ORIGINAL ARTICLE

Rovalpituzumab Tesirine as a Maintenance Therapy After First-Line Platinum-Based Chemotherapy in Patients With Extensive-Stage-SCLC: Results From the Phase 3 MERU Study

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ABSTRACT

Introduction: Rovalpituzumab tesirine (Rova-T) is an antibody-drug conjugate targeting DLL3, an atypical Notch ligand expressed in SCLC tumors. We evaluated the efficacy of Rova-T versus placebo as maintenance therapy in patients with extensive-stage–SCLC after platinum-based chemotherapy.

Methods: MERU was a phase 3 randomized, double-blinded, placebo-controlled study. Patients without disease progression after four cycles of platinum-based, front-line chemotherapy were randomized in a 1:1 ratio to receive 0.3 mg/kg Rova-T or placebo (every 6 wk, omitted every third cycle). Primary efficacy end points were progression-free survival (PFS) evaluated by the Central Radiographic Assessment Committee and overall survival (OS) in patients with DLL3-high tumors.

Results: Median age of all randomized patients (N = 748) was 64 years; 78% had TNM stage IV disease. At futility analysis of the subset with DLL3-high tumors, the hazard ratio for OS was 1.07 (95% confidence interval: 0.84–1.36) favoring the placebo arm, with median OS of 8.5 and 9.8 months in the Rova-T and placebo arms, respectively; futility criteria were met. Rova-T significantly improved PFS versus placebo by investigator assessment (4.0 versus 1.4 mo, hazard ratio = 0.48, $p < 0.001$). Any-grade adverse events (≥20%) in the Rova-T arm were pleural effusion (27%), decreased appetite (27%), peripheral edema (26%), photosensitivity reaction (25%), fatigue (25%), nausea (22%), and dyspnea (21%).

Conclusions: Because of the lack of survival benefit in the Rova-T arm, the study did not meet its primary end point and was terminated early. As a result, the Central Radiographic Assessment Committee evaluation of PFS was not performed. The frequency of grade greater than or equal to 3 and drug-related toxicities were higher with Rova-T versus placebo. Rova-T was associated with unique toxicities, such as pleural and pericardial effusions, photosensitivity reaction, and peripheral edema, which should be carefully considered in the population with extensive-stage–SCLC.

Keywords: Rovalpituzumab tesirine; Small cell lung cancer; Maintenance; Phase 3; DLL3; Platinum-based chemotherapy

Introduction

Platinum-based systemic chemotherapy (carboplatin or cisplatin combined with etoposide) is the mainstay of front-line treatment in extensive-stage–SCLC (ES-SCLC), with initial response rates of 60% to 80% including complete response (CR) rates of 15% to 20%. However, responses are not durable, and relapse is common.[1,2] Several recent trials have revealed moderate improvements in survival when immune checkpoint inhibitors are combined with first-line chemotherapy, leading to the regulatory approval of anti-programmed death-ligand 1 antibodies, atezolizumab and durvalumab, for first-line treatment of ES-SCLC.[3,4] Despite these advancements, median overall survival (OS) with atezolizumab and durvalumab combined with chemotherapy remains limited (12 mo and 13 mo, respectively).[3,4] Thus, ES-SCLC remains a rapidly progressing disease with poor prognosis.

DLL3 is an atypical ligand of the Notch receptor family identified as a novel therapeutic target in SCLC and other high-grade neuroendocrine carcinomas. DLL3 is expressed during embryonic development, in which one of its roles is in formation of axial skeleton, and a rare autosomal recessive genetic disorder, spondylocostal dysostosis type 1, is caused by mutations in the *DLL3* gene.[5] There is no detectable DLL3 protein expression in normal adult tissues; however, it is expressed in most SCLC and large-cell neuroendocrine carcinoma tumors.[6,7] Tumor DLL3 expression seems to remain unchanged pre- and post-chemotherapy, suggesting analysis of diagnostic

archival tissue is adequate to estimate posttreatment DLL3 expression level.[8]

Rovalpituzumab tesirine (Rova-T) is a first-in-class antibody-drug conjugate composed of a DLL3-targeting immunoglobulin G1 monoclonal antibody tethered to a toxic DNA crosslinking agent of pyrrolobenzodiazepine (PBD) class by means of a protease-cleavable linker.[6,9] In the first-in-human, phase 1 study of Rova-T in patients with ES-SCLC progressing on greater than or equal to 1 previous regimens, the objective response rate (ORR) as evaluated by an Independent Review Committee was 16% and the disease control rate was 64%, with better efficacy outcomes in patients with DLL3-high tumors (detectable DLL3 expression in $\geq$50% of tumor cells staining positive using a mouse anti-DLL3 antibody) versus those with DLL3-low tumors (detectable DLL3 expression in $<$50% of tumor cells).[9] Activity of Rova-T observed in phase 1 in patients with relapsed or refractory tumors, although difficult to interpret definitively owing to the small number of patients and the single-arm study design, seemed sufficiently promising to prompt initiation of several studies in ES-SCLC. These included a phase 2 single-arm study (TRINITY) in third and later lines of therapy and two randomized phase 3 studies, TAHOE (Rova-T versus topotecan in second-line ES-SCLC) and the MERU study described here. In the TRINITY study, Rova-T yielded an ORR (as evaluated by central radiographic assessment) of 12.4% and a disease control rate of 70%. For patients with DLL3-high tumors (defined in this study as $\geq$75% DLL3-positive tumor cells using a rabbit anti-DLL3 antibody), the ORR was 14.3%, whereas patients with DLL3-positive tumors (defined as $\geq$25% DLL3-positive tumor cells) had an ORR of 13.2%.[10]

When compared with standard-of-care platinum-based chemotherapy, Rova-T was found to substantially reduce the frequency of tumor-initiating cells in low-passage SCLC patient-derived xenografts.[6] By targeting this resistant, residual cell population, Rova-T has a compelling rationale for use in the postinduction chemotherapy maintenance setting. We hypothesized that the preclinical and clinical activities observed in patients with recurrent or relapsed SCLC would also be evident among patients with ES-SCLC who would be treated with Rova-T in the maintenance setting.[11,12] To this end, we evaluated whether Rova-T improves progression-free survival (PFS) and OS compared with placebo in patients with ES-SCLC after platinum chemotherapy.

