ORIGINAL ARTICLE

Efficacy and Safety of Rovalpituzumab Tesirine Compared With Topotecan as Second-Line Therapy in DLL3-High SCLC: Results From the Phase 3 TAHOE Study

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ABSTRACT

Introduction: DLL3, an atypical Notch ligand, is expressed in SCLC tumors but is not detectable in normal adult tissues. Rovalpituzumab tesirine (Rova-T) is an antibody-drug conjugate containing a DLL3-targeting antibody tethered to a cytotoxic agent pyrrolobenzodiazepine by means of a protease-cleavable linker. The efficacy and safety of Rova-T compared with topotecan as second-line therapy in patients with SCLC expressing high levels of DLL3 (DLL3-high) was evaluated.

Methods: The TAHOE study was an open-label, two-to-one randomized, phase 3 study comparing Rova-T with topotecan as second-line therapy in DLL3-high advanced or metastatic SCLC. Rova-T (0.3 mg/kg) was administered intravenously on day 1 of a 42-day cycle for two cycles, with two additional cycles available to patients who met protocol-defined criteria for continued dosing. Topotecan (1.5 mg/m^2) was administered intravenously on days 1 to 5 of a 21-day cycle. The primary end point was overall survival (OS).

Results: Patients randomized to Rova-T (n = 296) and topotecan (n = 148) were included in the efficacy analyses. The median age was 64 years, and 77% had the extensive disease at initial diagnosis. The median OS (95% confidence interval) was 6.3 months (5.6–7.3) in the Rova-T arm and 8.6 months (7.7–10.1) in the topotecan arm (hazard ratio, 1.46 [95% confidence interval: 1.17–1.82]). An independent data monitoring committee recommended that enrollment be discontinued because of the shorter OS observed with Rova-T compared with topotecan. Safety profiles for both drugs were consistent with previous reports.

Conclusions: Compared with topotecan, which is the current standard second-line chemotherapy, Rova-T exhibited an inferior OS and higher rates of serosal effusions, photosensitivity reaction, and peripheral edema in patients with SCLC. A considerable unmet therapeutic need remains in this population.

Keywords: Small cell lung cancer; Rovalpituzumab tesirine; Delta-like protein 3; Topotecan

Introduction

SCLC represents approximately 15% of all lung cancers.[1] SCLC arises from epithelial cells with neuroendocrine differentiation and is molecularly and clinically distinct from other lung cancers.[2] The Veterans Administration Lung Study Group stages SCLC as limited or extensive. The former is defined as a disease limited to the chest that can be encompassed by a radiation field and is treated with curative intent using combined modality chemoradiotherapy, or surgery and chemotherapy.

The extensive-stage disease includes all other cases and accounts for approximately two-thirds of newly diagnosed patients. The preferred combination regimens for first-line treatment of extensive-stage SCLC (ES-SCLC) include a platinum agent, etoposide, and a programmed death-ligand 1 (PD-L1) inhibitor followed by maintenance treatment with a PD-L1 inhibitor.[3] Although approximately 60% to 70% of patients respond to the initial combination of anti–PD-L1 blockade and platinum-based chemotherapy, most responses are not durable, and the median overall survival (OS) is only 12 to 13 months.[4,5] Options for patients with relapsed or recurrent SCLC are limited.

The topoisomerase I inhibitor topotecan has global approvals for patients with SCLC with platinum-sensitive disease who progressed 60 or more days after completion of first-line chemotherapy[6]; however, its activity is limited, with a median OS of less than 6 months,[7-9] and hematologic toxicity is substantial.[10] Therefore, a considerable unmet need exists for the second-line treatment of SCLC.

DLL3 is an atypical Notch receptor family ligand that is expressed on the surface of tumor cells in greater than 80% of SCLC and neuroendocrine carcinoma cases but is virtually undetectable in normal adult tissue.[11] Thus, DLL3 is a potentially promising target for an antibody-drug conjugate in SCLC. Furthermore, DLL3 expression prechemotherapy and postchemotherapy seems to be consistent over time, suggesting that treatment does not interfere with DLL3 expression.[12]

Rovalpituzumab tesirine (Rova-T) is a first-in-class antibody-drug conjugate composed of a DLL3-targeting immunoglobulin G1 monoclonal antibody tethered to pyrrolobenzodiazepine (PBD), a toxic DNA crosslinking agent, by means of a protease-cleavable linker.[11,13] In a first-in-human phase 1 study, Rova-T exhibited encouraging activity in recurrent SCLC, achieving a 31% and 85% confirmed objective response rate (ORR) and clinical benefit rate (CBR), respectively, on the basis of a central review, with a median OS of 5.8 months, in patients whose tumors expressed DLL3 in $\geq$50% of cells (on the basis of an anti-DLL3 mouse antibody immunohistochemistry [IHC] assay).[13] The phase 2 TRINITY study evaluated Rova-T in patients with DLL3-expressing SCLC that recurred after 2 or more systemic chemotherapy regimens. In contrast to the observations from the phase 1 study, Rova-T activity was modest in TRINITY, with a confirmed ORR of 12.4% (per central radiographic assessment) and a median OS of 5.6 months in all patients, and a confirmed ORR of 14.3% and a median OS of 5.7 months in a subset of DLL3-high patients (defined as $\geq$75% of DLL3-positive tumor cells using a rabbit anti-DLL3 antibody).[14] In this study (TAHOE), we evaluated the efficacy and safety of Rova-T compared with topotecan in the second-line setting among patients with DLL3-high advanced or metastatic SCLC.

