



A Phase 1-2 Study of Rovalpituzumab Tesirine in Combination With Nivolumab Plus or Minus Ipilimumab in Patients With Previously Treated Extensive-Stage SCLC

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ABSTRACT

Introduction: This open-label, phase 1–2 study evaluated the safety and efficacy of rovalpituzumab tesirine (Rova-T), an antibody-drug conjugate targeting DLL3, plus immune checkpoint inhibitors nivolumab plus or minus ipilimumab in previously treated extensive-stage SCLC (ES SCLC).

Methods: Patients with histologically or cytologically confirmed, previously treated (two or more lines of therapy) ES SCLC were enrolled into two cohorts. Cohort 1 received 0.3 mg/kg Rova-T (once every 6 wk for two cycles) plus 360 mg nivolumab (two 3-wk cycles beginning on week 4). Cohort 2 received the same dosage of Rova-T as cohort 1 plus 1 mg/kg nivolumab (four 3-wk cycles) and 1 mg/kg ipilimumab (beginning week 4). Both cohorts received 480 mg nivolumab every 4 weeks starting at week 10. Key objectives were to evaluate safety and tolerability and efficacy (per Response Evaluation Criteria in Solid Tumors version 1.1). The response-related results are based on centrally read data.

Results: A total of 42 patients received therapy: cohort 1, n = 30; cohort 2, n = 12. Overall, 43% received two or more previous lines of therapy. All patients experienced one or more treatment-emergent adverse event (TEAE); 41 patients reported AEs considered related to the study drug by the investigator. The most frequent TEAE was pleural effusion (n = 20, 48%); most common grade greater than or equal to 3 was anemia (n = 9, 21%). Three grade 5 TEAEs considered related to the study drug were reported (cohort 1): pneumonitis (n = 2), acute kidney injury (n = 1). The objective response rate was 30% (12 of 40): cohort 1, 27.6% (8 of 29); cohort 2, 36.4% (4 of 11); all partial responses.

Conclusions: Despite encouraging antitumor activity in previously treated ES SCLC, combination therapy with Rova-T and nivolumab plus or minus ipilimumab was not well tolerated at the dose levels and administration schedules evaluated.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide,¹ with the SCLC subtype accounting for approximately 15%² of total lung cancer diagnoses. SCLC has a unique biology with rapidly proliferating cells, neuroendocrine features, and frequent hematogenous metastases at onset.³ Most patients with SCLC are diagnosed with having extensive-stage disease (extensive-stage SCLC [ES SCLC]) and have a dismal 5-year survival rate of 2%.⁴ Even with the first-line approval of immunotherapy,^{5,6} clinical outcomes for patients with SCLC continue to be poor.^{7–9}

There is growing evidence to support a tumor-suppressor role for Notch-1 signaling in neuroendocrine tumors. DLL3 is an inhibitory Notch receptor ligand¹⁰ identified as a novel target in SCLC tumor-initiating cells. This initial observation was based on whole-transcriptome sequencing of tumor-initiating cells isolated from a patient with SCLC and large-cell neuroendocrine carcinoma-derived xenografts.¹¹ Most SCLC and large-cell neuroendocrine carcinoma expressed DLL3; conversely, there was little to no expression of DLL3 in nonmalignant adult tissues and non-neuroendocrine tumor types. In high-grade neuroendocrine tumors, including SCLC, DLL3 has been implicated in the regulation of cell-fate decisions during development and might function as an oncogenic driver. Thus, through inhibition of the Notch receptor pathway, DLL3 might promote neuroendocrine identity or tumorigenesis.^{10,11}

Immune checkpoint blockade therapy against programmed cell death protein-1 (PD-1) and agents targeting DLL3 has independently revealed positive treatment effects in SCLC. Rovalpituzumab tesirine (Rova-T) is a novel biomarker-specific antibody-drug conjugate consisting a humanized DLL3-specific immunoglobulin G1 monoclonal antibody, SC16; the DNA crosslinking agent SC-DR002 (D6.5); and a protease-cleavable linker that covalently links SC-DR002 to SC16.¹¹ Rova-T binds DLL3 on target-expressing cells, is internalized, and the toxin released to induce cell death. A phase 1 study of Rova-T monotherapy in patients with recurrent SCLC revealed encouraging antitumor activity

in patients with DLL3-expressing tumors, with a manageable safety profile.¹² Antitumor activity seemed to have been greatest among tumors expressing high levels of DLL3, suggesting DLL3 expression may help identify patients who are more likely to benefit from Rova-T treatment.¹² In a phase 2 study, modest anti-tumor activity was observed with Rova-T monotherapy in heavily pretreated patients with DLL3-expressing SCLC.¹³

In 2015, pembrolizumab and nivolumab, monoclonal antibodies that bind to PD-1, gained regulatory approval in the United States and Europe for the treatment of advanced NSCLC.^{14–17} Combination therapy with programmed death-ligand 1 (PD-L1) inhibitors and platinum-based chemotherapy gained regulatory approval in the United States for the treatment of ES SCLC: atezolizumab plus carboplatin-etoposide (March 2019)⁵ and durvalumab plus platinum-etoposide (November 2019).⁶ In a phase 1–2 study, nivolumab alone and in combination with ipilimumab (anti-CTLA-4 antibody) had antitumor activity with a manageable safety profile in patients with recurrent SCLC; objective response rates (ORRs) were 10% to 23%, depending on dose schedule administered.¹⁸

Here, we report the findings of a phase 1–2 study that evaluated the safety and antitumor activity of Rova-T in combination with nivolumab or nivolumab and ipilimumab in patients with previously treated (two or more lines of therapy) ES SCLC.

