Clinical Cancer Research

Efficacy and Safety of Rovalpituzumab Tesirine in Third-Line and Beyond Patients with DLL3-Expressing, Relapsed/Refractory Small-Cell Lung Cancer: Results From the Phase II TRINITY Study

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Abstract

Purpose: Although extensive-stage small-cell lung cancer (SCLC) is highly responsive to first-line therapy, virtually all patients develop resistance with short survival. Rovalpituzumab tesirine (Rova-T) is an antibody–drug conjugate targeting delta-like 3 protein (DLL3). This open-label, single-arm, phase II study (TRINITY) assessed safety and efficacy of Rova-T in patients with DLL3-expressing SCLC in the third-line and beyond (3L+) setting.

Patients and Methods: Patients with DLL3-expressing SCLC (determined by mouse antibody immunohistochemistry [IHC] assay), and ≥2 prior regimens, received 0.3 mg/kg Rova-T once every 6 weeks for two cycles. During study, a rabbit antibody IHC assay was developed and used for the final analysis, with DLL3-positive and DLL3-high defined as ≥25% and ≥75% of tumor cells positive for DLL3, respectively. The primary endpoints were objective response rate (ORR) and overall survival (OS).

Results: Among 339 patients enrolled, 261 (77%) had two prior lines of therapy and 78 (23%) had ≥3. DLL3-high and DLL3-positive tumors by rabbit IHC were seen in 238 (70%) and 287 (85%) patients, respectively. The remaining 52 (15%) were DLL3-negative only by rabbit IHC or had missing results. ORR was 12.4%, 14.3%, and 13.2% in all, DLL3-high, and DLL3-positive patients, respectively. Median OS was 5.6 months in all patients and 5.7 months in DLL3-high patients. The most common adverse events (AE) were fatigue, photosensitivity reaction, and pleural effusion. Grade 3–5 AEs were seen in 213 (63%) patients.

Conclusions: Rova-T is the first targeted agent in SCLC to use DLL3, a novel biomarker. However, results demonstrate modest clinical activity in 3L+ SCLC, with associated toxicities.

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Introduction

Small-cell lung cancer (SCLC) accounts for approximately 13% to 15% of all lung cancers with an estimate of more than 180,000 new cases diagnosed annually worldwide (1–3). This high-grade neuroendocrine tumor is characterized by rapid growth and early development of metastases to both regional lymph nodes and distant sites (4). Despite high initial responses to first-line (1L) platinum- and immunotherapy-based treatment regimens (5), which are associated with rapid responses and symptomatic improvement, virtually all patients with extensive-stage SCLC develop tumor progression, mostly within 6 months, with rare survivors at 5 years (6–8).

The topoisomerase I inhibitor topotecan, the only drug currently approved by the FDA and European Medicines Agency in the second-line (2L) setting, has been associated with overall response rates of 16.9% to 21.9%, median progression-free survival (PFS) of 3.4 to 3.5 months, and median overall survival (OS) of 7.8 to 8.7 months in randomized clinical trials (9, 10). Outcomes are particularly poor among patients with chemotherapy-resistant disease, generally defined by a period from the completion of 1L therapy to the development

Translational Relevance

Extensive-stage small-cell lung cancer (SCLC) is highly responsive to first-line therapy, although virtually all patients develop resistance with short survival. Rovalpituzumab tesirine (Rova-T) targets DLL3, which is widely expressed in SCLC but has minimal to no expression in normal tissues. The open-label, single-arm phase II TRINITY study was designed to assess safety and efficacy of Rova-T in patients with DLL3-expressing SCLC in the third-line and beyond (3L+) setting. We observed an objective response rate (ORR, by Central Radiographic Assessment [CRA]) of 12.4% and median overall survival (OS) of 5.6 months in all patients ($N = 339$). Patients with DLL3-high expression ($n = 238$) had an ORR (by CRA) of 14.3% and median OS of 5.7 months. Our findings demonstrate that Rova-T has modest antitumor activity in patients with previously treated SCLC.

of tumor progression of less than 90 days, with overall response rates usually below 10% (10, 11). There is no globally approved agent for patients with SCLC who recur following 2L treatment, although nivolumab is FDA-approved in this patient population and is associated with benefit in a small percentage of patients (12).

Delta-like 3 protein (DLL3) is an atypical Notch ligand that has been implicated in regulation of cell development and cell fate decisions (13), and is a downstream target of achaete-scute homolog-1 (ASCL1), suggesting its role in neuroendocrine tumorigenesis (14). DLL3 is highly expressed in SCLC and other neuroendocrine tumors, but has little to no expression in normal tissues or non-neuroendocrine tumor types (15). Furthermore, DLL3 expression appears to be stable over time in SCLC tumors pre- and post-chemotherapy (16). Although DLL3 is mostly found within the Golgi apparatus under physiological conditions, it may reach the cell surface in case of overexpression and lead to Notch inhibition in cis (13, 17).