Materials and Methods

Study Design

MERU was a phase 3 randomized, double-blinded, placebo-controlled study enrolling patients with ES-SCLC who have stable disease, partial response (PR), or CR after four cycles of first-line platinum-based chemotherapy. On completion of chemotherapy and before randomization, eligible patients were offered prophylactic cranial irradiation (PCI), if in accordance with local guidelines.

The primary end points were PFS determined by a Central Radiographic Assessment Committee (CRAC) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1) and OS in the population with DLL3-high tumors. The secondary end points included PFS (evaluated by CRAC) and OS in all randomized patients and change in patient-reported outcome with physical functioning as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) in randomized patients. Exploratory end points in both DLL3-high and randomized patients included PFS by investigator, ORR and clinical benefit rate (CBR) per CRAC and investigator (on the basis of RECIST v.1.1), and duration of response (DOR) per CRAC and investigator.

The study was approved by local institutional review boards of all participating centers, and all patients provided written informed consent. The study was designed according to Good Clinical Practice Guidelines and the Declaration of Helsinki. The trial is registered at www.clinicaltrials.gov (NCT03033511).

Randomization and Study Treatment

Patients were randomized in a 1:1 ratio to receive 0.3 mg/kg intravenous Rova-T or intravenous placebo on day 1 of each 6-week cycle, omitting every third cycle. Premedication and postmedication included 8 mg orally of dexamethasone or placebo twice daily on the day before, day of, and day after study drug administration. Randomization was stratified by postchemotherapy response (stable disease versus PR or CR) according to the RECIST v.1.1 criteria,[13] DLL3 expression (performed in a designated central IHC laboratory using Ventana DLL3 [SP347] assay (Ventana Medical Systems, Inc - Roche Diagnostics, Oro Valley, AZ); $<$75% defined as DLL3-low versus $\geq$75% defined as DLL3-high), history of central nervous system (CNS) metastases (yes versus no), and PCI versus no PCI for patients with no history of CNS metastases.

Patients

Eligible patients were aged greater than or equal to 18 years with histologically or cytologically confirmed ES-SCLC who had completed four cycles of front-line platinum-based chemotherapy (cisplatin or carboplatin with etoposide or irinotecan) at least 3 weeks but not more than 9 weeks before randomization and had stable

disease, PR, or CR per RECIST v.1.1, as evaluated by the investigator. ES disease was defined, on the basis of the Veterans Administration Lung Study Group staging, as SCLC with disease involvement of any anatomical location exceeding that of limited-stage disease (disease confined to the hemithorax of origin, with or without the involvement of regional lymph nodes, including ipsilateral and contralateral hilar, ipsilateral, and contralateral mediastinal and ipsilateral supraclavicular nodes).[14] All patients had representative tumor tissue available for central assessment of DLL3 expression. Patients with a history of CNS metastases were required to complete definitive local treatment and to have stable or improved CNS disease status on the basis of brain imaging within 28 days before randomization, off or on a stable dose of corticosteroids.

Main exclusion criteria were as follows: any previous systemic chemotherapy or targeted therapy for SCLC other than platinum-based front-line therapy; any previous disease-directed radiotherapy except PCI, palliative radiotherapy to a nonprogressing lesion, or preplanned radiotherapy for nonprogressing CNS metastases present before start of first-line therapy; documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association classes III to IV within 6 months before first dose of study therapy; documented capillary leak syndrome; grade greater than or equal to 2 pleural or pericardial effusion within four weeks of randomization or previous history requiring pericardiocentesis or thoracentesis; and previous exposure to a PBD-based drug.

Study Assessments and Statistical Methods

The study was designed with dual primary end points—PFS as evaluated by the blinded CRAC and OS in the population with DLL3-high tumors. The sample size was primarily determined on the basis of OS analysis. Considering the study population and the study hypothesis on Rova-T efficacy, the median OS in the placebo and Rova-T arms was expected to be approximately 9 months[11,12] and 13 months, respectively. Such an increase in median OS in the Rova-T arm corresponds to a hazard ratio (HR) of 0.69. With these assumptions, 319 deaths among patients with DLL3-high tumors were needed to achieve a 90% power on the basis of a log-rank test at a one-sided significance level of 0.0225. Assuming a 19-month accrual period and the last enrolled patient followed for 12 months, at least 480 patients with DLL3-high tumors were to be randomized (240 subjects in each arm). A target size of 740 patients (including 480 patients with DLL3-high tumors) was estimated, assuming an approximate prevalence of 65% for patients with DLL3-high tumors.

Because the study was terminated early as a result of OS-based futility analysis, CRAC evaluation of PFS was not performed. As a result, investigator-assessed PFS, ORR, CBR, and DOR, which are exploratory study end points, are reported here in a hypothesis-generating manner.

Investigator-assessed PFS was defined from randomization to disease progression as evaluated by the investigator per RECIST v.1.1, or death of any cause, whichever occurred first. OS was defined from randomization to death of any cause. Median PFS and OS were estimated using Kaplan-Meier method. Investigator-assessed ORR was defined as the proportion of patients with a best overall response (BOR) of CR or PR per investigator assessment according to RECIST v.1.1. CBR was defined as the proportion of patients with a BOR of CR or PR or stable disease by investigator assessment according to RECIST v.1.1. DOR was defined from the day the patient met the criteria for confirmed CR or PR per investigator assessment (whichever is recorded first) to the date of progressive disease or death, whichever comes first.