Materials and Methods

Study Design and Treatment

This multicenter, phase 1–2 study (NCT03026166) evaluated Rova-T administered in combination with nivolumab or nivolumab plus ipilimumab in patients with ES SCLC. The primary objective was to evaluate safety and tolerability; antitumor activity evaluation was the secondary objective. Exploratory objectives included investigation of DLL3 and PD-L1 expression in SCLC and their relationship to clinical outcomes from the treatment.

In a previous phase 1 study with Rova-T, the recommended phase 2 dose in SCLC was chosen as 0.3 mg/kg every 6 weeks on the basis of the toxicity and efficacy profile during multiple cycles of dosing.¹² Tolerable doses and schedules of nivolumab and nivolumab plus ipilimumab in patients with SCLC were also established clinically.¹⁸ The fact that the toxicities of these therapies have generally been nonoverlapping provided the rationale for selection of dosing regimens of the different combinations reported in this study.

Three dosing cohorts of up to 30 patients each were planned; results from only cohorts 1 and 2 are reported,

as cohort 3 did not open for enrollment. All cohorts received two cycles of 0.3 mg/kg Rova-T administered intravenously (IV) 6 weeks apart, on day 1 of weeks 1 and 7. All patients received dexamethasone 8 mg orally twice daily on day –1, day 1 (day of dosing), and day 2 of each cycle with Rova-T. Patients enrolled in cohort 1 received two cycles of nivolumab 360 mg IV administered 3 weeks apart beginning on week 4, followed by 480 mg nivolumab (monotherapy) every 4 weeks (Q4W) starting at week 10.

Patients enrolled in cohort 2 received four cycles of nivolumab 1 mg/kg IV and four cycles of ipilimumab 1 mg/kg IV beginning on week 4, each cycle 3 weeks apart, followed by 480 mg nivolumab (monotherapy) Q4W at week 20 (after a 6-wk washout period from ipilimumab).

Planned dose administration for patients in cohort 3 was four cycles of nivolumab 1 mg/kg IV and four cycles of ipilimumab 3 mg/kg IV beginning on week 4, each cycle 3 weeks apart, followed by 480 mg nivolumab (monotherapy) Q4W at week 22 (after an 8-wk washout period from ipilimumab).

Dose-limiting toxicities (DLTs) were evaluated during the first four cycles of treatment (12 wk). Up to 12 patients were initially enrolled into cohort 1 to obtain six assessable patients through the DLT evaluation period. If one (or none) of six patients being evaluated in each cohort experienced a DLT within the evaluation period, enrollment beyond 12 patients was allowed to proceed.

On the basis of tolerability of the initial six assessable patients enrolled into cohort 1, enrollment of cohort 2 commenced (up to 12 patients). Once at least six DLL3-positive patients were enrolled into cohort 2, enrollment was permitted to resume for cohort 1 (up to 30 patients).

Patients were eligible to continue treatment until unacceptable toxicity, progressive disease, withdrawal of consent, study termination, or completion of a planned course of treatment, whichever occurred first. Patients who discontinued study treatment before progressive disease were evaluated for response every 6 weeks until 24 weeks and then every 12 weeks until disease progression or initiation of new anticancer treatment, whichever occurred first. These patients were followed for survival until death or study termination (whichever occurred first).

The protocol and amendments received independent ethics committee and institutional review board approval. The study was conducted in accordance with Good Clinical Practice International Conference on Harmonization guidelines, the National Statement on Ethical Conduct in Human Research 2007, the Declaration of Helsinki, and national and local regulatory

guidelines. All patients provided written informed consent.

Patients

Eligible patients were 18 years or older, with histologically or cytologically confirmed ES SCLC with disease progression after at least one platinum-based chemotherapeutic regimen and assessable or measurable disease evaluated by computerized tomography scan per Response Evaluation Criteria in Solid Tumors version 1.1. Other major inclusion criteria were Eastern Cooperative Oncology Group performance status of 0 or 1; adequate hematologic, renal, and hepatic function; no active, known, or suspected autoimmune disease; and no previous exposure to an immuno-oncology or pyrrolbenzodiazepine-based drug. Asymptomatic central nervous system metastases were allowed, if stable in the absence of corticosteroids for at least 2 weeks before start of treatment. Patients were required to consent to provide archived tumor tissue or fresh tumor biopsy for immunohistochemistry analyses. A list of inclusion and exclusion criteria can be found at ClinicalTrials.gov.¹⁹

Safety and Tolerability

Safety evaluations were performed throughout the study. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Treatment-emergent AEs (TEAEs) were defined as any AEs with an onset date on or after the first dose of study drug and less than or equal to 100 days after the last dose of the study drug. Treatment-related AEs were those considered by the investigator as having reasonable possibility of being related to Rova-T, nivolumab, and/or ipilimumab.