Rovalpituzumab tesirine (Rova-T) is an antibody–drug conjugate (ADC) composed of SC16, a humanized IgG1 antibody against DLL3, conjugated to the cytotoxic pyrrolobenzodiazepine (PBD) dimer D6.5 (SC-DR002) via a protease-cleavable linker (15). Rova-T selectively binds to DLL3 on target-expressing cells, is internalized, and upon proteolytic cleavage releases the toxin. PBD dimers then bind to the DNA minor groove where they form covalent adducts causing stalling of the replication forks, cell-cycle arrest at the G_2–M boundary, and apoptosis.

In a first-in-human phase I study, Rova-T showed encouraging results with objective response rates (ORR) per independent review in nine (16%) of 56 assessable patients with 2L or 3L SCLC and any level of DLL3 expression (18). In an exploratory analysis of patients with available post-baseline scans, 26 patients with high levels DLL3 expression had an ORR of 31% by independent review (eight patients with $\geq$ 50% DLL3 expression by mouse antibody immunohistochemistry [IHC] assay). Here, we present the results of the phase II TRINITY study, which assessed the efficacy and safety of Rova-T in patients with DLL3-expressing SCLC previously treated with at least two lines of chemotherapy.

Patients and Methods

Study design and participants

TRINITY was an open-label, single-arm, phase II study of Rova-T in DLL3-expressing SCLC patients with relapsed or refractory disease. The key patient eligibility criteria included age $\geq$18 years, histologically confirmed, advanced stage DLL3-positive SCLC with measurable disease defined as at least one tumor lesion $\geq$10 mm in the longest diameter or a lymph node $\geq$15 mm in short axis measurement assessed by CT scan (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1; ref. 19), at least two prior systemic regimens including one platinum-based regimen, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, absent or stable central nervous system metastases, and adequate hematological, hepatic, and renal function. Primary exclusion criteria included uncontrolled hypertension and/or diabetes, clinically significant pulmonary disease, or neurological disorder, documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV within 6 months before first dose of study drug, recent or ongoing serious infection, history of another invasive malignancy that had not been in remission for at least 3 years, or prior exposure to a PBD-based drug.

Baseline screening assessments were performed for all patients meeting inclusion criteria, including a radiographic scan, complete medical history, physical exam, complete blood count, serum chemistries, electrocardiogram, and echocardiogram. Treatment response was assessed by radiographic tumor evaluation within 7 days before the next dose, and 42 days after the last dose of Rova-T. Clinical response was determined by investigator and Central Radiographic Assessment (CRA) according to RECIST v1.1. Safety assessments consisted of the surveillance and recording of adverse events (AEs) and serious AEs, graded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Final assessments during initial treatment were performed 42 days after the last dose of Rova-T. Patients in the long-term follow-up continued disease assessments every 6 weeks for 6 months, then every 12 weeks thereafter. Patients were followed until disease progression (PD) per RECIST v1.1 or initiation of new anticancer treatment, whichever occurred first, and subsequently were followed for survival until death or study termination, whichever occurred first.

Before study treatment, archived or fresh tumor tissue representative of the qualifying malignancy (primary or metastatic lesion permitted) was submitted to a central laboratory for determination of DLL3 expression by IHC. Only patients with tumors demonstrating DLL3 staining of $\geq$1% of tumor cells were enrolled on the basis of an investigational use only (IUO) DLL3 mouse antibody IHC assay. During the study, a new IHC assay was developed to be more feasible for commercialization, which employed a DLL3 rabbit antibody (Ventana SP347), and was used for the final analysis. Using a commercially available SCLC sample cohort, the cutoffs of $\geq$25% of tumor cells as DLL3-positive and $\geq$75% of tumor cells as DLL3-high by the rabbit IHC assay were determined by Ventana to be comparable with the DLL3 mouse IHC assay cutoff values. Patients were classified as DLL3-nonhigh if 0% to $\leq$74% of tumor cells stained positive for DLL3, and included those patients who were DLL3 discordant, defined as having a tumor which was DLL3-positive by the original mouse antibody IHC assay but

DLL3-negative (0%≤ to ≤24% of tumor cells) by the rabbit IHC assay.

This study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. All patients provided informed consent before enrollment according to national regulations. The study design was approved of by the Institutional Review Board/Ethics Committee of participating institutions. An independent data monitoring committee reviewed the safety and efficacy data approximately every 6 months.