Materials and Methods

Study Design and Patients

The TAHOE study was an open-label, two-is-to-one randomized, phase 3 study comparing the efficacy and safety of Rova-T and topotecan in patients at least 18 years old with histologically or cytologically confirmed, advanced, or metastatic, DLL3-high SCLC with first disease progression during or after first-line platinum-based chemotherapy. Patients with a history of central nervous system (CNS) metastases were required to have a radiographically confirmed stable or improved status of active CNS disease before randomization, assessed at least 2 weeks after completion of definitive treatment (surgical resection, whole-brain radiation therapy, or stereotactic radiotherapy) and at least 4 weeks after previous radiographic assessment, off or on a stable dose of corticosteroids. No radiographic evidence of progression of definitively treated CNS disease was to be present at the baseline tumor assessment.

Additional eligibility criteria included measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and adequate hematological, hepatic, and renal function. The key exclusion criteria were the following: (1) clinically substantial pulmonary disease, cardiac or neurologic disorder; (2) current occurrence or previous history of grade 2 or higher pleural or pericardial effusions with an ongoing requirement for pericardiocentesis or thoracentesis (given the occurrence of Rova-T–associated effusions in previous studies); (3) a history of capillary leak syndrome; (4) known leptomeningeal metastases; (5) another invasive malignancy in the previous 2 years; (6) more than 1 previous systemic therapy regimen for SCLC; (7) lack of adequate washout from previous anticancer therapy; or (8) previous exposure to a PBD- or indolinobenzodiazepine-based drug, Rova-T, or topoisomerase I inhibitor.

The primary end point was OS. The secondary end points included: (1) progression-free survival (PFS); (2) ORR; (3) CBR; (4) duration of response (DOR); and (5) patient-reported outcomes using the physical functioning domain of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care (EORTC QLQ-C15-PAL) questionnaire[15] (quality of life questionnaire for palliative care of patients with cancer) after 6 weeks of treatment (cycle two, d 1 for Rova-T and cycle three, d 1 for topotecan) and after the final visit.

The study was performed in accordance with the 2013 Declaration of Helsinki. All patients provided informed consent before screening procedures. The study design was approved by the institutional review board or ethics committee of participating institutions. An independent data monitoring committee (IDMC) periodically reviewed the safety and efficacy data. The study is registered with ClinicalTrials.gov (NCT03061812).

Procedures

Archived or fresh tumor material for DLL3 testing was collected after informed consent and before randomization. Eligibility required high DLL3 expression, which is defined as $\geq$75% tumor cells staining positive according to an IHC assay performed at a designated central laboratory using the DLL3 rabbit antibody Ventana SP347 (Ventana Medical Systems). Randomization (2:1) to Rova-T or topotecan was performed within 28 days of screening and was stratified through the following: (1) a previous history of brain metastases (yes versus no); (2) previous prophylactic cranial irradiation (PCI) (for patients with no previous history of brain metastases; yes versus no); (3) sensitivity to first-line platinum-based regimen (objective response or stable disease after first-line therapy and progression or recurrence-free interval $\geq$90 d versus progressive disease [PD] as the best response, or $<$90 d progression or recurrence-free interval); (4) and lactate dehydrogenase (LDH) level ($>$upper limit of normal [ULN] versus $\leq$ULN) at the screening.

Rova-T was administered intravenously (IV) at a dose of 0.3 mg/kg on day 1 of a 42-day cycle for two cycles. Dose interruptions or reductions were permitted for patients who exhibited treatment-related toxicities. Dexamethasone was coadministered orally twice daily at a dose of 8 mg on day -1, day 1, and day 2 of each cycle. Two additional cycles of Rova-T after disease progression were permitted for patients who had achieved stable disease or better, tolerated the initial treatment, did not progress for at least 12 weeks after the second dose, had not received additional anticancer therapy, and had not experienced clinically substantial symptoms related to disease progression or decline in PS. Topotecan was administered IV over 30 minutes at a dose of 1.5 mg/m^2 on days 1 through 5 of a 21-day cycle. Lower doses of topotecan were permitted if required per the local label. Treatment was continued until PD unless earlier discontinuation was warranted.

Radiographic assessment by computed tomography or magnetic resonance imaging was performed every 6 weeks for the first 30 weeks and every 9 weeks thereafter until PD or death. Patients discontinuing for reasons other than PD were followed up every 6 weeks until PD, initiation of a new anticancer therapy, or death. Response criteria were assessed by the investigator using RECIST v1.1. Treatment-emergent adverse events (TEAEs) were summarized using the Medical Dictionary for Regulatory Activities, version 19.1 and graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

Sample Size and Analyses

The target sample size was estimated to be 600 patients to reach approximately 489 deaths needed to detect a 25% reduction in the risk of death (corresponding to a hazard ratio [HR] of 0.75) with Rova-T versus topotecan at a one-sided significance level of 0.025 and a power of 85%. After their fourth safety review on December 4, 2018, the IDMC recommended that enrollment be discontinued because OS with Rova-T was shorter than that of topotecan. No new patients were enrolled after December 4, 2018 per IDMC recommendation; the already enrolled patients deriving treatment benefits could complete their assigned treatment. The last visit of the last patient (end-of-treatment visit) occurred on February 12, 2020, after which the database was locked. Data are reported as of February 12, 2020, and the target sample size was not reached. Of the 287 dosed patients at data cutoff, 174 (61%) had received 2 or more doses of Rova-T and completed the regimen, and 113 (39%) had received 1 dose of Rova-T.

