerase I inhibitor via a cleavable linker, was assessed in a phase 1 study, in which 33% of evaluable patients (n=15) with ES-SCLC achieved ORR, with median follow up of 5.3 months.[43] The most frequent treatment-related TEAEs with this ADC were stomatitis (59%) and nausea (35%).[43] As a Trop-2–directed ADC, SG differs mechanistically from all agents currently available for ES-SCLC, because it combines an anti–Trop-2 antibody with SN-38. Given the promising early-stage clinical results of investigational agents such as SG and ifinatamab deruxtecan, more options may be on the horizon. Although this evolution in the therapeutic landscape of relapsed ES-SCLC is exciting, no treatment has yet been demonstrated to confer a survival benefit over topotecan. Randomized phase 3 trials are ongoing.[19,44]

The safety profile of SG in this study was consistent with that established in clinical trials involving several different tumor types, with diarrhea and neutropenia being the most common TEAEs.[32,45-50] These TEAEs

are well characterized, and management strategies have been developed and are specified in the prescribing information for SG.[26] Importantly, no patient discontinued study treatment because of an adverse event. Of note, topotecan and lurbinectedin may also induce severe myelosuppression,[10,17] and tarlatamab may cause serious or life-threatening adverse events, such as cytokine release syndrome and neurologic toxicity, including immune effector cell–associated neurotoxicity syndrome.[21]

The limitations of this study include its open-label, single-arm design (ie, no control group) and relatively small sample size (N=43). Consequently, caution is warranted when extrapolating these data to a wider population. Nevertheless, these data suggest a promising role for SG in the treatment of patients with previously treated SCLC, a population with high unmet needs and limited effective, tolerable treatment options. Ongoing study of the TROPiCS-03 SCLC cohort includes exploratory biomarker analyses, including levels of Trop-2 expression and sensitivity of tumors to the topoisomerase inhibitor payload, which may help further elucidate benefit from SG in this patient population. On the basis of the clinical results presented here, a phase 3 trial of SG in patients with previously treated ES-SCLC is warranted.

CRediT Authorship Contribution Statement

Afshin Dowlati: Investigation, Writing - review and editing.

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Data Sharing Statement

Gilead Sciences, Inc, shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on 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.

References

1. Wang Q, Gümüş ZH, Colarossi C, et al. SCLC: epidemiology, risk factors, genetic susceptibility, molecular pathology, screening, and early detection. *J Thorac Oncol.* 2023;18:31-46.

2. Dingemans A-MC, Früh M, Ardizzoni A, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2021;32:839-853.

3. Cittolin-Santos GF, Knapp B, Ganesh B, et al. The changing landscape of small cell lung cancer. *Cancer.* 2024;130:2453-2461.

4. West HJ. Moving beyond limited and extensive staging of small cell lung cancer. *JAMA Oncol.* 2019;5:e185187.

5. Salem A, Mistry H, Hatton M, et al. Association of chemoradiotherapy with outcomes among patients with stage I to II vs stage III small cell lung cancer: secondary analysis of a randomized clinical trial. *JAMA Oncol.* 2019;5:e185335.

6. Khurshid H, Ismaila N, Bian J, et al. Systemic therapy for small-cell lung cancer: ASCO-Ontario health (Cancer Care Ontario) guideline. *J Clin Oncol.* 2023;41:5448-5472.

7. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer V.3.2024. ©National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed June 26, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer V.3.2024. ©National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed June 26, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

8. Zugazagoitia J, Paz-Ares L. Extensive-stage small-cell lung cancer: first-line and second-line treatment options. *J Clin Oncol.* 2022;40:671-680.

9. Das M, Padda SK, Weiss J, Owonikoko TK. Advances in treatment of recurrent small cell lung cancer (SCLC): insights for optimizing patient outcomes from an expert roundtable discussion. *Adv Ther.* 2021;38:5431-5451.

10. Hycamtin®. Prescribing information. Novartis Pharmaceuticals. 2019. Accessed August 12, 2024

11. Hycamtin®. Summary of product characteristics. Novartis Pharmaceuticals. 2023. Accessed August 12, 2024

12. Baize N, Monnet I, Greillier L, et al. Groupe Français de Pneumo-Cancérologie 01–13 investigators. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol.* 2020;21:1224-1233.

13. Blackhall F, Jao K, Greillier L, et al. Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-high SCLC: results from the phase 3 TAHOE study. *J Thorac Oncol.* 2021;16:1547-1558.