Procedures

All patients received 0.3 mg/kg Rova-T intravenously infused over 30 minutes once every 6 weeks for two cycles as the initial treatment. An additional two cycles of Rova-T (re-treatment) was allowed for patients who tolerated the initial treatment, achieved disease control as defined by stable disease (SD) or better, had CRA-confirmed progressive disease (PD) at least 12 weeks after the second dose, did not receive additional anticancer therapy before the re-treatment, and did not have ≥grade 2 edema or ≥grade 3 pleural or pericardial effusion. Additional retreatment beyond four cycles required approval from the medical monitor. Dose interruptions or reductions of Rova-T were permitted according to pre-specified dose adjustment guidelines for patients who exhibited treatment-related toxicities. All patients received premedication of oral dexamethasone at 8 mg twice daily administered for three consecutive days starting one day before each treatment with Rova-T. Because of the potential for Rova-T–related skin photosensitivity, patients were advised to avoid unprotected sun exposure and use a broad spectrum sunscreen (sun protection factor [SPF] ≥30), protective clothing, a broad-brimmed hat, and sunglasses when outdoors, with re-application of sunscreen as appropriate.

Outcomes and statistical analyses

Efficacy analyses were performed in all, DLL3-positive, and DLL3-high patients, based on the defined IHC assay specifications, and were prespecified as part of the protocol. The co-primary endpoints were ORR by CRA, and OS. Secondary endpoints were duration of response (DOR), disease control rate, and PFS per CRA and investigator, as well as ORR by investigator.

ORR was defined as the proportion of patients with a confirmed response status of complete response (CR) or partial response (PR) before receiving any subsequent anticancer therapy or retreatment. OS was defined as the interval from first treatment to the date of death of any cause. DOR was defined as the interval from initial response of confirmed responders to PD or death during the initial treatment period. Disease control rate was defined as the proportion of patients who achieved a best overall response of CR, PR, or SD, and PFS was defined as the interval from first treatment to the date of PD or death due to any cause. Median OS and PFS with the associated 95% confidence intervals (CIs) were estimated using the Kaplan–Meier method. Duration of disease control was defined as the interval from the initial CR, PR, or SD to PD or death. The best overall response rate, defined as the number of patients with CR or PR (regardless of confirmation) before receiving any subsequent anticancer therapy or retreatment, was also determined.

The sample size of the study was determined on the basis of the analysis of ORR using a Simon's two-stage design. If among the 60 evaluable patients in stage 1, more than nine (15%) achieved a CR or PR (confirmed or unconfirmed), then further enrollment of 63 DLL3-high patients in stage 2 was permitted. An ORR of 25% was hypothesized as the target for patients with relapsed/refractory DLL3-expressing SCLC receiving Rova-T in the third-line. As there was a lack of historical benchmark in this population to serve as a comparison, no target for median OS was specified in the protocol. Study size was further increased while ongoing to ensure adequate enrollment of 3L patients. No hypothesis testing was performed in this single-arm study. Assessments were made by the investigator and CRA. Other secondary and exploratory endpoints included pharmacokinetics, biomarker, and pharmacodynamics measures, not reported in this analysis. Data reported herein are as of January 19, 2018. The study is registered with ClinicalTrials.gov, number NCT02674568.

Results

Between March 7, 2016 and June 2, 2017, 1,358 patients were screened for the study, and 339 (25%) were enrolled, received at least one dose of Rova-T, and were included in all efficacy and safety analyses (Fig. 1). Demographic and baseline characteristics are shown in Table 1. Among the eligible patients, 238 patients (70%) were DLL3-high, 287 (85%) patients were DLL3-positive, 28 (8%) had a DLL3 discordant status (between mouse and rabbit antibody IHC assay), and 24 (7%) had a missing status, per the DLL3 rabbit antibody IHC assay, predominantly due to insufficient sample availability for re-testing. However, as all patients were DLL3-positive by the original mouse antibody IHC assay used for eligibility screening, the final efficacy and safety analyses included all patients. The median age of patients was 62 years, 50% were male, 261 (77%) had only two prior lines of therapy, and 248 (73%) had chemotherapy-sensitive disease to 1L therapy. All patients received a platinum-containing therapy, 133 (39%) received prior topotecan, 58 (17%) received a PD-1 inhibitor, and 148 (44%) received other therapies. As of the clinical data cutoff value of January 19, 2018, the median duration of follow-up for all patients was 19.1 weeks (range, 0.6–90.6). Two hundred twenty-five patients (66%) completed two cycles of Rova-T, and 20 of those underwent re-treatment; 114 (34%) completed only one cycle.

The primary endpoints were ORR by CRA and OS, and the secondary endpoints were DOR, PFS, and disease control rate. The ORR for all patients was 12.4% by CRA, and median OS was 5.6 months (Table 2). The median DOR was 4.0 months, the median PFS was 3.5 months, and the disease control rate was 69.6% in all patients. For patients with DLL3-high expression, the median OS was 5.7 months, and the median PFS was 3.8 months (Figure 2A-B). All primary and secondary endpoints were comparable for DLL3-high and DLL3-positive patients (Table 2, Supplementary Table S1). The ORR for other key subgroups is included in Supplementary Table S2.