DLTs were defined as follows: grade 4 thrombocytopenia (grade 3 with bleeding) lasting more than 7 days and/or requiring platelet transfusion; grade 4 neutropenia lasting more than 7 days, and/or requiring hematopoietic growth factor rescue, or any febrile neutropenia (grade 3 or 4 neutropenia with concurrent fever $\geq 38.3^{\circ}\text{C}$); grade 4 anemia (unrelated to underlying disease); clinically significant grade 3 or 4 non-hematologic laboratory abnormality that does not resolve to grade 0 or 1 or baseline in less than or equal to 7 days; grade 3 or 4 nonlaboratory AE excluding fatigue, asthenia, nausea, or other manageable constitutional symptom.

Efficacy

Treatment response was evaluated by radiographic tumor evaluations at protocol-specified time points. On applicable cycles, disease assessment occurred within 3

days (no >7 d) before day of dosing. Cohort 1 imaging was performed before cycle 3 day 1, before cycle 5 day 1 (if a response was observed, a mandatory 4-wk follow-up confirmatory scan was performed), and every 8 weeks thereafter. Cohort 2 imaging schedule was as follows: before cycle 3 day 1, before cycle 5 day 1, before cycle 6 day 1, and every 8 weeks thereafter.

ORR was assessed (central review) using Response Evaluation Criteria in Solid Tumors version 1.1 criteria and reported using 95% confidence intervals (CIs). Duration of response (DOR) was summarized by cohort for responders only: patients with complete response (CR) or partial response (PR). Progression-free survival (PFS) and overall survival (OS) were also summarized by cohort. Median DOR, PFS, and OS were obtained by Kaplan-Meier assessment.

Biomarker Analysis

Blood and/or tissue samples for biomarker testing were collected at prescreening or screening, end of treatment, and long-term follow-up visits. Assessments included analyses of tumor tissue for DLL3 and PD-L1 expression and analyses of blood samples for tumor markers, circulating tumor cells, and immune and soluble biomarkers (e.g., soluble DLL3).

For up to the first 12 patients enrolled into each cohort, tumor tissue was required to be DLL3 positive ($\geq 25\%$) per immunohistochemistry. Tumor tissue with greater than or equal to 75% DLL3 positivity was considered DLL3 high.

Results

Patient Demographics and Baseline Characteristics

A total of 42 patients were enrolled as of September 30, 2019; 30 patients in cohort 1 (Rova-T 0.3 mg/kg plus nivolumab 360 mg, followed by nivolumab 480 mg) and 12 patients in cohort 2 (Rova-T 0.3 mg/kg plus nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, followed by nivolumab 480 mg). Patient demographics and baseline characteristics are reported in [Table 1](#). The median age was 61.5 years (range: 25–79). Overall, 93% (39 of 42) of the patients were DLL3 positive and 55% (23 of 42) were DLL3 high (15 patients in cohort 1 and 8 patients in cohort 2). There were 43% of the patients (18 of 42) who had received two or more previous lines of therapy, and most (64%; 27 of 42) had sensitivity to frontline platinum-based therapy.

A total of 28 patients (67%) completed the two planned cycles of Rova-T: cohort 1, 70% (21 of 30); cohort 2, 58% (7 of 12). In cohort 1, 97% (29 of 30) of the patients received at least one dose of both Rova-T and nivolumab 360 mg. In cohort 2, 83% (10 of 12) of

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Cohort 1 n = 30	Cohort 2 n = 12	Total N = 42
Age, median (range), y	61.5 (48-79)	62 (25-72)	61.5 (25-79)
Sex, n (%)			
Male	16 (53.3)	7 (58.3)	23 (54.8)
Female	14 (46.7)	5 (41.7)	19 (45.2)
Race, n (%)			
White	29 (96.7)	10 (83.3)	39 (92.9)
Black	1 (3.3)	1 (8.3)	2 (4.8)
Not reported	0	1 (8.3)	1 (2.4)
ECOG performance status, n (%)			
0	7 (23.3)	4 (33.3)	11 (26.2)
1	23 (76.7)	8 (66.7)	31 (73.8)
DLL3 score, n (%)			
Positive (≥25%)	27 (90.0)	12 (100.0)	39 (92.9)
High (≥75%)	15 (50.0)	8 (66.7)	23 (54.8)
Missing	1 (3.3)	0	1 (2.4)
No. of previous therapies, n (%)			
1	16 (53.3)	8 (66.7)	24 (57.1)
2	10 (33.3)	3 (25.0)	13 (31.0)
3	3 (10.0)	0	3 (7.1)
>3	1 (3.3)	1 (8.3)	2 (4.8)
Response to frontline therapy, n (%) ^a			
Sensitive	19 (63.3)	8 (66.7)	27 (64.3)
Refractory	2 (6.7)	2 (16.7)	4 (9.5)
Resistant	9 (30.0)	1 (8.3)	10 (23.8)
Undetermined or missing	0	1 (8.3)	1 (2.4)
History of brain metastasis, n (%)			
Yes	21 (70.0)	8 (66.7)	29 (69.0)
No/unknown	9 (30.0)	4 (33.3)	13 (31.0)

^aClassification on the basis of number of relapse-free days after completion of chemotherapy (platinum sensitivity classification): sensitive response (>90 days); refractory (<45 days); resistant (<90 days).
ECOG, Eastern Cooperative Oncology Group.

the patients received at least one dose of Rova-T in combination with 1 mg/kg nivolumab and 1 mg/kg ipilimumab. There were 18 patients in cohort 1 and two patients in cohort 2 who received nivolumab 480-mg maintenance monotherapy.