Efficacy analyses were performed in all randomized patients. OS was defined as the time from randomization to death from any cause. For patients who were alive, data were censored at the last date they were documented to be alive. Patients with no postbaseline information were censored at the date of randomization plus 1 day. PFS was defined as the time from randomization to the first occurrence of investigator-assessed disease progression or death from any cause. DOR was defined as the time between first response (complete response [CR] or partial response [PR], whichever was recorded first) to first documented tumor progression (assessed as per RECIST v1.1) or death owing to any cause, whichever came first. The median OS, PFS, landmark OS and PFS rates, and DOR were estimated using the Kaplan-Meier method. HR was determined using a stratified Cox proportional hazards model with treatment and stratification factors as covariates. For PFS and DOR, patients without disease progression or death were censored at the time of the last radiographic assessment. ORR included confirmed CR and PR on the basis of RECIST v1.1, from randomization until disease progression or death. CBR included CR, PR, and stable disease

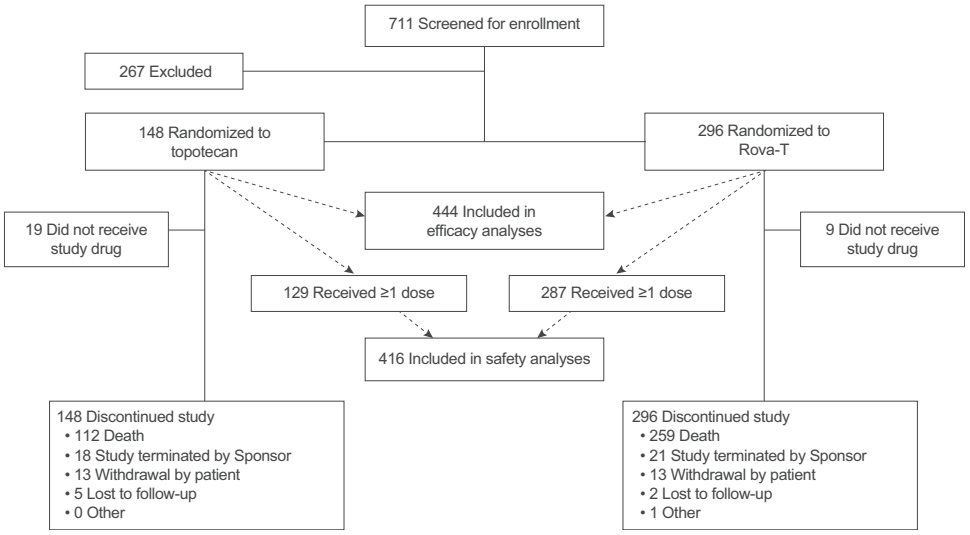

Figure 1. TAHOE CONSORT diagram. Rova-T, rovalpituzumab tesirine.

(on the basis of RECIST v1.1) from randomization until disease progression or death. Patients who did not meet CR or PR, including those who did not have postbaseline radiologic assessments, were considered nonresponders. TEAEs were defined as AEs with onset or increase in severity after the first dose of study drug but no more than 70 days after the last dose of study drug.

Patient-reported outcomes were collected using the EORTC QLQ-C15-PAL and the five-level EQ-5D (EQ-5D-5L) questionnaires at follow-up visits. The change from the baseline of the items and domains of the QLQ-C15-PAL were summarized by treatment arm. The change from baseline of the EQ-5D-5L utility score and visual analog scale were also summarized by treatment arm.

Results

Baseline Characteristics and Patient Disposition

A total of 711 patients were screened between April 11, 2017 and December 7, 2018, and 444 (62%) meeting high DLL3 expression and other inclusion criteria were enrolled and randomized to Rova-T (n = 296) or topotecan (n = 148) (Fig. 1). Demographic and baseline characteristics were balanced between treatment arms and are summarized in Table 1. The median age was 64 years (range: 32–85), 277 patients (62%) were men, and 265 patients (64%) had an Eastern Cooperative Oncology Group PS of 1. Most patients (n = 339; 77%) had extensive disease at diagnosis.

As of data cutoff in February 12, 2020, the median time on Rova-T was 12 weeks (range: 6–108), and the median number of cycles completed was 2 (1–4). A total of 178 patients (60%) discontinued Rova-T owing to the following primary reasons: (1) PD per RECIST v1.1 (n = 95; 32%); (2) AEs not related to disease progression (n = 38; 13%); (3) patient withdrawal (n = 12; 4%); (4) study termination by sponsor (n = 3; 1%); and (5) other reasons (n = 30; 10%). Eighteen patients (6%) had a dose reduction of Rova-T, with the reasons for dose reduction being AEs (n = 18; 6%) and other reasons (n = 1; 0.3%).