The best overall response rate was 20.1% (95% CI, 15.9–24.7) in all patients, 21.8% (95% CI, 16.8–27.6) in DLL3-high, and 20.6% (95% CI, 16.0–25.7) in DLL3-positive. The percentage of change in target lesion by CRA is shown in Fig. 3. Among the 20 patients who received re-treatment, none had a response of CR or PR, and 13 had SD, all by CRA.

As the majority of patients (261, 77%) were 3L, further analyses, although not prespecified, were performed in this population. Patients were categorized as DLL3-high ($n = 177$) or DLL3-nonhigh ($n = 63$). Twenty-one patients with missing DLL3 status by the rabbit IHC assay were included in the overall 3L

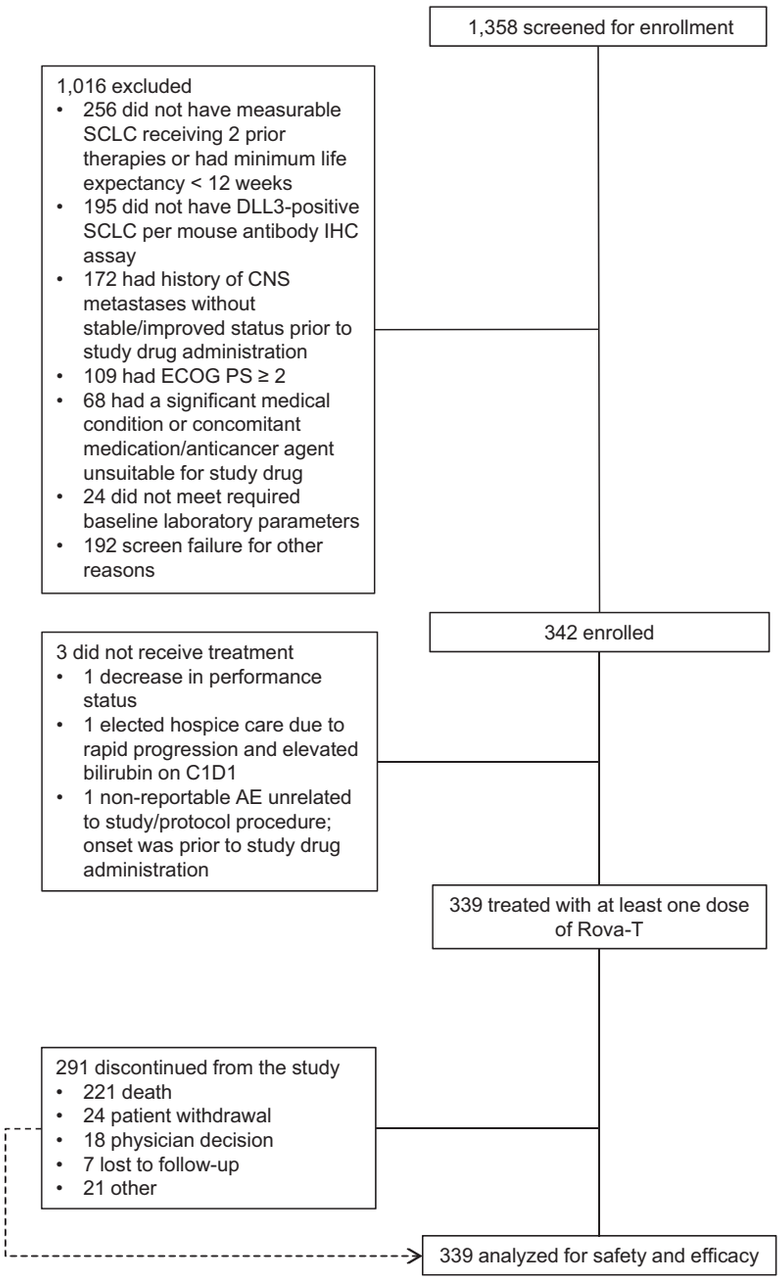

Figure 1.
CONSORT diagram.

population analyses (Supplementary Table S3). Among all 3L patients, the ORR was 13.0% by CRA. In DLL3-high and DLL3-nonhigh 3L patients, the ORR was 15.8% and 6.3%, respectively. Median overall survival was 5.6 months for all three groups. The median duration of objective response in DLL3-high 3L patients was 4.1 months (95% CI, 3.0–4.2) and in DLL3-nonhigh patients was 3.0 months (95% CI, 2.8–4.4).

At least one treatment-emergent adverse event (TEAE) was reported in 335 patients (99%), and at least one drug-related TEAE was reported in 308 patients (91%; all, Table 3). The most common TEAEs were fatigue (38%), photosensitivity reaction (36%), pleural effusion (32%), peripheral edema (31%), and decreased appetite (30%). Grade 3 or 4 TEAEs were observed in 179 patients (54%). There were 34 patients (10%) with grade 5 TEAEs, 10 (3%) of which were drug-related (Supplementary Table S4). Drug-related serious TEAEs were reported in 100 (30%) patients, 65 (19%) of which were grade 3–4.