An unblinded interim analysis was conducted and reviewed by the Independent Data Monitoring Committee. A futility analysis was planned when approximately 160 deaths in patients with DLL3-high ES-SCLC (approximately 50% of the planned deaths) were observed. If the estimated Cox HR for OS analysis of Rova-T to placebo exceeded 0.9, the trial would be stopped early.

The safety of Rova-T was evaluated through study drug exposure and adverse events assessed by NCI CTCAE version 4.0 until 70 days after the last dose of the study drug.

Results

Patient Characteristics and Disposition

A total of 1084 patients were screened between February 7, 2017, and July 29, 2019. Of the 748 patients enrolled, 372 patients were randomized to the Rova-T arm and 376 patients to the placebo arm (Fig. 1). Demographics and baseline characteristics were well balanced between the two arms (Table 1). The median age was 64 years (range: 38–94), 581 (78%) of patients had TNM stage IV disease, and 40 (5%) had stage IIIB disease at the start of first-line therapy. Of the 748 randomized patients, 457 (61%) had DLL3-high expression. On completion of four cycles of first-line platinum-based chemotherapy, 581 patients (78%) had a BOR of CR or PR and 167 (22%) had a BOR of stable disease per RECIST v.1.1 criteria as assessed by investigator. History of CNS metastases was documented in 110 (15%) of patients at baseline. Of the 320 patients

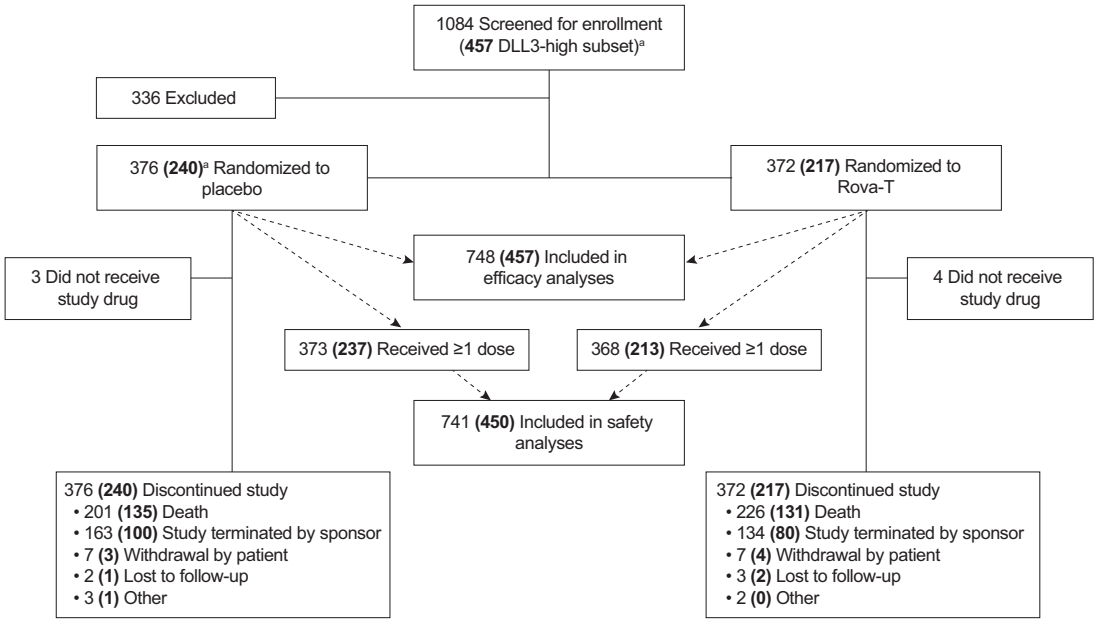

Figure 1. CONSORT diagram for all randomized patients in the MERU study. [a]Numbers in parentheses denote number of patients in the DLL3-high subset (≥75% DLL3-positive tumor cells using a rabbit anti-DLL3 antibody). Rova-T, rovalpituzumab tesirine.

from the placebo arm and 318 patients from the Rova-T arm without previous history of CNS metastases, PCI was administered to 72 patients (23%) and 73 patients (23%), respectively, before randomization (Table 1).

At the data cutoff date of February 19, 2019, the median time on the study was 8 months (range: 0.1–25.6). The median time from the last dose of platinum-based chemotherapy to randomization was 6.3 weeks for the placebo arm and 6.1 weeks for the Rova-T arm. The median time from initial diagnosis of ES-SCLC to randomization was 20.6 weeks for both Rova-T and placebo arms. A total of 156 patients (42%) in the Rova-T arm and 107 patients (29%) in the placebo arm had completed two cycles of study drug administration, and 127 (35%) and 225 (60%) of patients in the Rova-T and placebo arms, respectively, had completed one cycle of study drug administration. The median time on Rova-T was 18 weeks (range: 6.0–80.0), and the median time on placebo was 6 weeks (6.0–109.1).

All randomized patients had discontinued the study as of February 19, 2020. The primary reasons for study discontinuation in the Rova-T arm included death (n = 226; 61%), study termination by sponsor (n = 134, 36%), withdrawal by patient (n = 7; 2%), lost to follow-up (n = 3; 1%), and other reasons (n = 2; 1%). In the placebo arm, the primary reasons for study discontinuation were death (n = 201; 53%), study termination by sponsor (n = 163, 43%), withdrawal by patient (n = 7; 2%), lost to follow-up (n = 2; 1%), and others (n = 3, 1%).

