BRIEF REPORT

A Phase 1 Study Evaluating Rovalpituzumab Tesirine in Frontline Treatment of Patients With Extensive-Stage SCLC

Christine L. Hann, MD, PhD,[a,*] Timothy F. Burns, MD, PhD,[b] Afshin Dowlati, MD,[c] Daniel Morgensztern, MD,[d] Patrick J. Ward, MD, PhD,[e] Martina M. Koch, MD,[f] Chris Chen, PhD,[f] Carrianne Ludwig, BS,[f] Maulik Patel, PharmD, PhD,[g] Halla Nimeiri, MD,[f] Philip Komarnitsky, MD, PhD,[f] D. Ross Camidge, MD, PhD[h]

[a]*Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, Maryland*
[b]*UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, Pennsylvania*
[c]*University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, Ohio*
[d]*Division of Medical Oncology, Washington University School of Medicine, St. Louis, Missouri*
[e]*Oncology Hematology Care, Inc., Cincinnati, Ohio*
[f]*AbbVie Inc., North Chicago, Illinois*
[g]*AbbVie Inc., Redwood City, California*
[h]*Division of Medical Oncology, Department of Medicine, University of Colorado Denver, Aurora, Colorado*

Received 18 December 2020; revised 22 June 2021; accepted 23 June 2021
Available online - 6 July 2021

ABSTRACT

Introduction: Rovalpituzumab tesirine (Rova-T) is an antibody-drug conjugate targeting DLL3, a Notch pathway ligand highly expressed on SCLC cells. Rova-T was evaluated alone or in combination with platinum-based chemotherapy (cisplatin or carboplatin combined with etoposide [CE]) in frontline treatment of extensive-stage SCLC.

Methods: One cycle of CE pre-enrollment was permitted (later mandated). The following four cohorts were enrolled: Rova-T monotherapy (0.3 mg/kg, every 6 [q6] wk × 2; cohort 1; n = 4); Rova-T induction (0.3 mg/kg, q6 wk × 2) followed by CE every 21 days (q21) × 4 (cohort 2; n = 5); Rova-T (0.1 or 0.2 mg/kg, q6 wk × 2) overlapping with CE q21 × 4 (cohort 3; n = 14); and Rova-T maintenance (0.3 mg/kg, q6 wk × 2) after CE q21 × 4 (cohort 4; n = 3).

Results: A total of 26 patients were dosed (cohort 3: 14; cohorts 1, 2, and 4 combined: 12). Median age was 66 years, and 73% had Eastern Cooperative Oncology Group performance status of 1. In cohort 3, seven patients (50%) had

*Corresponding author.

Disclosure: Dr. Hann reports serving in a consulting or advisory role for AbbVie/StemCentrx, Ascentage, AstraZeneca, Bristol-Myers Squibb, and Genentech/Roche. Dr. Burns reports serving in a consulting or advisory role for AbbVie/Stemcentrx, Blueprint Medicines, Novartis, and Thermo Fisher Scientific. Dr. Dowlati reports receiving nonfinancial support from GlaxoSmithKline, during the conduct of the study; grants from EMD Serono, Tesaro, Regeneron, Roche, Eli Lilly, Takeda, Ipsen, United Therapeutics, Mirati, Bayer, Bristol-Myers Squibb, Incuron, and Vertex; grants and personal fees from AbbVie, AstraZeneca, Millennium, and Seattle Genetics; and personal fees from Ariad outside of the submitted work. Dr. Morgensztern reports serving as a consultant for AbbVie, Takeda, PharmaMar, and Gilead. Drs. Komarnitsky, Chen, and Patel and Ms. Ludwig are employees of AbbVie and hold AbbVie stock. Drs. Koch and Nimeiri are former employees of AbbVie and may hold AbbVie stock. Dr. Ross reports serving in an advisory role (ad hoc advisory boards/consultations) for Amgen, Anchiarno (SAB), Apollomics (SRC), AstraZeneca, Bio-Thera (DSMB), Bristol-Myers Squibb, Daiichi-Sankyo (ILD adjudication committee), EMD Serono, Elevation (SRC), Eli Lilly, GlaxoSmithKline, Helssin, Janssen, Onkure, Pfizer, Qilu, Roche, Sanofi, Seattle Genetics, Takeda, CBT Pharmaceuticals, G1 Therapeutics (DSMB), Blueprint Medicines, AbbVie, Achilles, BeyondSpring, Apollomics (SRC), Archer, Helssin, Medtronic, Ribon, Arrys/Kyn, Regeneron, Hengrui, Hansoh (SRC), Roche/Genentech, and Inivata; receiving research funding from Takeda for an investigator-initiated trial; and participating in company-sponsored trials for AbbVie, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Hansoh, Inhibrx, Karyopharm, Lycera, Medimmune, Merck, Pfizer, Phosplatin, Psioxus, Rain, Roche/Genentech, Seattle Genetics, Symphogen, Takeda, and Tolero. Dr. Ward declares no conflict of interest.