The TEAEs of special interest included pleural and pericardial effusions, edema, cutaneous reactions, and thrombocytopenia. One hundred and nine (32%) patients experienced an event of pleural effusion, 95 (28%) of which were drug-related (Supplementary Table S5). A total of 21 (5%) patients had a grade 3+ pleural effusion, including three deaths (one case where further medical intervention was declined, one case of pneumothorax arising from a prior serious TEAE of pleural effusion, and one case

Table 1. Patient demographics and baseline characteristics.

	All patients $N = 339$
Median age at baseline, y (range)	62 (24, 86)
Sex	
Male	170 (50)
Female	169 (50)
ECOG performance score at baseline	
0	73 (22)
1	262 (77)
2	4 (1)
Disease stage at initial diagnosis	
Ia	8 (2)
Ib	5 (1)
IIa	8 (2)
IIb	5 (1)
IIIa	38 (11)
IIIb	45 (13)
IV	225 (66)
Missing	5 (1)
Prior lines of therapy	
2	261 (77)
3	52 (15)
≥4	26 (8)
Prior systemic therapies	
Platinum-containing therapies	339 (100)
Topotecan	133 (39)
PD-1 inhibitor	58 (17)
All other therapies	148 (44)
Response to 1L therapy	
Sensitive[a]	248 (73)
Resistant[b]	58 (17)
Refractory[c]	20 (6)
Undetermined	13 (4)
Time to progression on 2L therapy	
≤3 months	113 (33)
>3 months	226 (67)
Tumor biopsy used for screening	
Primary lesion	161 (47)
Metastatic lesion	169 (50)
Unknown/missing	9 (3)
History of brain metastases	
Yes	134 (40)
No	205 (60)
History of pleural effusions	
Yes	85 (25)
No	254 (75)
DLL3 status	
DLL3-high (≥75%)	238 (70)
DLL3-positive (≥25%)	287 (85)
DLL3 discordant (0% ≤ to ≤ 24%)	28 (8)
Missing	24 (7)

NOTE: Data shown are *n* (%) unless otherwise indicated.
Abbreviations: 1L, first-line; 2L, second-line; DLL3, Delta-like 3 protein; ECOG, Eastern Cooperative Oncology Group.
[a]Defined as treatment-free interval (TFI) between first and second line of therapy of ≥90 days.
[b]Defined as TFI between first and second line of therapy of <90 days.
[c]Defined as best response to first-line therapy of PD.

of bilateral pleural effusion in the context of PD). Fifty-one (15%) patients had an event of pericardial effusion, 43 (13%) of which were drug-related, and 12 (4%) of which were grade 3 or 4, including three events of cardiac tamponade (Supplementary Table S6). There were no fatal events of pericardial effusion. Edema was observed in 129 (38%) patients, 110 (32%) of which were drug-related (Supplementary Table S7). Seventeen (4%) patients had a grade 3 TEAE of edema. Of note, events of edema were lengthy in duration, with a median time to resolution of 16 days (range, 1–196 days), and often required treatment with diuretics and steroids. Furthermore, 53 (16%) patients had a TEAE of hypoalbuminemia, which was noted to precede some of the cases of effusion (pleural or pericardial) and edema; 205 (60%) experienced at least one of the four TEAEs and 21 (6%) experienced all four. A cutaneous reaction was observed in 182 (54%) patients, 28 (8%) of which were grade 3; most were consistent with photosensitivity (Supplementary Table S8). Seventy-four (22%) patients had drug-related thrombocytopenia of any grade, and 21 (6%) had grade 4 (Table 3). There were no fatal events of thrombocytopenia, and no clinically significant bleeding events in those with a grade 4 TEAE.

TEAEs resulting in dose reduction occurred in 24 (7%) patients; treatment interruption, 32 (9%) patients; and study drug discontinuation, 33 (10%) patients. The most frequent TEAEs leading to dose reduction were photosensitivity reaction (10 patients); thrombocytopenia (seven), pleural effusion (six), and pericardial effusion (five). The most frequent TEAEs leading to dose interruption were pleural and pericardial effusion (six patients each), photosensitivity reaction (three), asthenia, fatigue, and vomiting (two each); all others resulting in discontinuation occurred only in one patient. Other than pleural effusion (three) and thrombocytopenia (two), all other AEs leading to discontinuation were reported only in one patient.