Efficacy

Efficacy analyses were performed in the randomized set and in the DLL3-high subset. There were 131 deaths (60%) in the Rova-T arm and 135 deaths (56%) in the placebo arm of the DLL3-high subset. Per protocol specifications, a futility analysis was performed after approximately 50% of the expected deaths in the DLL3-high patients. For this subset, the median OS was 8.5 months (95% confidence interval [CI]: 7.3–10.2) in the Rova-T arm and 9.8 months (95% CI: 8.4–10.9) in the placebo arm (stratified log-rank p value = 0.537), with 6-month OS rates of 70% and 66%, respectively (Fig. 2*A*). Using a Cox proportional hazards model, adjusting for randomization stratification factors, the HR for OS was 1.07 (95% CI: 0.84–1.36), favoring the placebo arm; hence, the futility criteria were met. As the study was terminated after the lack of OS benefit in futility analysis, PFS evaluation by CRAC was not conducted, and only the exploratory end point of PFS by investigator assessment is reported here. As assessed by investigator, the median PFS for the DLL3-high subset was 4 months (95% CI: 3.2–4.1) in the Rova-T arm and 1.4 months (95% CI: 1.4–1.5) in the placebo arm (HR 0.48, 95% CI: 0.39-0.59) (Fig. 2*B*). In the DLL3-high subset, 189 patients in the Rova-T arm and 214 patients in the placebo arm were evaluated for response; the investigator-assessed ORR was 10% and the CBR was 72% in the Rova-T arm versus an ORR of 5% and CBR of 30% in the placebo arm. Response rates and DOR for randomized and DLL3-high patients are summarized in Supplementary Table 1.

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Placebo n = 376	Rova-T n = 372
Median age (range), y	64 (38-85)	64 (39-94)
Male, n (%)	239 (64)	258 (69)
ECOG PS, n (%)		
0	149 (40)	146 (39)
1	224 (60)	222(60)
Missing	3 (1)	4 (1)
TNM stage at start of first-line therapy, n (%)		
IA	1 (0.3)[a]	0
IB	0	0
IIA	0	0
IIB	0	1 (0.3)[b]
IIIA	4 (1)	3 (1)
IIIB	16 (4)	24 (7)
IV	295 (78)	286 (77)
Missing	60 (16)	58 (16)
Response to platinum, n (%)		
Stable disease	84 (22)	83 (22)
PR or CR	292 (78)	289 (78)
Lactate dehydrogenase, n (%)		
>ULN	90 (24)	89 (24)
≤ULN	265 (71)	269 (72)
Missing	21 (6)	14 (4)
History of brain metastases, n (%)		
Yes	56 (15)	54 (15)
No	320 (85)	318 (85)
Previous PCI, n (%)[c]		
Yes	72 (23)	73 (23)
No	247 (77)	244 (77)
Missing	1 (0.3)	1 (0.3)
DLL3 status, n (%)		
High (≥75%)[d]	240 (64)	217 (58)
Low (0% to <75%)	120 (32)	148 (40)
Not evaluated (DLL3 status unknown)	16 (4)	7 (2)

[a]One patient in the Rova-T arm had TNM stage IIB disease at start of first-line therapy and progressed during or after first-line therapy before study entry (protocol deviation).
[b]One patient in the placebo arm had TNM stage IA at initial diagnosis in 2007 and subsequently progressed or showed recurrence after initial treatment and before initiation of first-line therapy for extensive disease (TNM stage not reported/not applicable).
[c]Previous PCI was only offered in patients with no history of brain metastases if permitted by institutional guidelines; percentages are calculated out of number of patients with no history of brain metastases.
[d]High DLL3 expression was defined as having greater than or equal to 75% tumor cells staining positive according to the Ventana DLL3 (SP347) immunohistochemical assay.
CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response; PCI, prophylactic cranial irradiation; PS, performance status; Rova-T, rovalpituzumab tesirine; ULN, upper limit of normal.

The median OS for all randomized patients (secondary end point) was 8.8 months (95% CI: 7.95–9.53) in the Rova-T arm and 9.9 months (95% CI: 8.6–11.0) in the placebo arm (95% CI: 0.92–1.36, HR = 1.12, p = 0.237). The median PFS as evaluated by the investigator (exploratory end point) for the randomized set was 3.7 months (95% CI: 2.9–4.0) in the Rova-T arm and 1.4 months (95% CI: 1.4–1.5) in the placebo arm (95% CI: 0.44–0.60, HR = 0.51). The investigator-assessed ORR for all randomized patients was 9% (28 of 318) in the Rova-T arm and 4% (14 of 330) in the placebo arm. Furthermore, the investigator-assessed CBR was 66% (211 of 318) in the Rova-T arm and 34% (112 of 330) in the placebo arm (Supplementary Table 1).

Physical functioning was evaluated in the randomized set, as measured by the EORTC QLQ-C30 questionnaire (Table 2 and Supplementary Fig. 1). At baseline, the mean EORTC QLQ-C30 score in the Rova-T and placebo arms was equivalent. At week 6 visit, the mean EORTC QLQ-C30 score had slightly declined in both arms. The mean EORTC QLQ-C30 score in the Rova-T arm further declined from baseline at week 12, week 18, and week 24 visits, although no appreciable change was observed at these time points in the placebo arm. The least square mean difference between the two arms at weeks 6, 12, 18, and 24 suggested more decline in physical functioning in the Rova-T arm compared with the placebo arm over time (Table 2 and Supplementary Fig. 1).

Subgroup Analysis of the Randomized Set

Analyses of OS and PFS (investigator-assessed) by protocol-specified stratification factors are summarized in Figure 3 and Supplementary Table 2. In the Rova-T arm, patients with DLL3-low tumors (<75% DLL3-positive cells) and patients with DLL3-high tumors (≥75% DLL3-positive cells) did not have a marked difference in median OS (9.0 mo versus 8.5 mo). No differences in outcome depending on DLL3 expression were found in the placebo arm as well. No significant improvement in median OS was observed with Rova-T versus placebo for any of the subgroups (Fig. 3*A*). Similar to the finding in the overall population, median PFS as evaluated by the investigator (exploratory end point) was markedly improved in the Rova-T arm compared with the placebo arm in all subgroups (Fig. 3*B*).