Dose-Limiting Toxicities

Four patients experienced DLTs, including one patient in cohort 1 and three patients in cohort 2. DLTs were rash (n = 2), photosensitivity reaction (n = 1), pneumonitis (n = 1), and colitis (n = 1). Recruitment of patients was completed for cohort 1, and cohort 2 enrollment was halted after the DLT evaluation phase owing to the observed rate of DLTs (three of six assessable patients). The planned enrollment of cohort 3 did not occur owing to the high rate of DLTs in cohort 2.

Safety

Table 2 summarizes TEAEs reported during the study. All 42 patients experienced one or more TEAEs, with 38 patients (91%) reporting grade greater than or

equal to 3 TEAEs: 26 patients (87%) in cohort 1 and 12 patients (100%) in cohort 2. Most TEAEs (n = 41, 98%) were considered related to the study drug by the investigator. The most frequent drug-related TEAEs were pleural effusion (n = 17, 41%) and fatigue (n = 16, 38%). Most common grade greater than or equal to 3 drug-related TEAEs were thrombocytopenia (n = 5; 12%) and anemia, fatigue, pericardial effusion, and pneumonitis (n = 4; 10% each). Serious drug-related TEAEs were reported in 19 patients (45%): 13 patients (43%) in cohort 1 and six patients (50%) in cohort 2. Three (7.1%) grade 5 TEAEs considered related to the study drug were reported (all in cohort 1). These were pneumonitis (n = 2) and acute kidney injury (n = 1). Serious TEAEs included pleural effusion (n = 7, 17%), pneumonitis (n = 4, 10%), dehydration, and pericardial effusion (n = 3, 7% each). The correlation between AEs and DLL3 expression levels was not examined.

Rova-T discontinuation owing to AEs occurred in 14% (n = 6) of the patients (cohort 1: n = 4; 13%; cohort 2: n = 2, 17%), whereas 39% of the patients discontinued nivolumab treatment owing to AEs (cohort

Table 2. Drug-Related TEAEs by Preferred Term Occurring in >20% (Any), >5% (Grade ≥ 3) of Patients, or One or More Patient (Serious) Treated With Study Drug

AEs, n (%)	TEAE With Reasonable Possibility of Relationship to Study Drug ^a			All TEAEs Regardless of Relationship to Study Drug		
	Cohort 1 n = 30	Cohort 2 n = 12	Total N = 42	Cohort 1 n = 30	Cohort 2 n = 12	Total N = 42
Any AE (>20%)	29 (97)	12 (100)	41 (98)	30 (100)	12 (100)	42 (100)
Pleural effusion	13 (43)	4 (33)	17 (41)	15 (50)	5 (42)	20 (48)
Fatigue	10 (33)	6 (50)	16 (38)	11 (37)	6 (50)	17 (40)
Pericardial effusion	9 (30)	2 (17)	11 (26)	9 (30)	2 (17)	11 (26)
Thrombocytopenia	7 (23)	4 (33)	11 (26)	9 (30)	5 (42)	14 (33)
Peripheral edema	7 (23)	3 (25)	10 (24)	12 (40)	3 (25)	15 (36)
Decreased appetite	7 (23)	2 (17)	9 (21)	9 (30)	5 (42)	14 (33)
Photosensitivity reaction	7 (23)	2 (17)	9 (21)	7 (23)	2 (17)	9 (21)
Dyspnea	7 (23)	1 (8)	8 (19)	14 (47)	5 (42)	19 (45)
Anemia	6 (20)	2 (17)	8 (19)	10 (33)	6 (50)	16 (38)
Constipation	1 (3)	0	1 (2)	8 (27)	3 (25)	11 (26)
Malignant neoplasm progression	1 (3)	0	1 (2)	8 (27)	2 (17)	10 (24)
Rash maculopapular	4 (13)	4 (33)	8 (19)	5 (17)	5 (42)	10 (24)
Vomiting	3 (10)	1 (8)	4 (10)	7 (23)	3 (25)	10 (24)
Abdominal pain	4 (13)	0	4 (10)	7 (23)	2 (17)	9 (21)
Facial edema	5 (17)	1 (8)	6 (14)	7 (23)	2 (17)	9 (21)
Any grade ≥ 3 AE ^b (>5%)	16 (53)	11 (92)	27 (64)	26 (87)	12 (100)	38 (91)
Thrombocytopenia	2 (7)	3 (25)	5 (12)	4 (13)	3 (25)	7 (17)
Anemia	3 (10)	1 (8)	4 (10)	5 (17)	4 (33)	9 (21)
Fatigue	2 (7)	2 (17)	4 (10)	2 (7)	2 (17)	4 (10)
Pericardial effusion	3 (10)	1 (8)	4 (10)	3 (10)	1 (8)	4 (10)
Pneumonitis	3 (10)	1 (8)	4 (10)	3 (10)	1 (8)	4 (10)
Dehydration	1 (3)	2 (17)	3 (7)	1 (3)	2 (17)	3 (7)
Pleural effusion	3 (10)	0	3 (7)	3 (10)	1 (8)	4 (10)
Hyponatremia	0	0	0	4 (13)	2 (17)	6 (14)
Hypertension	0	0	0	3 (10)	0	3 (7)
Hypotension	0	1 (8)	1 (2)	2 (7)	1 (8)	3 (7)
Hypophosphatemia	1 (3)	0	1 (2)	3 (10)	0	3 (7)
Dyspnea	0	0	0	2 (7)	1 (8)	3 (7)
Asthenia	0	0	0	2 (7)	1 (8)	3 (7)
Serious AE (≥ 1 patient)	13 (43)	6 (50)	19 (45)	23 (77)	9 (75)	32 (76)
Pleural effusion	7 (23)	0	7 (17)	8 (27)	0	8 (19)
Pneumonitis	3 (10)	1 (8)	4 (10)	3 (10)	1 (8)	4 (10)
Dehydration	1 (3)	2 (17)	3 (7)	1 (3)	2 (17)	3 (7)
Pericardial effusion	2 (7)	1 (8)	3 (7)	2 (7)	1 (8)	3 (7)
Acute respiratory failure	2 (7)	0	2 (5)	2 (7)	0	2 (5)
Dyspnea	2 (7)	0	2 (5)	3 (10)	0	3 (7)
Fatigue	0	2 (17)	2 (5)	0	2 (17)	2 (5)
Pneumonia	1 (3)	0	1 (2)	2 (7)	0	2 (5)
Sepsis	0	0	0	1 (3)	1 (8)	2 (5)
Respiratory failure	1 (3)	0	1 (2)	2 (7)	0	2 (5)
Atrial fibrillation	1 (3)	0	1 (2)	2 (7)	0	2 (5)
Hyponatremia	0	0	0	2 (7)	0	2 (5)