14. Spigel DR, Dowlati A, Chen Y, et al. RESILIENT trial investigators. RESILIENT part 2: a randomized, open-label phase III study of liposomal irinotecan versus topotecan in adults with relapsed small cell lung cancer. *J Clin Oncol.* 2024;42:2317-2326.

15. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol.* 2007;25:2086-2092.

16. Zepzelca®. Prescribing information. Jazz Pharmaceuticals, Inc. 2023. Accessed August 12, 2024

17. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol.* 2020;21:645-654.

18. Aix SP, Ciuleanu TE, Navarro A, et al. Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): a multicentre, randomised, open-label, phase 3 trial. *Lancet Respir Med.* 2023;11:74-86.

19. Besse B, Paz-Ares L, Peters S, et al. A phase III study of lurbinectedin alone or in combination with irinotecan vs investigator's choice (topotecan or irinotecan) in patients with relapsed small cell lung cancer (SCLC; LAGOON trial). *J Clin Oncol.* 2023;41:TPS8613-TPS8613.

20. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med.* 2023;389:2063-2075.

21. Imdelltra™. Prescribing Information. Amgen, Inc. 2024. Accessed August 12, 2024

22. Cardillo TM, Govindan SV, Sharkey RM, Trisal P, Goldenberg DM. Humanized anti-Trop-2 IgG-SN-38 conjugate for effective treatment of diverse epithelial cancers: preclinical studies in human cancer xenograft models and monkeys. *Clin Cancer Res.* 2011;17:3157-3169.

23. Goldenberg DM, Cardillo TM, Govindan SV, Rossi EA, Sharkey RM. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). *Oncotarget.* 2015;6:22496-22512.

24. Starodub AN, Ocean AJ, Shah MA, et al. First-in-human trial of a novel anti-Trop-2 antibody-SN-38 conjugate, sacituzumab govitecan, for the treatment of diverse metastatic solid tumors. *Clin Cancer Res.* 2015;21:3870-3878.

25. Goldenberg DM, Sharkey RM. Antibody-drug conjugates targeting TROP-2 and incorporating SN-38: A case study of anti-TROP-2 sacituzumab govitecan. *MAbs.* 2019;11:987-995.

26. Trodelvy®. Prescribing Information. Gilead Sciences, Inc. 2023. Accessed August 12, 2024

27. Trodelvy®. Summary of product characteristics. Gilead Sciences, Inc. 2021. Accessed August 12, 2024

28. Shvartsur A, Bonavida B. Trop2 and its overexpression in cancers: regulation and clinical/therapeutic implications. *Genes Cancer.* 2015;6:84-105.

29. Inamura K, Yokouchi Y, Kobayashi M, et al. Association of tumor TROP2 expression with prognosis varies among lung cancer subtypes. *Oncotarget.* 2017;8:28725-28735.

30. Bardia A, Rugo HS, Tolaney SM, et al. Final results from the randomized phase III ASCENT clinical trial in metastatic triple-negative breast cancer and association of outcomes by human epidermal growth factor receptor 2 and trophoblast cell surface antigen 2 expression. *J Clin Oncol.* 2024;42:1738-1744.

31. Loriot Y, Balar AV, Petrylak DP, et al. Sacituzumab govitecan demonstrates efficacy across tumor trop-2 expression levels in patients with advanced urothelial cancer. *Clin Cancer Res.* 2024;30:3179-3188.

32. Rugo HS, Bardia A, Marme F, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2023;402:1423-1433.

33. Kim YH, Mishima M. Second-line chemotherapy for small-cell lung cancer (SCLC). *Cancer Treat Rev.* 2011;37:143-150.

34. Gray JE, Heist RS, Starodub AN, et al. Therapy of small cell lung cancer (SCLC) with a topoisomerase-I-inhibiting antibody-drug conjugate (ADC) targeting Trop-2, sacituzumab govitecan. *Clin Cancer Res.* 2017;23:5711-5719.

35. Bernabé-Caro R, Chen Y, Dowlati A, Eason P. Current and emerging treatment options for patients with relapsed small-cell lung carcinoma: a systematic literature review. *Clin Lung Cancer.* 2023;24:185-208.

36. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol.* 1999;17:658-667.

37. PDQ® Adult Treatment Editorial Board. PDQ Small Cell Lung Cancer Treatment. Updated June 27, 2024. Accessed July 11, 2024. https://www.cancer.gov/types/lung/hp/small-cell-lung-treatment-pdq

38. Molloy ME, Aaron WH, Barath M, et al. HPN328, a trispecific T cell-activating protein construct targeting DLL3-expressing solid tumors. *Mol Cancer Ther.* 2024;23:1294-1304.