Safety

Safety analysis was conducted in patients who received at least one dose of Rova-T (n = 368) or placebo (n = 373). Overall, 343 (93%) patients in the Rova-T arm and 304 (82%) in the placebo arm experienced at least one treatment-emergent adverse event (TEAE). The most common any-grade TEAEs in the Rova-T arm were pleural effusion (27%), decreased appetite (27%), peripheral edema (26%), photosensitivity reaction (25%), fatigue (25%), nausea (22%), and dyspnea (21%). The

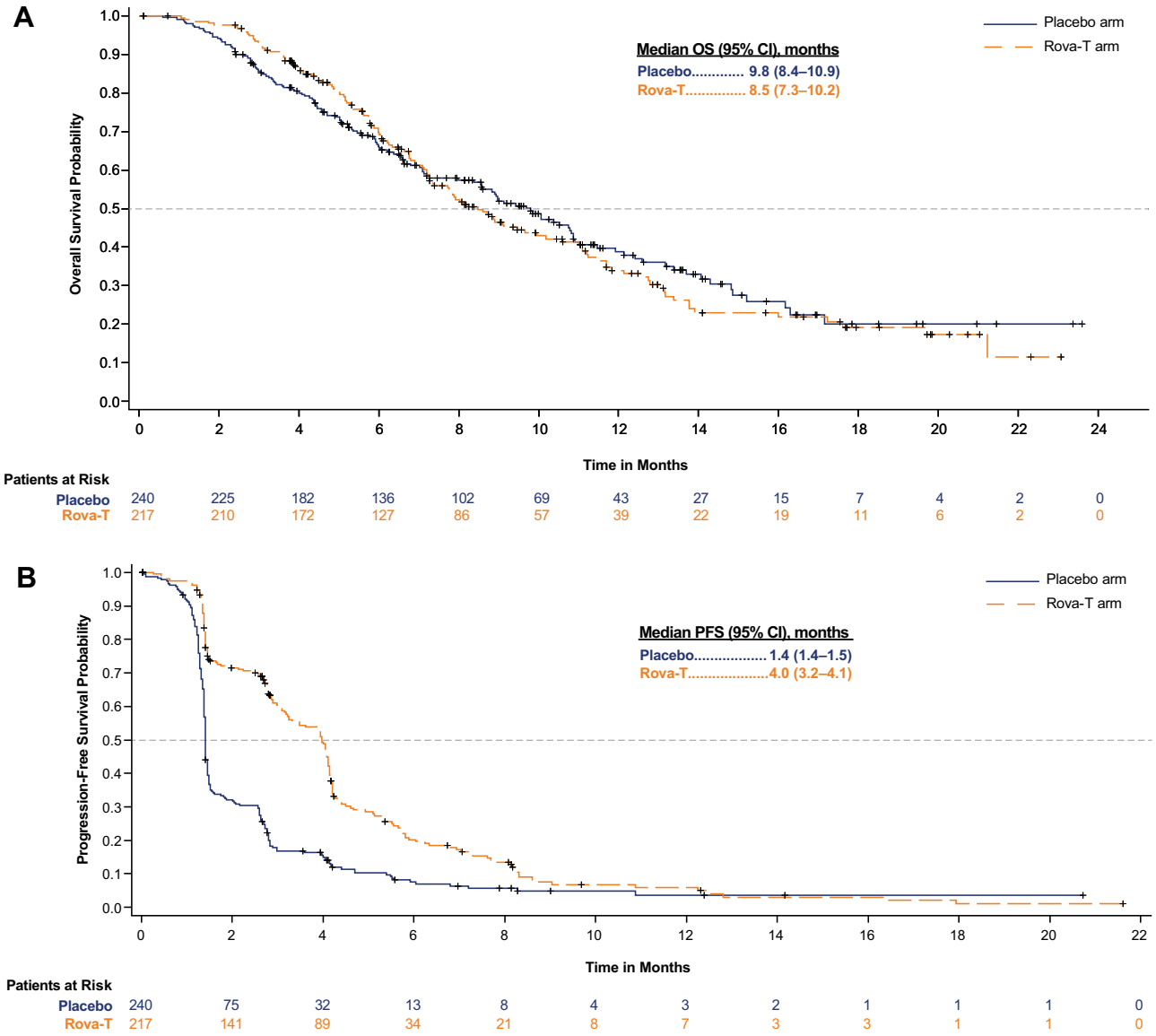

Figure 2. (*A*) OS and (*B*) PFS by investigator assessment (DLL3-high subset). CI, confidence interval; OS, overall survival; PFS, progression-free survival; Rova-T, rovalpituzumab tesirine.

most common any-grade TEAEs in the placebo arm were fatigue (16%), nausea (14%), and decreased appetite (13%) (Table 3). Grade greater than or equal to 3 TEAEs occurred in 217 patients (59%) in the Rova-T arm and 111 (30%) in the placebo arm, with the most common grade greater than or equal to 3 TEAE (excluding malignant neoplasm progression) being thrombocytopenia (9%) with Rova-T and hyponatremia with placebo (5%). Serious TEAEs were reported in 157 patients (43%) in the Rova-T arm and in 87 patients (23%) in the placebo arm. Serious TEAEs occurring in greater than 2% of patients in both treatment arms are summarized in Supplementary Table 3.