^aDrug-related events could be due to any of the three study drugs given during the study.

^bIncludes drug-related grade 5 AEs: pneumonitis (two), acute kidney injury (one); all cohort 1. AE, adverse event; TEAE, TEAE, treatment-emergent AE.

1: n = 10, 35%; cohort 2: n = 5, 50%). Three patients (33%) discontinued ipilimumab owing to AEs (cohort 2).

Efficacy

The efficacy-assessable population consisted of 40 patients (29 in cohort 1 and 11 in cohort 2). Time on

study and DOR are presented in [Figure 1](#) for both cohorts. Median DOR was 3.8 months (95% CI: 1.6–5.6) in cohort 1 and 3.3 months (95% CI: 1.4–not reached) in cohort 2 ([Table 3](#) and [Fig. 1](#)). The best percentage change in target lesion from baseline in all treated patients with a best overall response of CR or PR is illustrated in

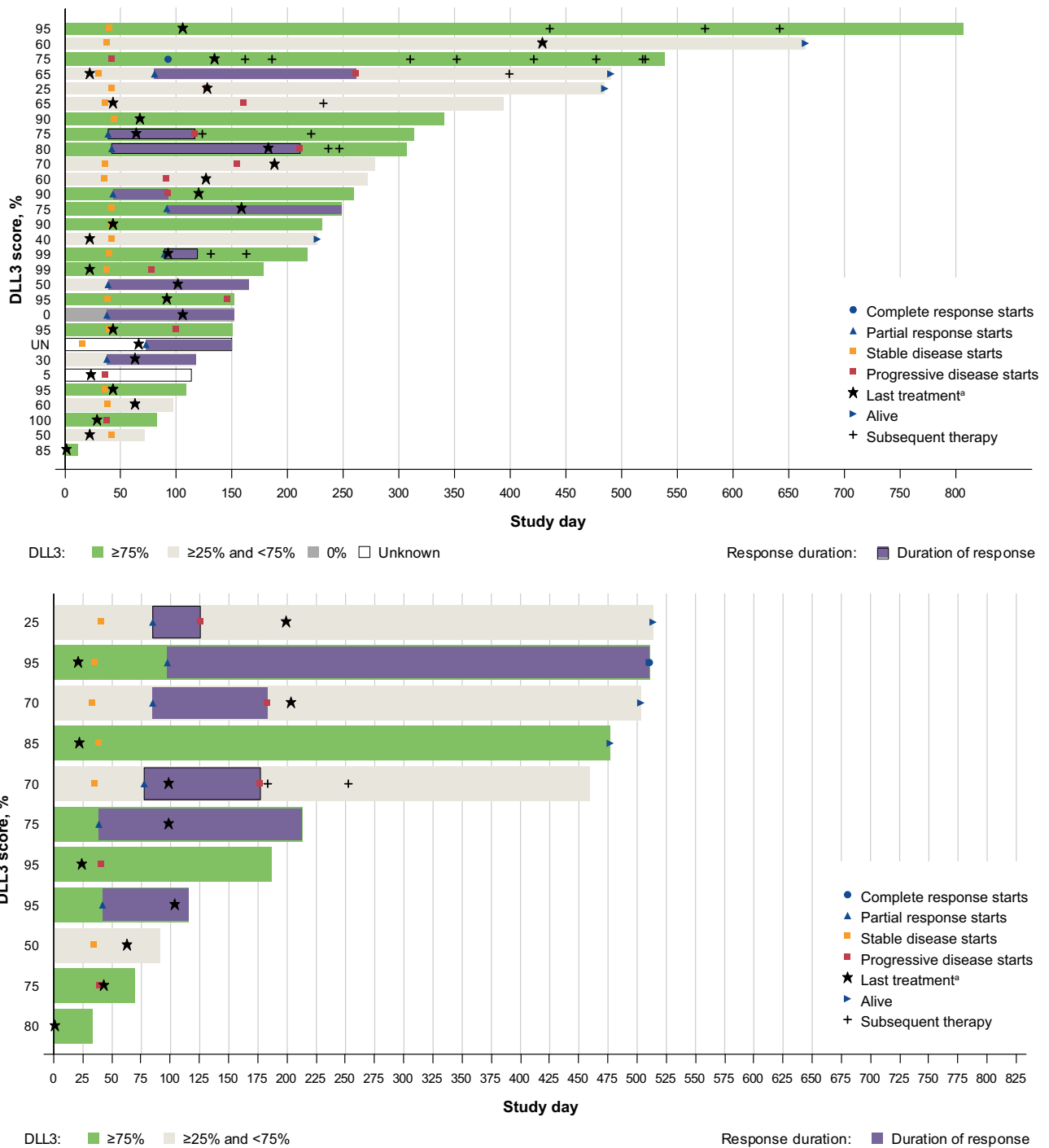


Figure 1. Time on study and response duration for patients treated in cohort 1 and cohort 2. ^aLatest treatment date with any study drug (Rova-T, nivolumab, or ipilimumab). Rova-T, rovalpituzumab tesirine; UN, unknown.

Figure 2. ORRs for all treated patients from each cohort are presented in Table 3. Median duration of follow-up was 7.3 months in cohort 1 and 11.0 months in cohort 2. No patients achieved a confirmed CR. Confirmed PR was achieved in eight patients (27.6%) and four patients (36.4%) in cohorts 1 and 2, respectively (Table 3 and Fig. 2). In cohort 1, the confirmed ORR was 27.6% (8 of 29; 95% CI: 12.7–47.2), median PFS was 4.8 months

(95% CI: 3.2–5.3), and median OS was 7.4 months (95% CI: 5.0–9.1) (Table 3). In cohort 2, the confirmed ORR was 36.4% (4 of 11; 95% CI: 10.9–69.2), median PFS was 4.1 months (95% CI: 1.3–6.0), and median OS was 11.0 months (95% CI: 2.3–17.0) (Table 3). Median DOR for patients in cohorts 1 and 2 was 3.8 months (95% CI: 1.6–5.6) and 3.3 months (95% CI: 1.4–not reached), respectively. Response, PFS, and OS were similar for

Table 3. Efficacy Summary for Patients Treated in Cohort 1 and Cohort 2

Efficacy	Cohort 1	Cohort 2	Total
N, efficacy analysis set ^a	29	11	40
Confirmed response			
ORR [CR + PR], % (95% CI)	27.6 (12.7-47.2)	36.4 (10.9-69.2)	30.0 (16.6-46.5)
CR	0	0	0