39. Rudin C, Ahn M, Johnson M, et al. Ifinatamab deruxtecan (I-DXd) in extensive-stage small cell lung cancer (ES-SCLC): interim analysis of IDeate-Lung01. Presented at: 2024 IASLC World Conference on Lung Cancer; September 7-10, 2024; San Diego, CA. Abstract OA04.03.

40. Wang J, Duan J, Wu L, et al. Efficacy and safety of HS-20093 in extensive stage small cell lung cancer in a multicenter, phase 1 study (ARTEMIS-001). Presented at: 2024 IASLC World Conference on Lung Cancer; September 7-10, 2024; San Diego, CA. Abstract OA04.06.

41. Rudin C, Johnson M, Girard N, et al. A phase 2 study of ifinatamab deruxtecan (I-DXd; DS-7300) in patients with previously treated ES-SCLC. *J Thorac Oncol.* 2023;18:S377.

42. Wang J, Duan J, Xing L, et al. ARTEMIS-001: phase 1 study of HS-20093, a B7-H3–targeting antibody-drug conjugate, in patients with advanced solid tumor. *J Clin Oncol.* 2023;41:3017-3017.

43. Wang J, Wu L, Li X, et al. SHR-A1921, a TROP-2 targeted antibody-drug conjugate (ADC), In patients (pts) with advanced small-cell lung cancer (SCLC). Presented at: 2024 IASLC World Conference on Lung Cancer; September 7-10, 2024; San Diego, CA. Abstract OA04.05.

44. Paz-Ares LG, Felip E, Ahn M-J, et al. Randomized phase 3 study of tarlatamab, a DLL3-targeting bispecific T-cell engager (BiTE), compared to standard of care in patients with relapsed small cell lung cancer (DeLLphi-304). *J Clin Oncol.* 2023;41:TPS8611.

45. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med.* 2021;384:1529-1541.

46. Bardia A, Messersmith WA, Kio EA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. *Ann Oncol.* 2021;32:746-756.

47. Paz-Ares LG, Juan-Vidal O, Mountzios GS, et al. Sacituzumab govitecan versus docetaxel for previously treated advanced or metastatic non–small cell lung cancer: the randomized, open-label phase III EVOKE-01 study. *J Clin Oncol.* 2024;42:2860-2872.

48. Rugo HS, Bardia A, Marme F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.* 2022;40:3365-3376.

49. Rugo HS, Tolaney SM, Loirat D, et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. *NPJ Breast Cancer.* 2022;8:98.

50. Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. *J Clin Oncol.* 2021;39:2474-2485.

TABLES

Table 1. Baseline Demographic and Disease Characteristics	
Characteristic	Patients N = 43
Median age, years (range)	67 (48–83)
<65 years, n (%)	17 (39.5)
≥65 years, n (%)	26 (60.5)
Male, n (%)	20 (46.5)
Race or ethnic group, n (%)	
White	36 (83.7)
Black	2 (4.7)
Asian	2 (4.7)
Other/not specified/not reported[a]	3 (7.0)
Current or former tobacco use, n (%)	42 (97.7)
ECOG PS score, n (%)	
0	8 (18.6)
1	35 (81.4)
Metastatic disease stage IV at initial diagnosis, n (%)	40 (93.0)
Metastatic disease at study enrollment, n (%)	43 (100.0)
Best response to most recent prior anticancer therapy, n (%)	
CR/PR	24 (55.8)
SD/PD	16 (37.2)
Not available/reported	3 (7.0)
Type of prior anticancer therapy, n (%)	
Platinum-based chemotherapy	43 (100.0)
Cisplatin and etoposide	7 (16.3)
Carboplatin and etoposide	37 (86.0)
Immune checkpoint inhibitors	43 (100.0)
Atezolizumab	32 (74.4)
Durvalumab	10 (23.3)
Nivolumab	1 (2.3)
Chemotherapy-free interval, n (%)	
<90 days	20 (46.5)
≥90 days	23 (53.5)
Metastatic disease sites, n (%)	
Liver	13 (30.2)
Brain	5 (11.6)

[a]Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or other.
CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. Efficacy Outcomes per Investigator Assessment