Presented in part at the annual meeting of the European Society for Medical Oncology (ESMO) in Barcelona, Spain, on September 2019.

Address for correspondence: Christine L. Hann, MD, PhD, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 201 North Broadway, Viragh Building, Room 8123, Baltimore, MD 21287. E-mail: chann1@jhmi.edu

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2021.06.022

confirmed objective responses, with a median progression-free survival of 5.2 months and median overall survival of 10.3 months. Compared with cohorts 1, 2, and 4 combined, cohort 3 had lower frequency of some Rova-T–related adverse events of special interest, such as pleural effusion (0 versus 33%), pericardial effusion (0 versus 17%), ascites (0 versus 8%), peripheral edema (36% versus 42%), generalized edema (0 versus 8%), pneumonia (7% versus 25%), and hypoalbuminemia (0 versus 17%).

Conclusions: Lower Rova-T doses may be associated with lower incidence of some Rova-T–related adverse events of special interest. Rova-T 0.2 mg/kg plus CE (cohort 3) was tolerable; however, there was no clear efficacy benefit of adding Rova-T to CE.

Keywords: Rovalpituzumab tesirine; Frontline; Small cell lung cancer; DLL3; Platinum-based chemotherapy

Introduction

Although response rates to initial chemotherapy are high (60%–80%) in extensive-stage SCLC (ES SCLC), most patients have a relapse with a median overall survival (OS) of approximately 10 months.[1–3] The recently approved immune checkpoint inhibitors, atezolizumab and durvalumab, in combination with platinum-based chemotherapy have improved survival marginally (12–13 mo) in the frontline setting.[4,5] Thus, there is a high unmet need to provide more effective therapies in the frontline ES SCLC setting.

DLL3, an atypical Notch receptor ligand, is highly expressed on the surface of greater than 80% of SCLC and neuroendocrine carcinoma cells, but it is not detectable on normal tissue.[6,7] Rovalpituzumab tesirine (Rova-T) is a first-in-class antibody-drug conjugate composed of a DLL3-targeting IgG1 monoclonal antibody tethered to a toxic DNA crosslinking agent and a protease-cleavable linker.[6,8] Rova-T was found to have encouraging to modest activity in relapsed or refractory patients with ES SCLC,[8,9] which prompted its evaluation in the frontline setting. Here, we report the safety and efficacy of Rova-T alone and in a series or combination with carboplatin or cisplatin combined with etoposide (CE) in the frontline treatment of ES SCLC.

Materials and Methods

This phase 1, multicenter, open-label study (NCT02819999) enrolled four cohorts after induction with one cycle of CE once every 21 days, which was initially permitted and later mandated. Rova-T was administered as monotherapy (cohort 1), in series (cohorts 2 and 4), or in combination with CE (cohort 3) (Supplementary Fig. 1). Additional details regarding study design, regimens and dosing, protocol amendments, planned sample size, and methodology are included in the Supplementary Data.

Key inclusion criteria included age more than or equal to 18 years, histologically or cytologically confirmed ES SCLC, with a response of stable disease or better after the prestudy CE cycle per the Response Evaluation Criteria in Solid Tumors version 1.1, Eastern Cooperative Oncology Group performance status of 0 to 1, and absent or treated central nervous system metastases. High DLL3 expression ($\geq$75% DLL3-positive tumor cells using the Ventana DLL3 (SP347) antibody by central immunohistochemistry assessment) in archived or representative tumor material was required per initial protocol but not mandated later. The planned enrollment was approximately 34 patients. The primary end point was safety, and the secondary end points included efficacy and pharmacokinetic (PK) assessment of Rova-T in the presence of CE.

This study was approved by local institutional review boards and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent.