The median time on topotecan was 17 weeks (range: 6–79), and the median number of cycles completed was 4 (range: 1–22). A total of 128 patients (86%) discontinued topotecan primarily because of the following: (1) PD per RECIST v1.1 (n = 65; 44%); (2) AEs not related to disease progression (n = 26; 18%); (3) patient withdrawal (n = 15; 10%); (4) study terminated by sponsor (n=2; 1%); (5) lost to follow-up (n = 1; 1%); and (6) other reasons (n = 19; 13%). Topotecan dose reductions occurred in 52 patients (40%), because of AEs (n = 44; 34%), logistical or scheduling problems (n = 2; 2%), or other reasons (n = 9; 7%). At cycle one day 1, 11 patients (9%) received topotecan at 1 mg/m^2, a dose level lower than the protocol-defined level of 1.5 mg/m^2.

After data lock (February 12, 2020), all patients discontinued from the study. The primary reasons for study discontinuation in the Rova-T arm were death (n = 259; 88%), termination by sponsor (n = 21; 7%), withdrawal by patient (n = 13; 4%), lost to follow-up (n = 2; 1%), and other (n = 1; 0.3%); those in the topotecan arm were death (n = 112; 76%), termination by sponsor (n = 18; 12%), withdrawal by patient (n = 13; 9%), and lost to follow-up (n = 5; 3%).

Efficacy

Following the recommendation by the IDMC to discontinue study enrollment, the data collection plan was

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Rova-T n = 296	Topotecan n = 148
Median age (range), y	63.0 (36-85)	64.0 (32-85)
Male, n (%)	191 (65)	86 (58)
ECOG PS, n (%)		
0	95 (33)	53 (41)
1	191 (67)	74 (57)
2	1 (0.3)	2 (2)
Missing	9	19
VALG stage at initial diagnosis, n (%)		
Extensive disease	224 (76)	115 (78)
Limited disease	69 (24)	32 (22)
Missing	3	1
Response to first-line platinum-based chemotherapy, n (%)		
PD	155 (52)	79 (53)
Objective response or stable disease	141 (48)	69 (47)
Lactate dehydrogenase, n (%)		
>ULN	149 (50)	74 (50)
≤ULN	147 (50)	74 (50)
History of brain metastases,[a] n (%)		
Yes	175 (59)	87 (59)
No	121 (41)	61 (41)
Previous PCI,[b] n (%)		
Yes	3 (2)	3 (5)
No	118 (98)	58 (95)
DLL3 expression level[c]		
0 to <25%	0	0
25% to <75%	0	0
≥75%	296 (100%)	148 (100%)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PCI, prophylactic cranial irradiation; PD, progressive disease; PS, performance status; Rova-T, rovalpituzumab tesirine; ULN, upper limit of normal; VALG, Veterans Administration Lung Study Group.

[a]Patients with a history of CNS metastases had received definitive treatment for CNS disease and were required to have no active CNS disease before randomization.

[b]Previous PCI is only conducted in patients without any history of brain metastases; percentages are calculated out of the number of patients without any history of brain metastases.

[c]High DLL3 expression is defined as having ≥75% tumor cells staining positive using the Ventana DLL3 (SP347) (Ventana Medical Systems) immunohistochemistry assay.

minimized, and statistical testing for efficacy end points was not performed as originally planned. For efficacy end points that did have enough data to implement the statistical models, results were descriptively summarized by treatment arms.

After a median follow-up of 8.3 months (range: 0.03–32.1), 262 patients (86%) in the Rova-T arm and 115 patients (78%) in the topotecan arm had died. The median OS (primary end point) was 6.3 months (95% confidence interval [CI]: 5.6–7.3) in the Rova-T arm and 8.6 months (95% CI: 7.7–10.1) in the topotecan arm (HR = 1.46 [95% CI: 1.17–1.82]) (Fig. 2*A*).

Subgroup analysis for OS was also performed on the basis of various stratification factors (Supplementary Table 1). Similar to the observations in the overall population, a significantly shorter median OS in the Rova-T arm versus the topotecan arm was observed for patients without brain metastases at baseline, patients without previous PCI (permitted only in patients without a history of brain metastases), patients who were refractory or resistant to the first-line platinum-based regimen, patients with LDH levels greater than ULN, and patients with extensive disease at initial diagnosis. A similar trend in the median OS was observed in other subgroups, although the differences in median OS were not statistically significant. Notably, in the topotecan arm, the median OS was substantially longer in patients with LDH levels less than or equal to ULN (11.6 mo) and in patients who initially had limited disease (11.0 mo) versus the corresponding subgroups in the Rova-T arm (8.9 mo for patients with LDH ≤ULN and 8.5 mo for patients with limited disease), although these differences were not statistically significant. Within the Rova-T arm and within the topotecan arm, the median OS was numerically longer in patients with LDH less than or equal to ULN (versus those with LDH >ULN), in patients with limited disease (versus those with extensive disease on the basis of the Veterans Administration Lung Study Group stage at initial diagnosis), and in patients sensitive to first-line platinum-based chemotherapy (versus those resistant or refractory to first-line platinum-based therapy). Within the Rova-T arm, the median OS was substantially longer in patients with a previous history of brain metastases versus those without a history of brain metastases (Supplementary Table 1).