	All Patients N = 43	Chemotherapy-free <90 Days n = 20	Chemotherapy-free ≥90 Days n = 23
ORR, % (95% CI)	41.9 (27.0–57.9)	35.0 (15.4–59.2)	47.8 (26.8–69.4)
BOR, n (%)			
Confirmed PR	18 (41.9)	7 (35.0)	11 (47.8)
SD	18 (41.9)	7 (35.0)	11 (47.8)
PD	4 (9.3)	4 (20.0)	0
Not assessed	3 (7.0)	2 (10.0)	1 (4.3)
DCR, % (95% CI)[a]	83.7 (69.3–93.2)	70.0 (45.7–88.1)	95.7 (78.1–99.9)
CBR, % (95% CI)[b]	48.8 (33.3–64.5)	40.0 (19.1–63.9)	56.5 (34.5–76.8)
Median DOR, months (95% CI)[c,d]	4.73 (3.52–6.70)	6.31 (1.54–6.87)	4.44 (3.02–NR)
DOR rate at 6 months, % (95% CI)[c]	48.15 (23.86–68.88)	57.14 (17.19–83.71)	41.56 (13.11–68.42)
Median PFS, months (95% CI)[c]	4.40 (3.81–6.11)	3.81 (1.38–7.56)	4.98 (4.07–7.43)
Median OS, months (95% CI)[c]	13.60 (6.57–14.78)	6.57 (4.73–17.71)	14.72 (7.72–NR)

[a]Patients with confirmed PR + SD.
[b]Patients with confirmed PR + SD duration ≥6 months. SD duration was defined as the time from the date of the first dose of study drug to first documented PD or death from any cause.
[c]Based on Kaplan-Meier estimates.
[d]Calculated for patients with confirmed PR.
BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NR, not reached; OS, overall survival; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 3. Safety Summary		
	Patients (N = 43)	
Event	Any Grade	Grade ≥3
TEAEs, n (%)[a,b]	43 (100.0)	32 (74.4)
TEAEs reported in ≥10% of patients		
Diarrhea	33 (76.7)	4 (9.3)
Fatigue	26 (60.5)	1 (2.3)
Neutropenia	24 (55.8)	19 (44.2)
Constipation	18 (41.9)	0
Nausea	17 (39.5)	0
Alopecia	13 (30.2)	0
Anemia	13 (30.2)	2 (4.7)
Decreased appetite	10 (23.3)	0
Abdominal pain	8 (18.6)	0
Hypomagnesemia	7 (16.3)	0
Rash	7 (16.3)	0
Vomiting	7 (16.3)	0
Dizziness	6 (14.0)	0
Dysgeusia	6 (14.0)	0
Stomatitis	6 (14.0)	2 (4.7)
COVID-19	5 (11.6)	0
Cough	5 (11.6)	0
Hypokalemia	5 (11.6)	0
Hyponatremia	5 (11.6)	3 (7.0)
Hypotension	5 (11.6)	1 (2.3)
Edema peripheral	5 (11.6)	0
Treatment related[c]	42 (97.7)	26 (60.5)
TEAEs leading to treatment discontinuation	0	
Treatment related[c]	0	
TEAEs leading to death	3 (7.0)	
Treatment related[d]	1 (2.3)	
TEAEs leading to dose reduction	16 (37.2)	
TEAEs leading to treatment interruption	30 (69.8)	

[a]TEAE was defined as any safety event with an onset on or after the study drug start date and no later than 30 days after last dose of study drug.
[b]Coded per the Medical Dictionary for Regulatory Activities version 26.1. TEAE severity was graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Multiple TEAEs were counted only once per patient, with the highest severity grade for each preferred term.
[c]Determined by the investigator.
[d]Neutropenic sepsis was the treatment-related TEAE leading to death.
COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

FIGURE CAPTIONS

Figure 1. *(A)* Spider plot of tumor response by week per investigator assessment and *(B)* best percentage change from baseline in total sum of target lesion diameter per investigator assessment. [a]Three patients without any post-baseline assessments were counted as not assessed for response.