Results

On February 14, 2018, the Safety Monitoring Committee recommended closing cohorts 1, 2, and 4 to allow for collection and evaluation of data in a timely manner. On the basis of preliminary safety and efficacy data, cohort 3, consisting patients receiving lower doses of Rova-T (0.1 mg/kg or 0.2 mg/kg) in combination with CE, was selected for further evaluation.

Patient Characteristics

At a data cutoff of June 28, 2019, a total of 28 patients were randomized in phase 1A; 26 patients were dosed (Supplementary Table 1) and comprised the full analysis set. One patient from cohort 4 received prestudy CE but discontinued the study before receiving Rova-T; this patient was included in the analysis. Patient baseline characteristics are summarized in Table 1.

PK and Safety

Dose-normalized PK parameters maximum plasma concentration observed (C_{max}) and area under the plasma concentration–time curve from time 0 to infinity (AUC_{inf}) for Rova-T in cohort 3 were within the range observed in cohorts 1 and 2 and in previous Rova-T studies[8,10] (Supplementary Fig. 2). Coadministration of Rova-T plus CE had no marked effect on Rova-T exposure.

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Cohort 1 n = 4	Cohort 2 n = 5	Cohort 3		Cohort 4 n = 3	Total N = 26
			0.1 mg/kg n = 8	0.2 mg/kg n = 6		
Age, median (range), y	64.5 (57.0-73.0)	60.0 (59.0-75.0)	67.0 (53.0-70.0)	62.0 (50.0-71.0)	71.0 (53.0-74.0)	66.0 (50.0-75.0)
Male, n (%)	4 (100)	2 (40)	5 (63)	4 (67)	2 (67)	17 (65)
ECOG PS, n (%)						
0	3 (75)	1 (20)	1 (13)	2 (33)	0	7 (27)
1	1 (25)	4 (80)	7 (88)	4 (67)	3 (100)	19 (73)
Previous platinum + etoposide therapy, n (%)						
Yes	4 (100)	5 (100)	8 (100)	6 (100)	2 (67)	26 (100)
No or missing record	0	0	0	0	0/1 (33)[a]	–
Previous radiotherapy to brain, n (%)						
Yes	0	0	4 (50)	1 (17)	1 (33)	6 (23)
No	4 (100)	5 (100)	4 (50)	5 (83)	2 (67)	20 (77)
History of brain metastases, n (%)						
Yes	0	0	4 (50)	1 (17)	2 (67)	7 (27)
No	4 (100)	5 (100)	4 (50)	5 (83)	1 (33)	19 (73)
Sum of target lesions at baseline, mm						
Median	106.5	76.3	109.8	56.0	133.0	100.5
Range	35.0-218.0	14.0-35.0	19.0-171.0	45.0-147.0	103.0-203.0	14.0-218.0

[a]One patient from cohort 4 has no previous CE record, because the prestudy CE cycle was not required at the time of enrollment (early protocol version).
CE, cisplatin or carboplatin combined with etoposide; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Study drug doses by cohort are found in Supplementary Table 1. The reasons for study drug discontinuation and study discontinuation are listed in Supplementary Table 2. Grade greater than or equal to 3 treatment-emergent adverse events (TEAEs) occurred in 13 patients (93%) in cohort 3 and 12 patients (83%) in cohorts 1, 2, and 4 combined. In cohort 3, grade greater than or equal to 3 TEAEs occurring in greater than or equal to two patients included neutropenia (43%), thrombocytopenia (29%), anemia (21%), and fatigue, febrile neutropenia, pulmonary embolism, and leukopenia (14% each) (Table 2).

Any-grade drug-related TEAEs occurred in 14 patients (100%) in cohort 3 and 10 patients (83%) in cohorts 1, 2, and 4 combined. Common drug-related TEAEs in cohort 3 were fatigue (71%); neutropenia, photosensitivity reaction, and thrombocytopenia (43% each); anemia, decreased appetite, and dysgeusia (36% each); constipation (29%); and leukopenia, nausea, peripheral edema, and pruritus (21% each; Supplementary Table 3). Serious TEAEs are found in Supplementary Table 4.