PR	27.6	36.4	30.0
Median DOR, mo (95% CI)	3.8 (1.6-5.6)	3.3 (1.4-NR)	3.3 (2.4-5.2)
Median PFS, mo (95% CI)	4.8 (3.2-5.3)	4.1 (1.3-6.0)	4.2 (3.2-5.3)
N, full analysis set	30	12	42
Median OS, mo (95% CI)	7.4 (5.0-9.1)	11.0 (2.3-17.0)	7.4 (5.0-10.1)

Note: The median duration of follow-up in cohort 1 was 7.3 months. The median duration of follow-up in cohort 2 was 11.0 months.

^aOne patient in each cohort was not assessable for efficacy: one did not have a postbaseline radiographic assessment and one did not have a target lesion identified by central review.

CI, confidence interval; CR, complete response; DOR, duration of response; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

patients with DLL3-high tumors (DLL3 expressed in $\geq 75\%$ of tumor cells) and those with tumors that were DLL3 positive but not high (25%–75% of tumor tissue).

Discussion

Here, we report the results of the first formal clinical study of Rova-T, a DLL3-targeted antibody-drug conjugate, in combination with the checkpoint inhibitors nivolumab and ipilimumab. Previous studies evaluating either Rova-T^{12,20} or nivolumab and ipilimumab¹⁸ have independently revealed encouraging efficacy in patients with advanced-stage SCLC. However, neither approach alone seems sufficient to afford the clinical benefit needed for most patients with ES SCLC.

Our results revealed an ORR of 30% (12 of 40) in patients with previously treated ES SCLC administered Rova-T in combination with either nivolumab (27.6% [8 of 29]) or nivolumab and ipilimumab (36.4% [4 of 11]). Median DOR was 3.8 months for Rova-T in combination with nivolumab and 3.3 months for the combination with nivolumab and ipilimumab. Median OS and PFS was 7.4 and 4.8 months for Rova-T plus nivolumab, 11.0 and 4.1 months for Rova-T plus nivolumab and ipilimumab, and 7.4 and 4.2 months for the total population. Enrollment in cohort 2 was halted after 12 patients were accepted, owing to the observed 50% DLT rate in the first six patients. Of the 12 patients, 11 were assessable for efficacy. The sample size used to determine the response to treatment in this cohort was therefore much smaller than originally planned, limiting its significance.