The median PFS (by investigator assessment) in the randomized population was also reduced in the Rova-T arm (3.0 mo [95% CI: 2.9–3.6]) versus the topotecan arm (4.3 mo [95% CI: 3.8–5.4]; HR = 1.51 [95% CI: 1.22–1.87]) (Fig. 2*B*). Among randomized patients with measurable disease at baseline (n = 416), the ORR was 15% (42 of 287) in the Rova-T arm, and 21% (27 of 129) in the topotecan arm (Table 2). One CR was observed in the Rova-T arm and none in the topotecan arm. A total of 41 (14%) had PR in the Rova-T arm compared with 27 patients (21%) in the topotecan arm. The median DOR was 3.5 months (95% CI: 2.8–4.2) and 4.9 months (95% CI: 3.9–7.9) in the Rova-T and topotecan arms, respectively. The CBR was 36% (103 of 287) with Rova-T and 43% (56 of 129) with topotecan (Table 2).

Global health and physical functioning per the mean EORTC QLQ-C15-PAL scores were not appreciably different between the Rova-T and topotecan arms at baseline and after 6 weeks of treatment (Table 3). At week 7, the mean difference in scores between the Rova-T and topotecan arms was −3.53 (range: −8.23 to 1.16)

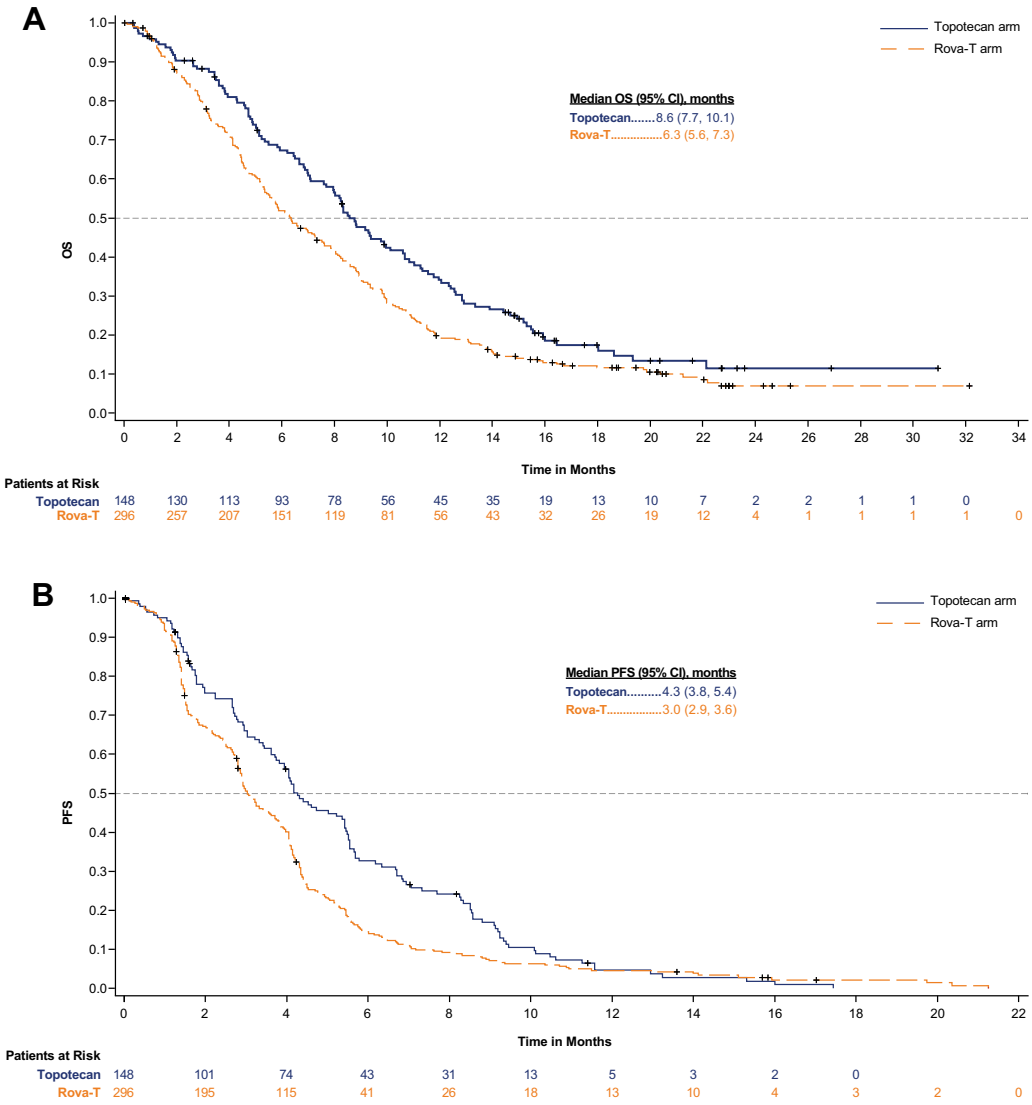

Figure 2. (*A*) OS and (*B*) PFS in all randomized patients. CI, confidence interval; OS, overall survival; PFS, progression-free survival; Rova-T, rovalpituzumab tesirine.

for global health and −0.50 (range: −5.66 to 4.65) for physical functioning. However, at the final visit (the last valid postbaseline record of a patient), the mean difference in scores between the arms of –7.17 (95% CI: −11.39 to −2.94) for global health and −6.45 (95% CI: −11.73 to −1.18) for physical functioning suggested a further decline in global health and physical functioning in the Rova-T arm over time (Table 3).