Overall, 290 patients (79%) and 145 patients (39%) experienced TEAEs possibly related to the study drug in the Rova-T and placebo arms, respectively. Common possible study drug-related TEAEs in the Rova-T arm included photosensitivity reaction (24%), peripheral edema (22%), pleural effusion (20%), fatigue (18%), thrombocytopenia (17%), decreased appetite (16%), pericardial effusion (14%), nausea (13%), increased aspartate aminotransferase (10%), face edema (10%), and dyspnea (10%). Common TEAEs possibly related to the study drug in the placebo arm were fatigue (9%), nausea (6%), peripheral edema (5%), and decreased appetite (5%). The TEAEs of special interest included cutaneous reaction, generalized edema, pleural effusion, pericardial effusion, edema, photosensitivity reaction, pneumonitis, hypoalbuminemia, and thrombocytopenia, all of which occurred at higher

Table 2. Patient-Reported Outcomes Using the EORTC QLQ-C30 Physical Functioning Scale

EORTC QLQ-C30 Questionnaire[a]	Rova-T n = 368			Placebo n = 373			
	N	Visit Mean (SD)[b]	LS Mean Change From Baseline (95% CI)	N	Visit Mean (SD)	LS Mean Change From Baseline (95% CI)	LS Mean of Difference Between Arms (95% CI)[c]
Baseline	317	78.49 (18.78)	–	301	78.18 (18.26)	–	–
Wk 6	296	74.18 (20.76)	−7.69 (−12.40 to −2.98)	287	74.29 (22.32)	−8.26 (−14.69 to −1.82)	−0.26 (−2.98 to 2.47)
Wk 12	191	65.32 (22.54)	−14.04 (−19.64 to −8.44]	104	77.40 (21.56)	–	−10.46 (−14.62 to −6.29)
Wk 18	14	56.19 (26.37)	–	9	73.33 (14.91)	–	−23.50 (−45.92 to −1.08)
Wk 24	11	55.76 (26.71)	–	7	87.62 (19.02)	–	−23.09 (−45.07 to −1.11)
Final visit	312	65.09 (24.49)	−16.24 (−21.91 to −10.58)	298	74.07 (22.65)	−8.32 (−15.03 to −1.60)	−9.38 (−12.38 to −6.39)

CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; LS, least square; Rova-T, rovalpituzumab tesirine.
[a]Score ranges 0 to 100, with a higher score indicating a higher level of physical functioning.
[b]Only patients with baseline and postbaseline data are included.
[c]Calculated relative to placebo.

frequency in the Rova-T arm compared with the placebo arm (Supplementary Table 4).

TEAEs led to death in 35 patients (10%) in the Rova-T arm and 37 patients (10%) in the placebo arm, with malignant neoplasm progression being the most common AE causing death in both arms (4% in Rova-T arm and 5% in placebo arm). Other common causes of death owing to TEAEs were pneumonitis, general physical health deterioration, and sepsis in the Rova-T arm (n = 3 each), and general physical health deterioration and metastasis to the CNS (n = 2 each) in the placebo arm. Rova-T discontinuation owing to TEAEs was reported in 74 patients (20%), and placebo discontinuation owing to TEAEs was reported in 26 patients (7%). TEAEs led to Rova-T interruptions or delay in 63 patients (17%) and placebo interruptions or delay in 12 patients (3%). A total of 58 patients (16%) in the Rova-T arm and 5 patients (1%) in the placebo arm had dose reductions as a result of TEAEs.

Discussion

On the basis of the clinical activity and manageable safety profile of Rova-T observed in previous phase 1 or 2 studies, MERU was the first phase 3 study designed to evaluate the efficacy of Rova-T in a maintenance setting after first-line platinum-based chemotherapy. Rova-T failed to reveal OS benefit compared with placebo. Further efficacy analysis by stratification factors revealed similar overall trends, with shorter OS in the Rova-T versus placebo arms. Because the OS futility boundary was met during the futility analysis, the CRAC review of PFS was not performed, and the primary end point of PFS by CRAC and related secondary efficacy end points were not evaluated. Thus, in addition to OS, only preplanned exploratory efficacy end points of PFS, ORR, DOR, and CBR by investigator assessment are reported here. In line with the current MERU study, a lack of marked improvement in survival has been a common theme in several previous trials evaluating maintenance therapy for ES-SCLC after platinum chemotherapy.[11,15–18]

The ORR per RECIST v.1.1 criteria for the overall randomized population was 9% with Rova-T and 5% with placebo, and the CBR for the overall population was higher with Rova-T versus placebo (66% versus 34%). Similar response rates were observed in the DLL3-high patients. The lower ORR observed in the Rova-T arm of MERU, as compared with other Rova-T studies, is perhaps not unexpected in the maintenance setting and could be attributed to the ongoing response or disease control after four cycles of platinum-based front-line chemotherapy administered before randomization.