Grade greater than or equal to 3 drug-related AEs occurred in 27 of 42 patients (64%) treated with Rova-T plus nivolumab with or without ipilimumab, with thrombocytopenia (12%) the most often reported. Drug-related serious AEs occurred in 43% of patients, the most frequent including pleural effusion and pericardial effusion.¹² The effusions were best classified as serositis and did not reliably respond to steroids, diuretics, or

other medications. Three grade 5 drug-related AEs were reported with the combination of Rova-T with nivolumab. In the CheckMate 032 phase 1–2 study (N = 216) of nivolumab alone or in combination with ipilimumab, grade greater than or equal to 3 drug-related AEs occurred in 13 patients (13%) in the nivolumab monotherapy cohort; the most often reported drug-related TEAEs were increased lipase and diarrhea.¹⁸ Excluding malignant neoplasm, the most frequent serious AEs reported were dyspnea and diarrhea.¹⁸

Although our sample size is small, our observed ORR using the combination of Rova-T plus nivolumab with or without ipilimumab compares favorably with response rates reported for nivolumab with or without ipilimumab in the CheckMate 032 study, approximately 10% and 19%, respectively.¹⁸ Our findings also compare favorably with the results revealed in a phase 1 study of Rova-T monotherapy in SCLC (N = 82), which reported ORR of 18% in assessable patients and a median DOR and PFS of 5.6 and 3.1 months, respectively.¹² Another limitation of the study is that patients received premedication with dexamethasone 8 mg orally twice daily with the two Rova-T doses, which may limit the efficacy of checkpoint inhibitors. However, dexamethasone was only given with one dose of nivolumab and ipilimumab (cycle 3); this was the only time that Rova-T was administered on the same day as the checkpoint inhibitors. Moreover, data from other completed studies have not revealed a considerable effect on the efficacy of checkpoint inhibitors when dexamethasone premedication is given for concurrently administered chemotherapy.^{21,22}

In this trial, the combination of Rova-T with nivolumab with or without ipilimumab had encouraging antitumor activity revealed in a heavily pretreated population of patients with ES SCLC. However, Rova-T administered in combination with nivolumab alone or as a triplet with ipilimumab was not well tolerated at the dose levels and administration schedules evaluated.