Compared with cohorts 1, 2, and 4 combined, cohort 3 had a lower frequency of AEs of specific interest (AESI), such as pleural effusion (0 versus 33%), pericardial effusion (0 versus 17%), ascites (0 versus 8%), peripheral edema (36% versus 42%), face edema (8% versus 17%), generalized edema (0 versus 8%), pneumonia (7% versus 25%), dizziness (7% versus 25%), and hypoalbuminemia (0 versus 17%) (Supplementary Table 5). Cohort 3 had a higher frequency of skin and subcutaneous disorders versus cohorts 1, 2, and 4 combined, particularly photosensitivity reactions (43% versus 17%) and pruritus (21% versus 8%). Nevertheless, the severity of photosensitivity reaction and pruritus was similar between the two groups, with most of these AEs being of grade 1 or 2. Compared with cohorts 1, 2, and 4 combined, cohort 3 also had a higher frequency of other toxicities (any grade), such as neutropenia (43% versus 25%; grade 3: 43% versus 17%), febrile neutropenia (25% versus 0; grade 3: 14% versus 0), thrombocytopenia (43% versus 17%; grade 3: 29% versus 0), and hematuria, conjunctival hemorrhage, and gastrointestinal hemorrhage (7% each versus 0; no grade 3 AEs in either group), many of which are often associated with chemotherapeutic regimens.

The proportion of patients who had dose reductions, treatment interruptions, and discontinuations owing to TEAEs is found in Supplementary Table 6. One patient (Rova-T 0.2 mg/kg; cohort 3) experienced a grade 3 dose-limiting toxicity of bullous dermatitis (considered drug related). Two patients experienced grade 5 AEs: encephalopathy (0.1 mg/kg, drug related) and cardiac arrest (0.2 mg/kg, unrelated to the drug). The patient with encephalopathy had grade 4 neutropenia, despite prophylactic filgrastim support; the investigator attributed the grade 5 event to Rova-T as a sequela of sepsis owing to neutropenia.

Efficacy

Response rates for cohorts 1, 2, and 4 are summarized in Supplementary Table 7. Table 3 and

Table 2. Treatment-Emergent Adverse Events Occurring in Greater Than or Equal to 20% of Patients in Cohort 3 and Cohorts 1, 2, and 4 Combined