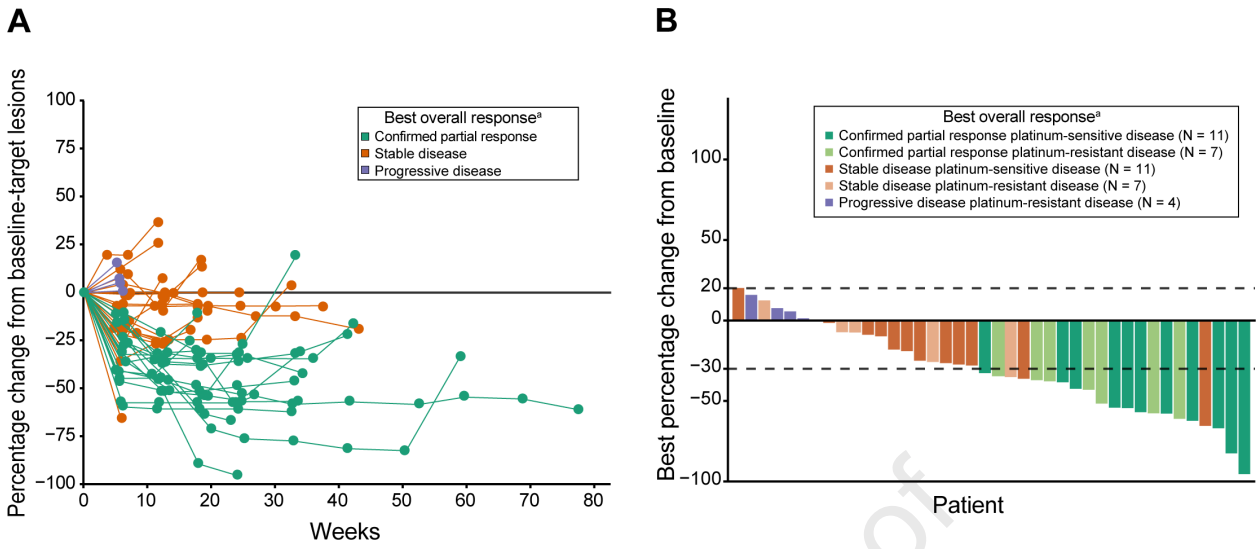
Figure 2. Kaplan-Meier plots for *(A)* progression-free survival per investigator assessment and *(B)* overall survival.

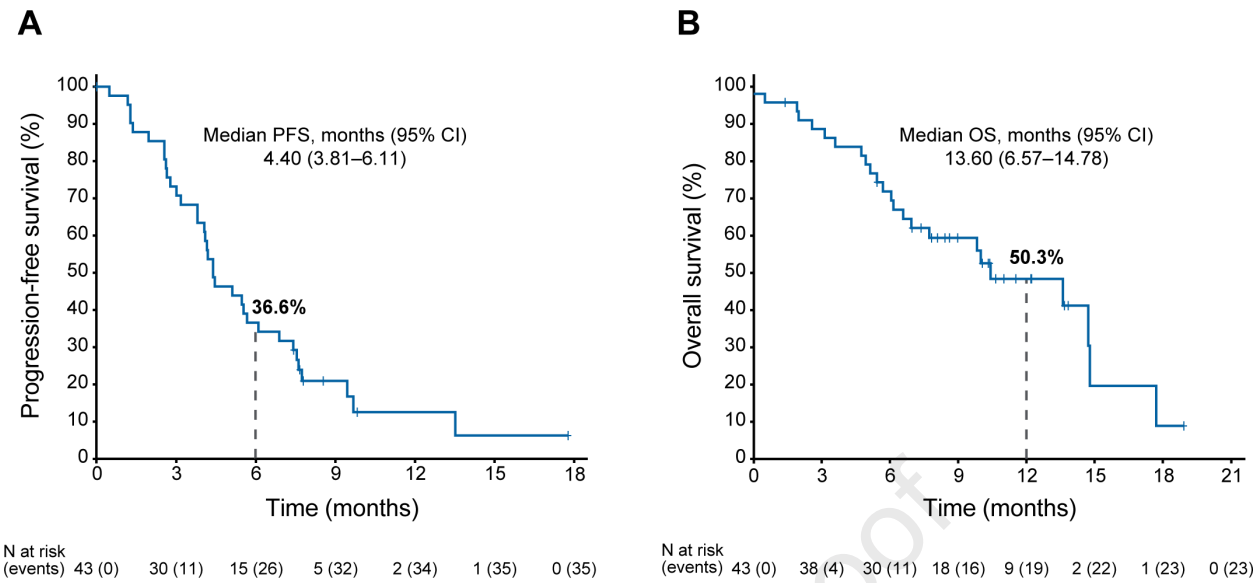
Supplemental Figure S1: Best percentage change from baseline in total sum of target lesion diameter by blinded independent central review.

Supplemental Figure S2: Flowchart of patients with ES-SCLC screened in the phase 2 TROPiCS-03 clinical trial.

SUPPLEMENTARY MATERIAL

Supplemental Data 1. Study Protocol.pdf
Supplemental Table 1.docx
Supplemental Table 2.docx
Supplemental Figure 1.tif
Supplemental Figure 2.tif





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