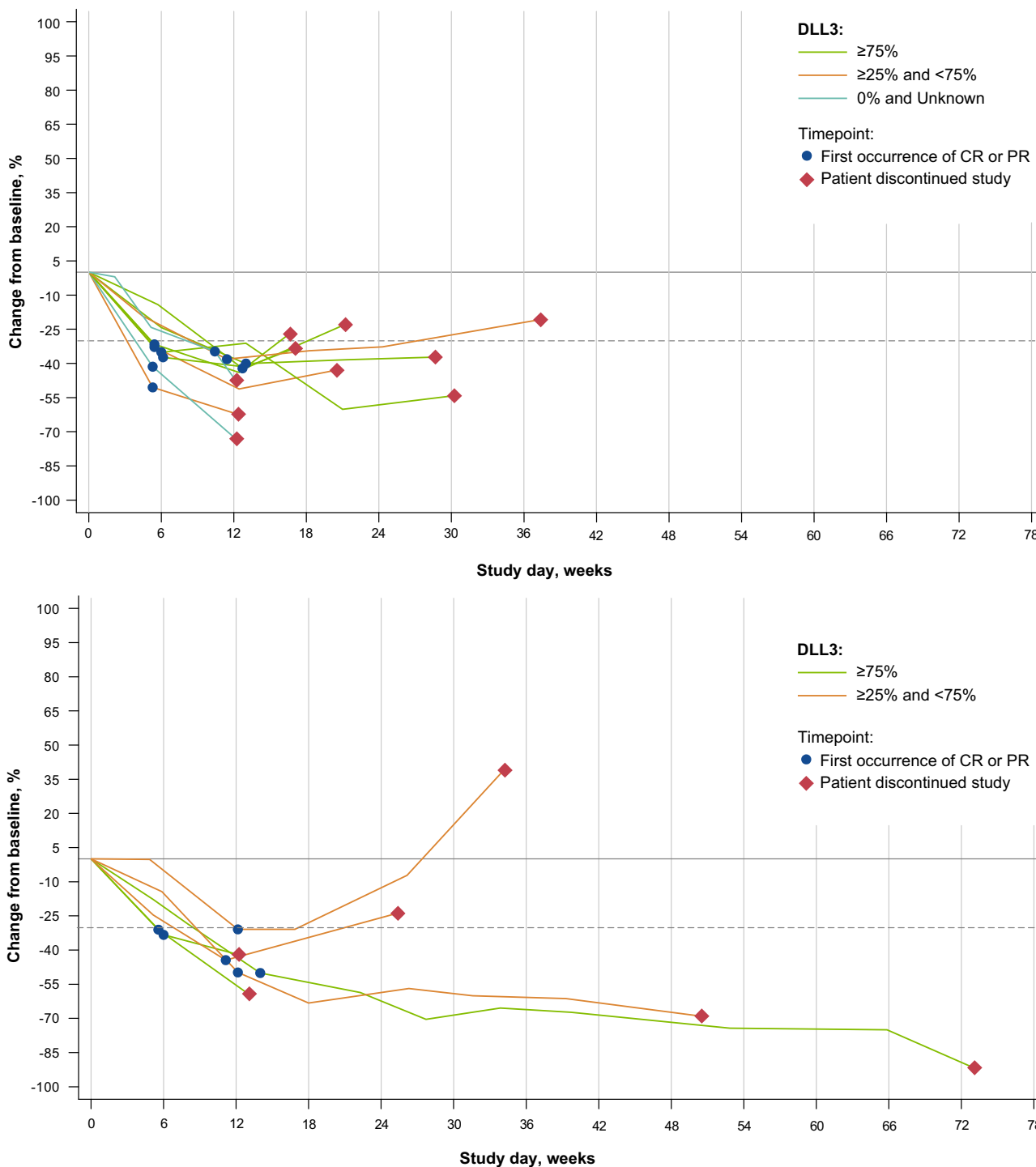


Figure 2. Best percentage change in target lesion measurement from baseline in patients with best overall response of CR or PR. CR, complete response; PR, partial response.

Because of the DLT rate observed with this triple-combination therapy, enrollment was stopped and a third planned cohort at 3 mg/kg ipilimumab was deemed not feasible. The safety profile of the combination of Rova-T with nivolumab suggests that dose and schedule optimization would be required to further pursue this combination.

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. These 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.html>.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. National Institutes of Health. National Cancer Institute. Small cell lung cancer treatment (PDQ®)-health professional version. <https://www.cancer.gov/types/lung/hp/small-cell-lung-treatment-pdq>. Accessed July 1, 2020.
3. Alvarado-Luna G, Morales-Espinosa D. Treatment for small cell lung cancer, where are we now? A review. *Transl Lung Cancer Res*. 2016;5:26-38.
4. Jackman DM, Johnson BE. Small-cell lung cancer. *Lancet*. 2005;366:1385-1396.
5. US Food and Drug Administration. FDA approves atezolizumab for extensive-stage small cell lung cancer. <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-extensive-stage-small-cell-lung-cancer>. Accessed July 1, 2020.
6. AstraZeneca. Imfinzi granted FDA Priority Review for the treatment of patients with extensive-stage small cell lung cancer. <https://www.astrazeneca.com/media-centre/press-releases/2019/imfinzi-granted-fda-priority-review-for-the-treatment-of-patients-with-extensive-stage-small-cell-lung-cancer.html>. Accessed July 1, 2020.
7. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol*. 1992;10:282-291.
8. Koinis F, Kotsakis A, Georgoulas V. Small cell lung cancer (SCLC): no treatment advances in recent years. *Transl Lung Cancer Res*. 2016;5:39-50.
9. Waqar SN, Morgensztern D. Treatment advances in small cell lung cancer (SCLC). *Pharmacol Ther*. 2017;180:16-23.
10. Chapman G, Sparrow DB, Kremmer E, Dunwoodie SL. Notch inhibition by the ligand DELTA-LIKE 3 defines the mechanism of abnormal vertebral segmentation in spondylocostal dysostosis. *Hum Mol Genet*. 2011;20:905-916.
11. Saunders LR, Bankovich AJ, Anderson WC, et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. *Sci Transl Med*. 2015;7:302ra136.
12. Rudin CM, Pietanza MC, Bauer TM, et al. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. *Lancet Oncol*. 2017;18:42-51.
13. Morgensztern D, Besse B, Greillier L, et al. 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. *Clin Cancer Res*. 2019;25:6958-6966.
14. Drugs.com. FDA approves Keytruda (pembrolizumab) for advanced non-small cell lung cancer. <https://www.drugs.com/newdrugs/fda-approves-keytruda-pembrolizumab-advanced-non-small-cell-lung-cancer-4273.html>. Accessed July 1, 2020.
15. Drugs.com. FDA expands approved use of Opdivo (nivolumab) to treat lung cancer. <https://www.drugs.com/newdrugs/fda-expands-approved-opdivo-nivolumab-lung-cancer-4179.html>. Accessed July 1, 2020.
16. Bristol-Myers Squibb Pharma EEIG. Opdivo: summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf. Accessed July 1, 2020.
17. Merck Sharp & Dohme BV. Keytruda: summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf. Accessed July 1, 2020.
18. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent

- small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol.* 2016;17:883-895.
19. National Institutes of Health. US National Library of Medicine. ClinicalTrials.gov. A study of rovalpituzumab tesirine administered in combination with nivolumab and with or without ipilimumab for adults with extensive-stage small cell lung cancer. <https://clinicaltrials.gov/ct2/show/NCT03026166>. Accessed July 1, 2020.
 20. Tolcher AW. Antibody drug conjugates: lessons from 20 years of clinical experience. *Ann Oncol.* 2016;27:2168-2172.
 21. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med.* 2018;378:2288-2301.
 22. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med.* 2018;378:2078-2092.