Safety

Patients who received at least one dose of Rova-T (n = 287) or topotecan (n = 129) were included in safety analyses. A total of 273 patients (95%) experienced a TEAE in the Rova-T arm, and 125 patients (97%) experienced a TEAE in the topotecan arm (Table 4). The most common TEAEs (≥20%) with Rova-T were pleural effusion (29%), decreased appetite (25%), dyspnea (25%), fatigue (25%), nausea (23%), and pericardial effusion (20%). In the topotecan arm, anemia (61%), neutropenia (43%), thrombocytopenia (43%), nausea (31%), decreased appetite (28%), fatigue (27%), constipation (22%), and leukopenia (20%) were most common. Grade 3 or higher AEs were observed in 183 patients (64%) in the Rova-T arm and 113 patients (88%) in the topotecan arm and were primarily hematologic AEs in both arms (Table 4). Serious TEAEs occurred in 160 patients (56%) in the Rova-T arm and in 74 patients (57%) in the topotecan arm. The most common serious TEAEs included malignant neoplasm progression (10%), pneumonia (7%), pleural effusion (6%), and dyspnea (6%) in the Rova-T arm, and malignant neoplasm progression (13%), febrile neutropenia (9%), and thrombocytopenia (8%) in the topotecan arm

Table 2. Efficacy Outcomes for Patients With Measurable Disease at Baseline

Outcome	Rova-T n = 287	Topotecan n = 129
Objective response,[a] n (%)		
Complete response	1 (0.3)	0 (0)
Partial response	41 (14)	27 (21)
Stable disease	61 (21)	29 (22)
Progressive disease	154 (54)	58 (45)
Not assessable or incomplete data	30 (10)	15 (12)
Objective response rate,[a] n (%)	42/287 (15)	27/129 (21)
Clinical benefit rate,[a] n (%)	103/287 (36)	56/129 (43)
Median duration of response (95% CI),[a] mo	3.5 (2.8, 4.2)	4.9 (3.9, 7.9)

CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors; Rova-T, rovalpituzumab tesirine.
[a]Per investigator assessment on the basis of RECIST version 1.1.

(Supplementary Table 2). A total of 17% of patients (50 of 287) in the Rova-T arm and 30% (39 of 129) in the topotecan arm had drug-related serious AEs.

The AEs of special interest (AESI), such as cutaneous reaction (39% versus 12%), edema (30% versus 10%), pleural effusion (29% versus 4%), pericardial effusion (20% versus 2%), and photosensitivity reaction (16% versus 0%), were more common in the Rova-T arm than in the topotecan arm. Hematologic AESI of thrombocytopenia (19% versus 48%), anemia (16% versus 62%), neutropenia (10% versus 62%), and febrile neutropenia (1% versus 12%) were less common in the Rova-T arm than in the topotecan arm. A complete summary of AESI is provided in Supplementary Table 3.

TEAEs led to death in 64 patients (22%) in the Rova-T arm and 28 patients (22%) in the topotecan arm. The most common AEs leading to death in the Rova-T arm were malignant neoplasm progression (n = 26; 9%), pneumonia (n = 7; 2%), and general physical health deterioration (n = 6; 2%), and those in the topotecan arm were malignant neoplasm progression (n = 17; 13%) and general physical health deterioration (n = 3; 2%). Five patients in the Rova-T arm had drug-related AEs leading to death, which included pneumonia (n = 2), pancreatitis (n = 1), atypical pneumonia (n = 1), and interstitial lung disease (n = 1). No deaths due to drug-related AEs were reported in the topotecan arm.

Discussion

Rova-T targets a novel SCLC biomarker, DLL3. The TAHOE study enrolled patients with pretreated SCLC with high expression of DLL3, with the intent to select patients most likely to benefit from Rova-T. However, a shorter OS was observed in the Rova-T arm compared with the topotecan arm. The same trend of shorter OS in the Rova-T versus topotecan arm was observed in subsets defined by stratification factors such as platinum-sensitive versus refractory or resistant disease at baseline, the presence or absence of CNS metastases at baseline, a previous PCI (permitted only in patients without a history of brain metastases), and extensive versus limited disease at initial diagnosis. Notably, median OS was numerically longer within the Rova-T and topotecan arms for patients with favorable prognostic stratification factors, such as LDH less than or equal to ULN (versus LDH > ULN), limited disease (versus extensive disease), and platinumsensitivity (versus platinum resistance or refractoriness). Most patients had extensive disease at diagnosis, which could explain the high number of patients with brain metastases at baseline.