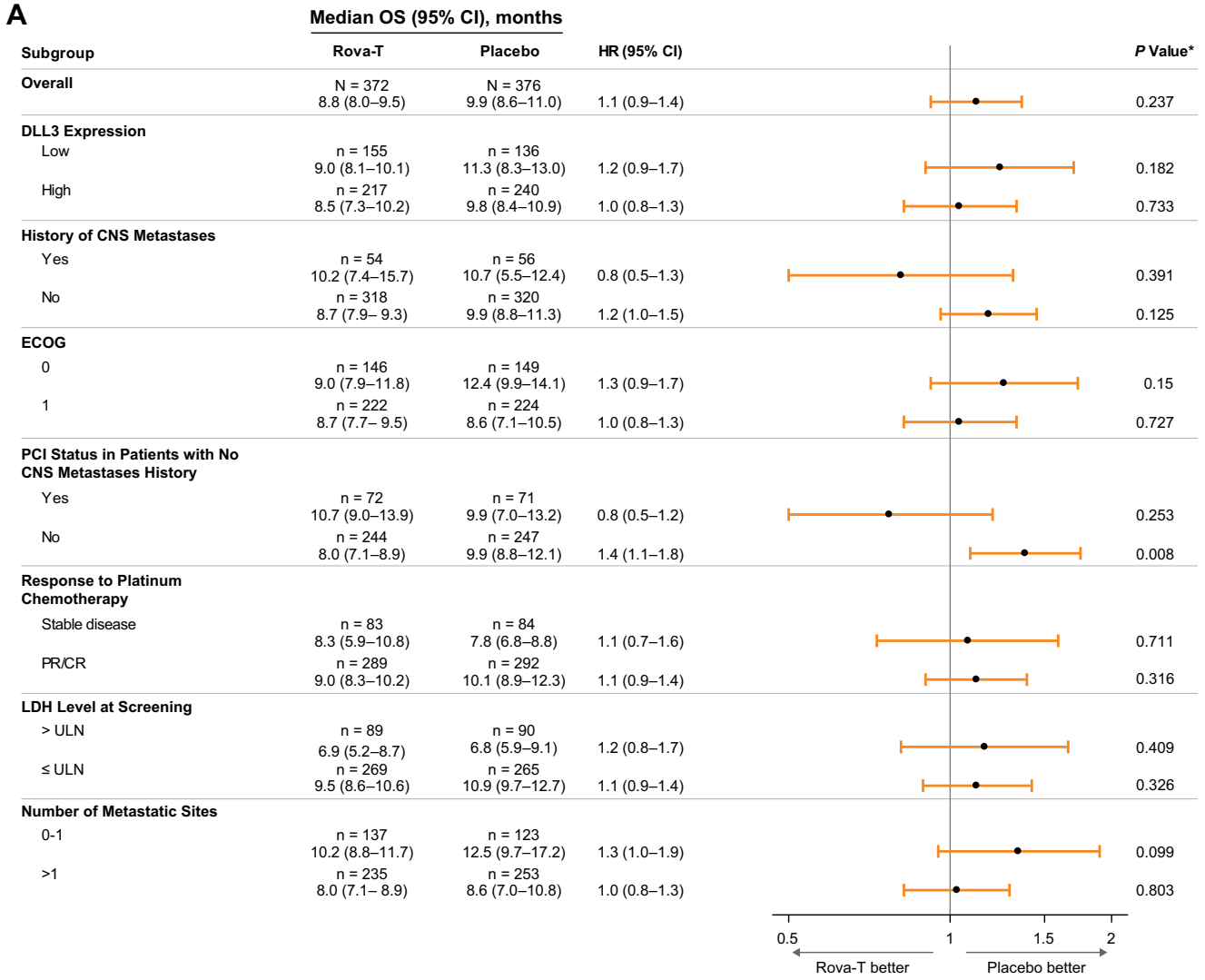

Figure 3. Subgroup analysis of (*A*) OS and (*B*) PFS in prespecified subgroups (randomized set). A HR of less than 1 indicates a lower risk of disease progression or relapse or death with Rova-T compared with placebo. The sizes of the circles are proportional to the sizes of the subgroups, and the error bars denote 95% CIs. *Calculated using a Cox proportional hazard regression model with treatment as covariate. CI, confidence interval; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PCI, prophylactic cranial irradiation; PFS, progression-free survival; PR, partial response; PS, performance status; Rova-T, rovalpituzumab tesirine; ULN, upper limit of normal.

The incidence of grade greater than or equal to 3 TEAEs, drug-related AEs, and serious TEAEs was higher in the Rova-T arm versus the placebo arm. Consistent with previous phase 1 and phase 2 studies,[9,10] Rova-T was associated with a unique toxicity profile characterized by pleural and pericardial effusions, cutaneous reaction, edema, photosensitivity reaction, pneumonitis, hypoalbuminemia, and thrombocytopenia; these AEs of special interest occurred at a much higher frequency in the Rova-T arm compared with the placebo arm. The unique toxicity profile of Rova-T has been attributed to the PBD payload, with some of the characteristic toxicities also observed with other PBD-based ADCs.[19–21] Previous Rova-T trials have described serosal effusions and edema[9,10,22] as particular hallmarks of Rova-T, which were also observed in the present study.

Analysis of patient-reported outcome using the EORTC QLQ-C30 questionnaire suggested a Rova-T–induced decline in physical functioning, which was observed in the Rova-T arm relative both to its baseline and to the placebo arm at the same time points. The decline in physical functioning over time along with the toxicity profile of Rova-T suggests challenges with Rova-T treatment in the MERU study. However, lower doses of Rova-T used in other studies have revealed better tolerability.[23]