	Cohort 3 by Rova-T Dose				Cohort 3 Combined		Cohorts 1, 2, and 4 Combined			
	0.1 mg/kg n = 8		0.2 mg/kg n = 6		(0.1 + 0.2 mg/kg) n = 14		0.3 mg/kg n = 12		Overall N = 26	
Adverse Event, n (%)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	5 (63)	1 (13)	5 (83)	1 (17)	10 (71)	2 (14)	7 (58)	0	17 (65)	2 (8)
Neutropenia	5 (63)	5 (63)	1 (17)	1 (17)	6 (43)	6 (43)	3 (25)	2 (17)	9 (35)	8 (31)
Anemia	4 (50)	3 (38)	1 (17)	0	5 (36)	3 (21)	5 (42)	0	10 (38)	3 (12)
Constipation	4 (50)	0	3 (50)	0	7 (50)	0	3 (25)	0	10 (38)	0
Thrombocytopenia	4 (50)	3 (38)	2 (33)	1 (17)	6 (43)	4 (29)	2 (17)	0	8 (31)	4 (15)
Decreased appetite	3 (38)	0	2 (33)	0	5 (36)	0	3 (25)	0	8 (31)	0
Cough	2 (25)	0	2 (33)	0	4 (29)	0	0	0	4 (15)	0
Decreased weight	2 (25)	0	0	0	2 (14)	0	2 (17)	0	4 (15)	0
Diarrhea	2 (25)	0	3 (50)	0	5 (36)	0	3 (25)	0	8 (31)	0
Dysgeusia	2 (25)	0	3 (50)	0	5 (36)	0	1 (8)	0	6 (23)	0
Febrile neutropenia	2 (25)	2 (25)	0	0	2 (14)	2 (14)	0	0	2 (8)	2 (8)
Hypomagnesemia	2 (25)	0	0	0	2 (14)	0	1 (8)	0	3 (12)	0
Nausea	2 (25)	0	1 (17)	0	3 (21)	0	6 (50)	1 (8)	9 (35)	1 (8)
Photosensitivity reaction	2 (25)	0	4 (67)	1 (17)	6 (43)	1 (7)	2 (17)	1 (8)	8 (31)	2 (8)
Pulmonary embolism	2 (25)	2 (25)	0	0	2 (14)	2 (14)	1 (8)	1 (8)	3 (12)	3 (12)
Pruritus	2 (25)	0	1 (17)	0	3 (21)	0	1 (8)	0	4 (15)	0
Dyspnea	1 (13)	0	2 (33)	0	3 (21)	0	4 (33)	1 (8)	7 (27)	1 (8)
Dizziness	1 (13)	0	0	0	1 (7)	0	3 (25)	0	4 (15)	0
Insomnia	1 (13)	0	1 (17)	0	2 (14)	0	4 (33)	0	6 (23)	0
Leukopenia	1 (13)	0	2 (33)	2 (33)	3 (21)	2 (14)	1 (8)	1 (8)	4 (15)	3 (12)
Pain	1 (13)	0	2 (33)	0	3 (21)	0	2 (17)	0	5 (19)	0
Peripheral edema	1 (13)	0	2 (33)	0	3 (21)	0	5 (42)	0	8 (31)	0
Pneumonia	1 (13)	1 (13)	0	0	1 (7)	1 (7)	3 (25)	2 (17)	4 (15)	3 (12)
Productive cough	1 (13)	0	2 (33)	0	3 (21)	0	3 (25)	0	6 (23)	0
Urinary tract infection	1 (13)	0	2 (33)	0	3 (21)	0	4 (33)	0	7 (27)	0
Vomiting	1 (13)	0	0	0	1 (7)	0	3 (25)	0	4 (15)	0
Anxiety	0	0	0	0	0	0	3 (25)	0	3 (12)	0
Headache	0	0	1 (17)	0	1 (7)	0	3 (25)	0	4 (15)	0
Hypophosphatasemia	0	0	2 (33)	1 (17)	2 (14)	1 (7)	0	0	2 (8)	1 (4)
Increased ALT	0	0	2 (33)	0	2 (14)	0	2 (17)	1 (8)	4 (15)	1 (4)
Increased AST	0	0	2 (33)	0	2 (14)	0	2 (17)	1 (8)	4 (15)	1 (4)
Increased blood ALP	0	0	2 (33)	0	2 (14)	0	0	0	2 (8)	0
Increased lacrimation	0	0	2 (33)	0	2 (14)	0	0	0	2 (8)	0
Malignant neoplasm progression	0	0	0	0	0	0	3 (25)	3 (25)	3 (12)	3 (12)
Tachycardia	0	0	2 (33)	0	2 (14)	0	0	0	2 (8)	0
Tremor	0	0	2 (33)	0	2 (14)	0	0	0	2 (8)	0
Upper abdominal pain	0	0	0	0	0	0	3 (25)	1 (8)	3 (12)	1 (4)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Supplementary Figure 3 show the efficacy outcomes for cohort 3; the confirmed objective response rate (ORR) was 63% at 0.1 mg/kg Rova-T and 33% at 0.2 mg/kg Rova-T. Three patients in the 0.2 mg/kg Rova-T subset of cohort 3 discontinued the study before confirmatory computed tomography imaging for response assessment, a prerequisite for ORR but not for best overall response, which likely contributed to a marked discrepancy between ORR (33%) and best overall response (83%) in this subgroup. The week 6 computed tomography scans of these three patients revealed a partial response (one patient discontinued owing to grade 1 fatigue [grade 2 fatigue; grade 4 neutropenia and leukopenia recorded earlier], one owing to grade 3 bullous dermatitis, and one patient died of cardiac arrest [not drug related]).

Table 3. Efficacy Outcomes in Cohort 3 (Rova-T + Concurrent Platinum-Based Chemotherapy)

	Confirmed Objective Response[a]			Best Overall Response[b]		
Efficacy Outcome	0.1 mg/kg n = 8	0.2 mg/kg n = 6	All Patients (Cohort 3) N = 14	0.1 mg/kg n = 8	0.2 mg/kg n = 6	All Patients (Cohort 3) N = 14
Overall response rate, n (%), [95% CI]	5 (63) [24.5-91.5]	2 (33) [4.3-77.7]	7 (50) [23.0-77.0]	5 (63) —	5 (83) —	10 (71) —
Complete response, n (%)	1 (13)	0	1 (7)	1 (13)	0	1 (7)
Partial response, n (%)	4 (50)	2 (33)	6 (43)	4 (50)	5 (83)	9 (64)
Median PFS, mo (95% CI)	5.3 (2.7-6.3)	5.2 (3.6-8.6)	5.2 (3.7-6.3)			
Median DOR, mo (95% CI)	3.3 (1.8-5.8)	2.8 (1.1-6.1)	2.9 (1.1-5.8)			
Median OS, mo (95% CI)	10.3 (1.6-15.4)	NE (2.3-NE)	10.3 (3.9-15.4)			

[a]Assessed according to RECIST v1.1. Objective responses were confirmed by radiographic imaging performed every 6 weeks until week 24 and then every 12 weeks thereafter per RECIST v1.1 criteria. Baseline for response assessments was determined before the prestudy cycle.
[b]Confirmation of complete response and partial response by computed tomography imaging was not required for best overall response assessment.
CI, confidence interval; DOR, duration of response; NE, not evaluable; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Rova-T, Rovalpituzumab tesirine.