In the overall population, PFS was shorter and ORR was lower with Rova-T versus topotecan. Similarly, DOR was also shorter in the Rova-T arm compared with the topotecan arm. The MERU study, another phase 3 trial evaluating Rova-T as first-line maintenance therapy for advanced SCLC, although exhibiting longer PFS in the Rova-T arm versus the placebo arm, found no OS benefit at a preplanned interim analysis. The MERU trial was closed in August 2019. As a result, the development of Rova-T was discontinued on the basis of results from the TAHOE and MERU studies.[16,17]

The present results from TAHOE are similar to a subset analysis of 238 DLL3-high patients in the TRINITY study, which evaluated Rova-T (0.3 mg/kg every 6 wk for two cycles) as a third-line or later therapy in SCLC—the ORR was 14.3%, the median PFS was 3.8 months, and the median OS was 5.7 months.[14] However, the current efficacy results are inferior to those observed in the initial phase 1 study evaluating Rova-T in patients with recurrent ES-SCLC, which exhibited an investigator-assessed ORR of 38% at active doses of 0.2 mg/kg or 0.4 mg/kg every 3 weeks or 0.3 mg/kg or 0.4 mg/kg every 6 weeks, with a median PFS of 4.3 months and also a DOR of 4.3 months in DLL3-high patients.[13] It should be noted that the analysis of the DLL3-high patients in the phase 1 study was exploratory and retrospective, the overall sample size and the size of the DLL3-high patient subset were small, not all enrolled patients had assessable tissue, and a different IHC assay was used to quantify DLL3 expression. All these factors may have contributed to the reported higher response rate in the DLL3-high subset of the early phase 1 study. In addition, the Rova-T dose in

Table 3. Patient-Reported Outcomes Using the QLQ-C15-PAL and the EQ-5D-5L VAS Questionnaires

	Rova-T			Topotecan			
QoL Scale	n	Visit Mean (SD)	LS Mean Change From Baseline (95% CI)	n	Visit Mean (SD)	LS Mean Change From Baseline (95% CI)	LS Mean of Difference Between Groups (95% CI)[a]
EORTC QLQ-C15-PAL[b]							
Global health							
Baseline	255	64.84 (20.52)	NA	117	65.38 (21.46)	NA	NA
Wk 7	217	61.37 (21.95)	−5.86 (−9.19 to −2.54)	93	62.90 (21.72)	−2.33 (−6.70 to −2.04)	−3.53 (−8.23 to 1.16)
Final visit	255	52.71 (21.50)	−13.29 (−16.36 to −10.22)	117	59.90 (22.64)	−6.12 (−10.09 to −2.16)	−7.17 (−11.39 to −2.94)
Physical functioning							
Baseline	255	71.32 (21.54)	NA	117	73.28 (20.29)	NA	NA
Wk 7	217	66.4 1(23.80)	−7.66 (−11.31 to −4.01)	93	66.38 (26.72)	−7.16 (−11.95 to −2.36)	−0.50 (−5.66 to 4.65)
Final visit	255	56.71 (26.96)	−16.03 (−19.86 to −12.21)	117	63.93 (28.68)	−9.58 (−14.52 to −4.65)	−6.45 (−11.73 to −1.18)
EQ-5D-5L VAS[c]							
Baseline	247	70.13 (18.19)	NA	116	68.60 (18.85)	NA	NA
Wk 7	212	68.45 (20.08)	−3.65 (−6.57 to −0.73)	92	67.01 (20.03)	−2.2 (-6.10, 1.55)	−1.37 (−5.49 to 2.75)
Final visit	247	59.32 (20.50)	−11.28 (−14.11 to −8.46)	116	65.34 (21.11)	−4.23 (−7.86 to −0.61)	−7.05 (−10.93 to −3.16)

CI, confidence interval; EORTC QLQ-C15-PAL, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care; EQ-5D-5L, five-level EQ-5D; LS, least square; NA, not applicable; QoL, quality of life; Rova-T, rovalpituzumab tesirine; VAS, visual analog scale.

[a]Calculated relative to the topotecan arm.

[b]Scores range from 0 to 100, with higher scores indicating a higher level of functioning.

[c]Scores range from 0 to 100, with higher scores indicating higher levels of self-perceived health.

the TAHOE study was selected on the basis of a maximum tolerated dose and recommended phase 2 dose established in the phase 1 study.[13] The dose-limiting toxic effects at higher doses of Rova-T (0.8 mg/kg every 3 wk) observed in the phase 1 study limited the longer duration of treatment or higher dosing in the TAHOE study.

The analysis of quality of life using the EORTC QLQ-C15-PAL and EQ-5D-5L VAS scores indicated a higher decline in global health and physical functioning over time in the Rova-T arm compared with the topotecan arm. The safety profile of Rova-T in the TAHOE study was similar to that reported in other clinical studies.[13,14] Pleural effusions, pericardial effusions, edema, cutaneous reactions, photosensitivity reaction, and thrombocytopenia were AESI in the Rova-T arm. It has been postulated that the unique toxicity profile of Rova-T is because of the premature lysis of the linker, causing a systemic release of cytotoxic PBD.[18] Alternatively, a free drug may have a "bystander effect" on surrounding cells through diffusion out of the target cells or cleavage before internalization by cathepsin B, which is released by tumor cells or tumor-associated macrophages.[14,19]

An overall deterioration in the quality of life over time along with the unique toxicity profile associated with Rova-T, such as serosal effusions, suggest challenges for the tolerability of Rova-T treatment and warrant careful consideration of its potential toxicity in the fragile ES-SCLC population. In addition, topotecan exhibited a superior median OS (8.6 mo versus 6.3 mo) and CBR (43% versus 36%) compared with Rova-T, which supports the continued use of topotecan in the second-line ES-SCLC setting.