Discussion

Rova-T is the first targeted agent in SCLC to use a novel biomarker, DLL3, and our findings showed that Rova-T has modest activity in patients with previously treated SCLC. As such, we developed a companion IHC assay to determine DLL3 expression in patients to select those most likely to benefit. All patients were enrolled on the basis of an IUO mouse antibody IHC assay for DLL3 and thus all patients had some level of DLL3 expression. However, during the study, a new IHC assay was developed using a DLL3 rabbit antibody. This assay was used to stratify patients by DLL3 expression for the final analyses, as this was the "market-ready" assay to be employed for commercialization purposes. Although in this single-arm study, the rabbit antibody IHC assay was not an optimal predictor for outcome, this method is being used in ongoing randomized studies comparing Rova-T with standard-of-care therapy where it can be better evaluated.

Rova-T is associated with a unique toxicity profile, with pleural effusion, pericardial effusion, edema, cutaneous reactions, and thrombocytopenia as TEAEs of interest, many of which required risk management specified per protocol. However, given that these patients were being treated in the 3L and up to 7L setting, this population may be predisposed toward more frequent adverse events, such as pleural and pericardial effusion. Although considered drug-related, 81 of the 95 cases of pleural effusion (85%), and 33 of 42 cases of pericardial effusions (79%) were grade 1–2 events, managed through drainage procedures and the administration of steroids, NSAIDs, and colchicine. Patients with edema were treated with diuretics and monitored with a weight diary. For patients with cutaneous reactions, events were managed with steroids (topical for grade 1–2, topical and oral for grade 3–4), and sun protective measures.

The most likely explanation for Rova-T toxicities is the premature lysis of the linker, causing systemic release of the PBD payload, since DLL3 is not highly expressed in normal tissues (20). Another possible mechanism is a bystander effect, where the free

Table 2. Efficacy by Central Radiographic Assessment.

	All patients $N = 339$	DLL3-high $N = 238$	DLL3-positive $N = 287$
Primary endpoints			
Objective response rate, *n* (%)	42 (12.4)	34 (14.3)	38 (13.2)
(95% CI)	(9.1–16.4)	(10.1–19.4)	(9.5–17.7)
Overall survival, median (mo)	5.6	5.7	5.8
(95% CI)	(4.9–6.1)	(4.9–6.7)	(5.1–6.7)
Secondary endpoints			
Duration of objective response, median (mo)	4.0	3.7	3.7
(95% CI)	(3.0–4.2)	(2.9–4.2)	(2.9–4.2)
Progression-free survival, median (mo)	3.5	3.8	3.8
(95% CI)	(3.0–3.9)	(3.2–4.1)	(3.2–4.0)
Disease control rate, *n* (%)	236 (69.6)	175 (73.5)	206 (71.8)
(95% CI)	(64.4–74.5)	(67.4–79.0)	(66.2–76.9)

Abbreviations: CI, confidence interval; DLL3, delta-like 3 protein; mo, months.

drug can affect surrounding cells, regardless of their surface expression of the target protein. This occurs through diffusion out of the target cells or cleavage before internalization by extracellular enzymes such as cathepsin B, which is released by tumor cells or tumor-associated macrophages (21). In a phase I dose-escalation study of the PBD dimer SJG-136, 10 of the 16 patients (62%) developed a delayed onset vascular leak syndrome characterized by hypoalbuminemia, edema, ascites, and pleural effusion (22). A second dose-escalation phase I study with SJG-136 used lower doses and showed better tolerability (23). It is unknown if strategies such as altered dosing and scheduling of Rova-T will mitigate these side effects, and they are being currently tested in ongoing randomized studies of Rova-T.

Results from this trial demonstrated that Rova-T has modest antitumor activity in 3L+ patients with SCLC. In DLL3-high patients, the ORR was 14.3%, the median PFS was 3.8 months, and median OS was 5.7 months. Responses in DLL3-high patients were numerically higher compared with the DLL3-nonhigh patients. However, responses in the DLL3-nonhigh population were expected as all patients enrolled on study expressed DLL3 at some level. There are limited data on treatment outcomes in 2L and beyond for patients with SCLC. However, the outcomes from