Discussion

In this study, Rova-T was evaluated as a monotherapy at 0.3 mg/kg for 2 doses and at lower doses (0.1 mg/kg or 0.2 mg/kg × 2 doses) in combination with CE. We found that Rova-T at lower doses, in combination with CE (cohort 3), was generally tolerable and manageable.

There was a higher frequency of Rova-T–related AESI, such as pleural effusion, pericardial effusion, ascites, edema, dizziness, hypoalbuminemia, and pneumonia in cohorts 1, 2, and 4 combined compared with cohort 3. In addition, compared with previous studies, such as TRINITY, that tested Rova-T 0.3 mg/kg (every 6 wk ×2),[9] lower doses of Rova-T plus CE (0.1 or 0.2 mg/kg) given in this study had no occurrence of AESI, such as pleural effusion (0 versus 28%), pericardial effusion (0 versus 12%), and hypoalbuminemia (0 versus 12%), and a slightly lower frequency of peripheral edema (21% versus 26%). Many of these AESI required protocol-specified risk management in previous studies.[9] In contrast, the incidence of hematologic AESI (thrombocytopenia and neutropenia) was much higher in cohort 3 compared with cohorts 1, 2, and 4 combined and with TRINITY,[9] which can be attributed to the coadministration of CE in cohort 3. Furthermore, cohorts 1, 2, and 4 combined revealed a higher frequency of serious TEAEs versus cohort 3 (67% versus 43%) and higher rate of discontinuation owing to TEAEs versus cohort 3 (42% versus 29%). Thus, from our limited sample size observation and within the limitations of cross-trial comparison, it seems that the frequency of some AESI may be dose dependent, and lower doses of Rova-T may be more tolerable. In addition, coadministration of CE with Rova-T had no marked impact on Rova-T PK.

CE, the mainstay of treatment for ES SCLC to date, produces response rates of 60% to 70% (15%–20% complete responses)[11] and a median OS of approximately 10 months.[1–5,12] Addition of immune checkpoint inhibitors to chemotherapy in the frontline setting has not resulted in greater response rates, with modest improvement in OS.[4,5] The combination of Rova-T with CE (cohort 3) yielding a median OS of 10.3 months, a median progression-free survival of 5.2 months, and a confirmed ORR of 50% suggests no efficacy benefit of adding Rova-T to frontline chemotherapy.

In a recent study, Rova-T in combination with nivolumab with or without ipilimumab was found to have encouraging antitumor activity in relapsed ES SCLC, but it was not well tolerated at the dose levels and administration schedules tested, leading to termination of enrollment.[13] The entire Rova-T research and development program has been recently terminated after suboptimal results of the phase 3 MERU and TAHOE trials.[4,14,15]

In this study, lower doses of Rova-T were tolerable in combination with CE; however, Rova-T had no clear efficacy benefit when added to CE in frontline ES SCLC. Compared with normal tissues, DLL3 is selectively expressed on SCLC cells and continues to represent an attractive target in SCLC for antibody-drug conjugates and T-cell redirecting strategies. HPN328 and AMG-757 are DLL3-targeted bispecific T-cell engagers that currently are currently evaluated in phase 1 trials in SCLC.[16,17] It remains to be seen if these novel approaches targeting DLL3 will prove to be more successful than Rova-T or current therapies in ES SCLC.

CRediT Authorship Contribution Statement

Christine L. Hann, Daniel Morgensztern, D. Ross Camidge: Conceptualization (ideas; formulation or evolution of overarching research goals/aims), Methodology

(development or design of methodology or creation of models), Investigation (conducting a research and investigation process, performing experiments, or data/evidence collection), Resources (provision of study materials, reagents, patients, laboratory samples, animals, instrumentation, computing resources, or other tools), and Writing (original draft or reviewing and editing of subsequent drafts).