Although Rova-T did not improve the standard of care in second-line treatment of SCLC, it proved feasible in this study to select patients on the basis of tissue expression of DLL3 in the attempt to improve the therapeutic index of this approach. Other DLL3-targeting agents are being evaluated in this setting. AMG 757, a bispecific T-cell engager antibody against DLL3 and CD3, and AMG 119, an adoptive cellular therapy designed to target DLL3-expressing cells, are both under evaluation in phase 1 studies in patients with SCLC.[20,21] DLL3 is also typically expressed in castration-resistant neuroendocrine prostate cancer,[22] gastrointestinal neuroendocrine carcinomas,[23] and small cell bladder cancer,[24] and thus, may be a useful target in a number of cancers.

Despite recent approvals of PD-L1 and programmed cell death protein-1 inhibitors in the

Table 4. TEAEs by Severity Reported in at Least 10% of Either Treatment Group

	Rova-T n = 287				Topotecan n = 129			
TEAE, n (%)	Grade 1-2	Grade 3-4	Grade 5	Any-Grade	Grade 1-2	Grade 3-4	Grade 5	Any-Grade
Any TEAE	90 (31)	119 (42)	64 (22)	273 (95)	12 (9)	85 (66)	28 (22)	125 (97)
Pleural effusion	70 (24)	12 (4)	0	82 (29)	5 (4)	0	0	5 (4)
Decreased appetite	64 (22)	9 (3)	0	73 (25)	31 (24)	5 (4)	0	36 (28)
Dyspnea	50 (17)	21(7)	1 (0.3)	72 (25)	24 (19)	1 (1)	0	25 (19)
Fatigue	56 (20)	15 (5)	0	71 (25)	27 (21)	8 (6)	0	35 (27)
Nausea	64 (22)	3 (1)	0	67 (23)	40 (31)	0	0	40 (31)
Pericardial effusion	53 (19)	4 (1)	0	57 (20)	3 (2)	0	0	3 (2)
Peripheral edema	50 (17)	2 (1)	0	52 (18)	11 (9)	0	0	11 (9)
Anemia	27 (9)	19 (7)	0	46 (16)	34 (26)	45 (35)	0	79 (61)
Photosensitivity reaction	41 (14)	5 (2)	0	46 (16)	0	0	0	0
Thrombocytopenia	17 (6)	27 (9)	0	44 (15)	19 (15)	36 (28)	0	55 (43)
Cough	41 (14)	1 (0.3)	0	42 (15)	16 (12)	0	0	16 (12)
Asthenia	34 (12)	3 (1)	1 (0.3)	38 (13)	18 (14)	3 (2)	0	21 (16)
Constipation	33 (12)	4 (1)	0	37 (13)	29 (23)	0	0	29 (23)
Malignant neoplasm progression	5 (2)	5 (2)	26 (9)	36 (13)	0	1 (1)	17 (13)	18 (14)
Pneumonia	13 (5)	12 (4)	7 (2)	32 (11)	5 (4)	6 (5)	0	11 (9)
omiting	28 (10)	3 (1)	0	31 (11)	17 (13)	1 (1)	0	18 (14)
Back pain	20 (7)	2 (1)	0	22 (8)	10 (8)	3 (2)	0	13 (10)
Diarrhea	21 (7)	1 (0.3)	0	22 (8)	25 (19)	0	–	25 (19)
Headache	20 (7)	1 (0.3)	0	21 (7)	9 (7)	4 (3)	0	13 (10)
Hypokalemia	11 (4)	7 (2)	0	18 (6)	10 (8)	4 (3)	0	14 (11)
Neutropenia	5 (2)	9 (3)	0	14 (5)	7 (5)	49 (38)	0	56 (43)
Epistaxis	9 (3)	0	0	9 (3)	11 (9)	3 (2)	0	14 (11)
Febrile neutropenia	0	4 (1)	0	4 (1)	1 (1)	13 (10)	1 (1)	15 (12)
Leukopenia	0	4 (1)	0	4 (1)	4 (3)	22 (17)	0	26 (20)
Alopecia	3 (1)	0	0	3 (1)	20 (16)	0	0	20 (16)

Rova-T, rovalpituzumab tesirine; TEAE, treatment-emergent adverse event.

first-[4,5] and third-line settings,[25-27] no treatment has substantially improved OS in ES-SCLC since the 1970s.[28] The TAHOE study joins several setbacks in second-line therapy, including the recent phase 3 CheckMate-331 study, in which the programmed cell death protein-1 inhibitor nivolumab failed to improve OS versus topotecan or amrubicin.[29] Albeit disappointing, improvements in the understanding of SCLC gained in these trials may contribute to eventual breakthroughs in the treatment of SCLC.

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not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided after review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.h.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.02.009.

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