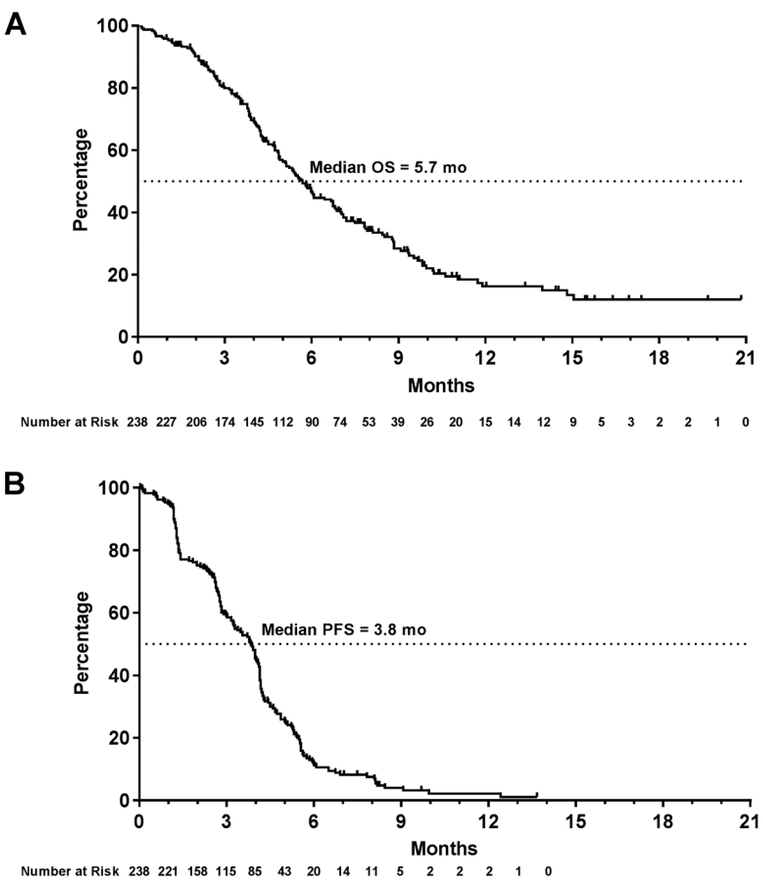

Figure 2.
Survival in DLL3-high patients. **A,** Overall survival. **B,** Progression-free survival by Central Radiographic Assessment. Mo, months.

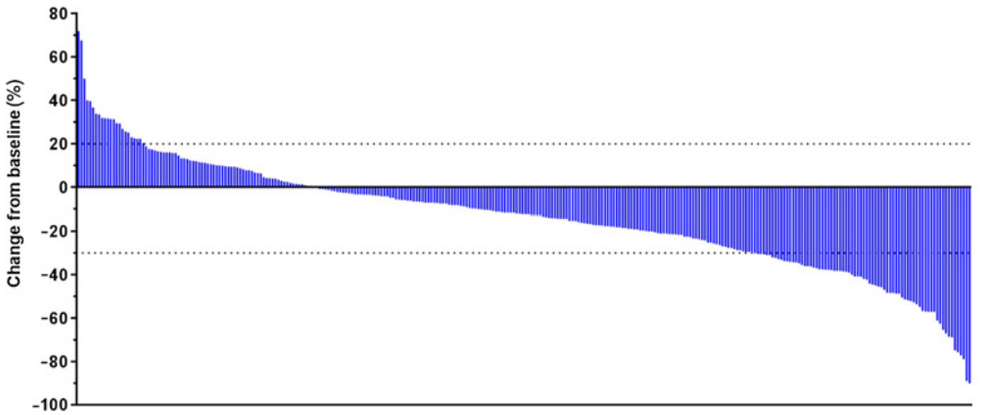

Figure 3.
Change in target lesions from baseline. Percentage of change in target lesions from baseline measured by RECIST v1.1 in 304 patients who had a baseline scan and at least one follow-up scan with an evaluable response. Dotted line at 20% indicates threshold for PD, and dotted line at −30% indicates threshold for PR. Response category determined by Central Radiographic Assessment.

TRINITY compare favorably to a retrospective multicenter study involving 120 3L patients treated with chemotherapy, with a median PFS of 2.0 months, and median OS of 4.7 months (24). In a subset analysis of patients treated with third-line nivolumab in the CheckMate 032 trial, the ORR was 11.9%, with median PFS of 1.4 months and median OS of 5.6 months (25). Nevertheless, the duration of response of 17.9 months was longer than with Rova-T. In a phase II randomized trial comparing temozolomide alone or in combination with veliparib, the ORR was 38% (six of 16 responders) among patients with the combination and 8% (one of 13 responders) with single-agent temozolomide in the third-line setting (26). Nevertheless, there are no data on PFS or OS for patients treated in the third-line and, despite the improvement in ORR, the addition of veliparib did not result in improved PFS or OS compared with temozolomide alone.

With no major advances in systemic therapy despite multiple trials, including cytotoxic chemotherapy and targeted drugs, it is not surprising that the survival for SCLC has not improved over the past 3 decades (27). The current standard in the 1L setting is the combination of a platinum agent plus etoposide (28), with a modest improvement in PFS and OS with the addition of atezolizomab (5). Topotecan remains the only agent approved worldwide in the 2L setting and nivolumab is approved by the FDA in the 3L+ setting, where a small percentage of patients achieve benefit (12, 25).

The impact of this study is limited by the single-arm study design, and heterogeneity of the enrolled patient population. These limitations will be addressed in ongoing studies with Rova-T that include an active or placebo-controlled comparator arm. Although the results from this phase II study were not as promising based on the initial phase I study, they suggest that DLL3 is a clinically relevant target, particularly with its common expression in SCLC and minimal to no expression in normal tissues. Enrollment in the phase III trial

Table 3. Treatment-emergent adverse events.