Timothy F. Burns: Investigation (conducting a research and investigation process, performing experiments, or data/evidence collection), Resources (provision of study materials, reagents, patients, laboratory samples, animals, instrumentation, computing resources, or other tools), and Writing (original draft or reviewing and editing of subsequent drafts).

Afshin Dowlati, **Patrick J. Ward:** Investigation (conducting a research and investigation process, performing experiments, or data/evidence collection).

Martina M. Koch: Writing (original draft or reviewing and editing of subsequent drafts).

Chris Chen, Carrianne Ludwig: Validation (verification of the overall replication/reproducibility of results/experiments and other research outputs), Formal analysis (application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data), Data curation (management activities to annotate, scrub data, and maintain research data for initial and later use), and Writing (original draft or reviewing and editing of subsequent drafts).

Maulik Patel: Formal analysis (application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data), Data curation (management activities to annotate, scrub data, and maintain research data for initial and later use), Writing (original draft or reviewing and editing of subsequent drafts), and Visualization (preparation, creation, and/or presentation of data in published work).

Halla Nimeiri: Validation (verification of the overall replication/reproducibility of results/experiments and other research outputs), Writing (original draft or reviewing and editing of subsequent drafts), Supervision (oversight and leadership for research activity planning and execution, including mentorship to the core team), and Project administration (management and coordination for research activity planning/execution).

Philip Komarnitsky: Validation (verification of the overall replication/reproducibility of results/experiments and other research outputs), Formal analysis (application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data), Investigation (conducting a research and investigation process, performing experiments, or data/evidence collection), Supervision (oversight and leadership for research activity planning and execution, including mentorship to the core team), Project administration (management and coordination for research activity planning/execution), and Writing (original draft or reviewing and editing of subsequent drafts).

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials they 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.

Acknowledgments

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Rovalpituzumab tesirine has been developed by AbbVie, Inc. Medical writing support was provided by Swati Ghatpande, PhD, of Bio Connections, LLC, funded by AbbVie, Inc. This work was supported by AbbVie, which provided financial support for the conduct of the research and preparation of the article. The authors thank all the trial investigators and the patients who participated in this clinical trial.

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.2021.06.022.

References

1. Yang S, Zhang Z, Wang Q. Emerging therapies for small cell lung cancer. *J Hematol Oncol*. 2019;12:47.
2. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United

States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol*. 2006;24:4539–4544.
3. Farago AF, Keane FK. Current standards for clinical management of small cell lung cancer. *Transl Lung Cancer Res*. 2018;7:69–79.
4. Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220–2229.
5. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929–1939.
6. 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.
7. 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.
8. 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.
9. 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.
10. Udagawa H, Akamatsu H, Tanaka K, et al. Phase I safety and pharmacokinetics study of rovalpituzumab tesirine in Japanese patients with advanced, recurrent small cell lung cancer. *Lung Cancer*. 2019;135:145–150.
11. Demedts IK, Vermaelen KY, van Meerbeeck JP. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. *Eur Respir J*. 2010;35:202–215.
12. Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol*. 2020;38:2369–2379.
13. Malhotra J, Nikolinakos P, Leal T, et al. A phase 1–2 study of rovalpituzumab tesirine in combination with nivolumab plus or minus ipilimumab in patients with previously treated extensive-stage SCLC. *J Thorac Oncol*. 2021;16:1559–1569.
14. AbbVie. AbbVie discontinues rovalpituzumab tesirine (Rova-T) research and development program. https://news.abbvie.com/news/press-releases/abbvie-discontinues-rovalpituzumab-tesirine-rova-t-research-and-development-program.htm. Accessed January 27, 2021.
15. AbbVie. Phase 3 trial of Rova-T as second-line therapy for advanced small-cell lung cancer (TAHOE study) halted. https://news.abbvie.com/news/phase-3-trial-rova-t-as-second-line-therapy-for-advanced-small-cell-lung-cancer-tahoe-study-halted.htm. Accessed January 27, 2021.
16. Aaron WH, Austin R, Barath M, et al. HPN328: an anti-DLL3 T cell engager for treatment of small cell lung cancer. *Mol Cancer Ther*. 2019;18(suppl 12). C033–C033.
17. Smit MD, Borghaei H, Owonikoko TK, et al. Phase 1 study of AMG 757, a half-life extended bispecific T cell engager (BiTE) antibody construct targeting DLL3, in patients with small cell lung cancer (SCLC). *J Clin Oncol*. 2019;37(suppl 15). TPS8577–TPS8577.