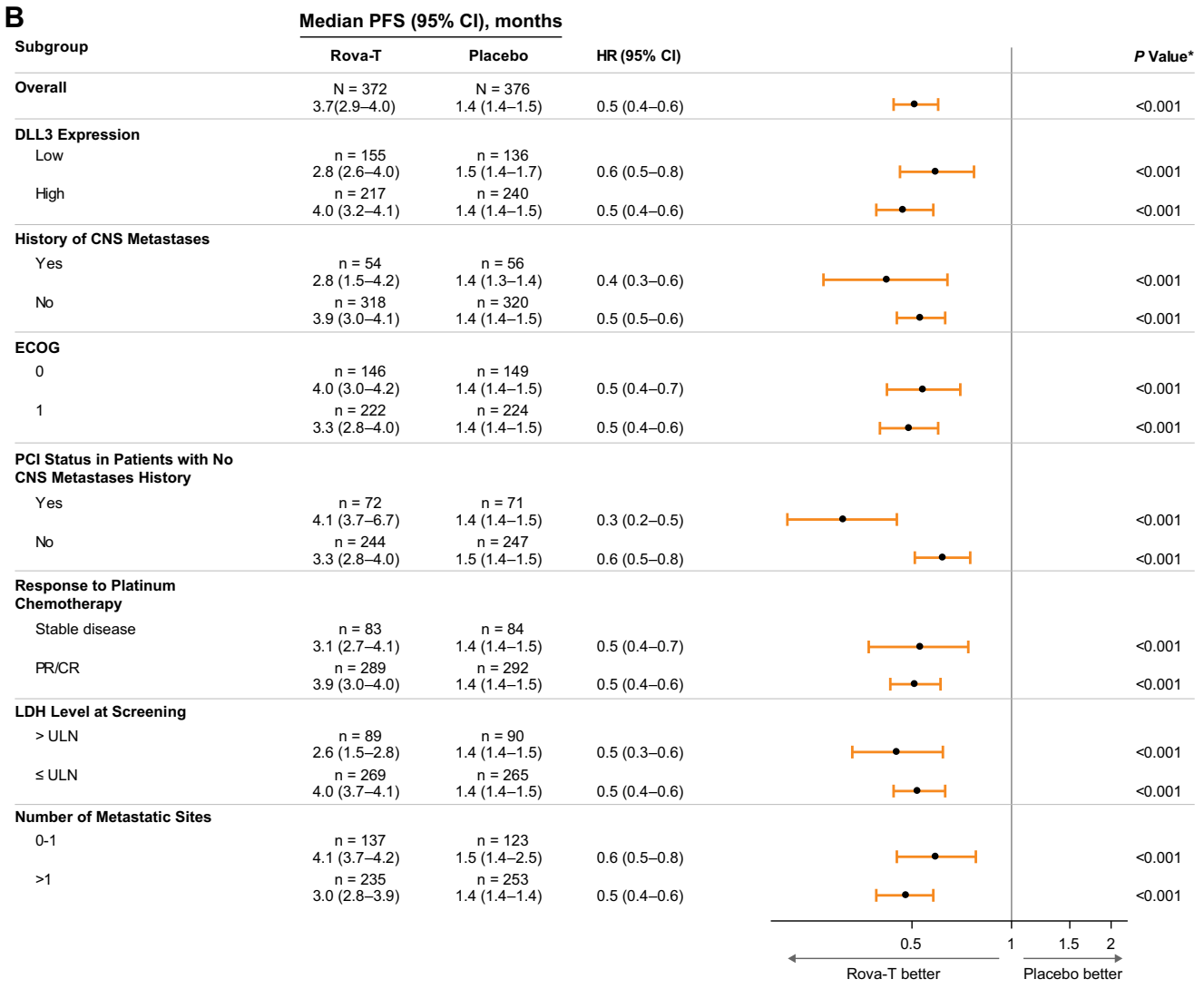

Figure 3. (*continued*).

Because of the lack of survival benefit in the Rova-T arm compared with the placebo arm at a preplanned interim analysis, the MERU trial has been terminated per the recommendation of the Independent Data Monitoring Committee.[24] The phase 3 TAHOE study was also terminated on the basis of the recommendation of the Independent Data Monitoring Committee owing to a shorter median OS observed in the Rova-T arm versus the topotecan control arm.[25] Because of these suboptimal results, the Rova-T research and development program has been fully discontinued.[24]

In summary, Rova-T failed to improve OS in the maintenance setting versus placebo in patients with ES-SCLC. The primary end point of PFS assessment by CRAC was not tested. The toxicities associated with Rova-T are important risk factors to be considered during Rova-T treatment. Although the development of Rova-T has been terminated, safety and efficacy findings reported herein highlight the need to carefully consider the toxicity profile of novel therapeutics being tested in the fragile population with ES-SCLC and may provide useful insights for future studies in front-line maintenance after platinum-based chemotherapy in ES-SCLC.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), and other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. The clinical trial

Table 3. TEAEs Occurring in Greater Than or Equal to 10% of Patients in Either Treatment Group

	Rova-T n = 368			Placebo n = 373		
TEAE, n (%)	Grades 1-2	Grade ≥3	Any Grade	Grades 1-2	Grade ≥3	Any Grade
Any TEAE	126 (34)	217 (59)	343 (93)	193 (52)	111 (30)	304 (82)
Pleural effusion	83 (23)	15 (4)	98 (27)	11 (3)	2 (1)	13 (4)
Decreased appetite	92 (25)	6 (2)	98 (27)	48 (13)	2 (1)	50 (13)
Peripheral edema	91 (25)	4 (1)	95 (26)	28 (8)	0	28 (8)
Fatigue	84 (23)	9 (2)	93 (25)	59 (16)	1 (0.3)	60 (16)
Photosensitivity reaction	75 (20)	16 (4)	91 (25)	5 (1)	0	5 (1)
Nausea	76 (21)	4 (1)	80 (22)	49 (13)	2 (1)	51 (14)
Dyspnea	68 (19)	11 (3)	79 (21)	38 (10)	5 (1)	43 (12)
Thrombocytopenia	35 (10)	34 (9)	69 (19)	5 (1)	9 (2)	14 (4)
Pericardial effusion	58 (16)	4 (1)	62 (17)	7 (2)	1 (0.3)	8 (2)
Cough	53 (14)	3 (1)	56 (15)	43 (12)	1 (0.3)	44 (12)
Constipation	48 (13)	1 (0.3)	49 (13)	35 (9)	1 (0.3)	36 (10)
Increased aspartate aminotransferase	39 (11)	9 (2)	48 (13)	7 (2)	6 (2)	13 (4)
Increased alanine aminotransferase	30 (8)	9 (2)	39 (11)	7 (2)	1 (0.3)	8 (2)
Face edema	41 (11)	1 (0.3)	42 (11)	5 (1)	0	5 (1)
Vomiting	35 (10)	1 (0.3)	36 (10)	35 (9)	2 (1)	37 (10)
Asthenia	26 (7)	11 (3)	37 (10)	22 (6)	4 (1)	26 (7)
Diarrhea	30 (8)	0	30 (8)	34 (9)	2 (1)	36 (10)

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

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.html.

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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.2021.03.012.

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