	All patients, $N = 339$					
	Any adverse event				Drug-related	
	Gr 1-2	Gr 3	Gr 4	Gr 5	Any grade	Gr 3-4
Any event	122 (36)	144 (43)	36 (11)	34 (10)	308 (91)	135 (40)
Abdominal pain	41 (12)	7 (2)	1 (0.3)	0	18 (5)	3 (1)
Anemia	38 (11)	20 (6)	0	0	44 (13)	12 (4)
Asthenia	42 (12)	6 (2)	0	1 (0.3)	40 (12)	5 (2)
Constipation	72 (21)	3 (1)	0	0	15 (4)	1 (0.3)
Cough	55 (16)	0	0	0	7 (2)	0
Decreased appetite	96 (28)	7 (2)	0	0	53 (16)	3 (1)
Dyspnea	78 (23)	5 (2)	0	1 (0.3)	33 (10)	0
Edema peripheral	97 (29)	7 (2)	0	0	89 (26)	6 (2)
Fatigue	114 (34)	16 (5)	0	0	0	0
Hypoalbuminemia	50 (15)	3 (1)	0	0	40 (12)	2 (1)
Nausea	81 (24)	7 (2)	0	0	55 (16)	6 (2)
Pericardial effusion	39 (12)	6 (2)	6 (2)	0	42 (12)	9 (3)
Photosensitivity reaction	100 (29)	23 (7)	0	0	120 (35)	23 (7)
Pleural effusion	88 (26)	18 (5)	0	3 (1)	95 (28)	14 (4)
Thrombocytopenia	38 (11)	24 (7)	21 (6)	0	74 (22)	37 (11)
Vomiting	55 (16)	4 (1)	0	0	28 (8)	3 (1)

NOTE: Data shown are *n* (%). Shown are adverse events reported in at least 15% of all patients.
Abbreviation: Gr, grade.

of Rova-T in the 2L setting was stopped early due to shorter overall survival in the Rova-T arm compared with the topotecan control arm; however, Rova-T continues to be investigated as maintenance therapy, and in combination with immune checkpoint inhibitors (29–31).

Disclosure of Potential Conflicts of Interest

D. Morgensztern is an employee/paid consultant for Abbvie, Bristol-Myers Squibb, Takeda, and PharmaMar. B. Besse reports receiving commercial research grants from Abbvie. R. Santana-Davila reports receiving commercial research grants from and is an advisory board member/unpaid consultant for Abbvie. N. Ready is an employee/paid consultant for Abbvie, Bristol-Myers Squibb, Merck, AstraZeneca, Celgene, G1 therapeutics, Genetech, EMDSerano, and Tesaro, reports receiving commercial research grants from Merck, and speakers bureau honoraria from Bristol-Myers Squibb and Celgene. C.L. Hann is an employee/paid consultant for AbbVie, Bristol-Myers Squibb, Ascentage, and Genentech, and reports receiving commercial research grants from AbbVie, Bristol-Myers Squibb, Merrimack, and GlaxoSmithKline. A.F. Farago is an employee/paid consultant for AbbVie, Stemcentrx, Pharmamar, Bristol-Myers Squibb, Loxo, Bayer, Boehringer Ingelheim, AstraZeneca, Genentech, and Roche, and reports receiving other commercial research support from AbbVie, AstraZeneca, Pharmamar, Genentech/Roche, Bayer, Amgen, Bristol-Myers Squibb, and Merck. A. Dowlati is an advisory board member/unpaid consultant for Abbvie, Takeda, Seattle Genetics, and Bristol-Myers Squibb. C.M. Rudin is an employee/paid consultant for AbbVie, Amgen, Ascentage, Bicycle, Celgene, Daiichi Sankyo, Genentech/Roche, Ipsen, Loxo, PharmaMar, Vavotek, Bridge, and Harpoon. S. Lally is an employee/paid consultant for and holds ownership interest (including patents) in AbbVie. S. Yalamanchili holds ownership interest (including patents) in AbbVie.J. Wolf is an employee/paid consultant for AbbVie, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Chugai, Blueprint, Ignyta, Janssen, Lilly, Loxo, MSD, Novartis, Roche, and Takeda, and reports receiving commercial research grants from Bristol-Myers Squibb, Janssen, MSD, Novartis, and Pfizer. R. Govindan is an employee/paid consultant for Jounce Therapeutics and Achilles, and reports receiving speakers bureau honoraria from Genentech and Amgen. D.P. Carbone is an employee/paid consultant for AbbVie, Adaptimmune, Agenus, Amgen, Ariad, AstraZeneca, Biocept, Boehringer Ingelheim, Bristol Myers-Squibb, Celgene, EMD Serono, Foundation Medicine, Genentech/Roche, Gritstone, Guardant Health, Inovio, Merck, MSD, Novartis, Palobiofarma, Pfizer, prIME Oncology, and Takeda, and reports receiving commercial research grants from Bristol Myers-Squibb.

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