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Phase I safety and pharmacokinetics study of rovalpituzumab tesirine in Japanese patients with advanced, recurrent small cell lung cancer

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ABSTRACT

Objectives: Rovalpituzumab tesirine (Rova-T™) is an antibody-drug conjugate that targets delta-like protein 3 (DLL3) on small cell lung cancer (SCLC) tumors, is internalized and releases the toxin pyrrolobenzodiazepine to induce cell death. This open label phase I study was the first study of Rova-T in Japanese patients. The aim of this study was to evaluate, safety, pharmacokinetics, and preliminary efficacy of Rova-T in Japanese patients with advanced recurrent SCLC.

Materials and methods: Patients received Rova-T (0.2 or 0.3 mg/kg) by intravenous infusion on Day (D) 1 of each 6-week cycle for 2 doses and dexamethasone (8 mg BID oral) on D-1, D1, and D2 of each 6-week cycle. Retreatment with Rova-T was permitted for patients who tolerated their initial doses and then progressed after disease control (defined as stable disease or better) was observed for at least 12 weeks after their last dose of Rova-T.

Results: Rova-T exhibited toxicity that was generally manageable in Japanese patients (N = 29). No dose-limiting toxicities were experienced. The most common treatment-related adverse events (≥25% of patients, all grades) were platelet count decreased, pleural effusion, peripheral edema, aspartate aminotransferase increased, white blood cell count decreased, neutrophil count decreased, alanine aminotransferase increased, hypoalbuminaemia, anemia and decreased appetite. Safety and pharmacokinetics exposures were similar to previous observations in non-Japanese populations. Per investigator assessment of DLL3 high patients, 17% (3/18) had confirmed partial responses, and the disease control rate was 56%, mPFS was 2.9 months, and mOS was 7.4 months.

Conclusions: These preliminary data support further exploration of Rova-T treatment in Japanese patients with SCLC in global studies. This trial was registered with ClinicalTrials.gov as NCT03086239.

1. Introduction

Small cell lung cancer (SCLC) accounts for more than 15% of all lung cancers worldwide, and it is one of the leading causes of cancer-related death globally [1,2]. Although SCLC shows high response rates to first-line platinum-based therapy, disease rapidly recurs [3,4], and patients with extensive disease have a median overall survival time of approximately 10 months [5]. The Japanese treatment guidelines for

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SCLC recommend the use of irinotecan or etoposide in combination with platinum as first-line treatment, and recommends amrubicin, nogitecan, topotecan, or a re-challenge with platinum-based therapy for recurrent SCLC treatment [6]. There is currently no third-line treatment for SCLC approved in Japan [7]. The reported historical response rates with third-line therapy for ED-SCLC are low (approximately 18%), with a median progression-free survival of 2 months and a median overall survival of 4.7–5.1 months [8,9].

Delta-like protein 3 (DLL3) is an atypical Notch receptor ligand implicated in regulating cell fate determination during development [10], and is highly expressed on the surface of SCLC and other neuroendocrine tumors, with little to no expression in normal tissue [11]. Rovalpituzumab tesirine (Rova-T™) is an antibody-drug conjugate (ADC) that targets DLL3, comprised of a humanized DLL3-specific IgG1 monoclonal antibody tethered to a toxic DNA cross-linking agent pyrrolobenzodiazepine (PBD) by a protease-cleavable linker. Rova-T binds DLL3 on target-expressing cells, is internalized, and the PBD toxin is released via proteolytic cleavage of the linker in late endosomes to induce cell death by interstrand crosslinking of cellular DNA [11–13].

A first-in-human (FIH) study of Rova-T in patients with SCLC demonstrated antitumor activity in DLL3-high patients and a manageable safety profile [14]. Given the need for improved treatment options in Japan [15], we conducted a phase I study of Rova-T in Japanese patients with SCLC. The aim of this study was to evaluate the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity of Rova-T in Japanese patients with advanced, recurrent SCLC.

2. Methods

2.1. Study design

This phase I, open-label, dose escalation study was conducted at five sites in Japan (NCT03086239). Enrollment began on May 10, 2017, and the trial was completed on August 20, 2018. Up to 78 patients were planned to participate in this trial, which was comprised of Part A dose escalation and Part B dose expansion.

For Part A, three cohorts were planned at dose levels of 0.2 mg/kg, 0.3 mg/kg, and 0.4 mg/kg, escalating with a standard 3 + 3 design. For Part B dose expansion, up to approximately 20 patients were planned to be enrolled at one or more dose regimens not to exceed the maximum tolerated dose (MTD).

The study enrolled adult Japanese patients with advanced, recurrent SCLC who had disease progression after ≥2 prior systemic regimens, including at least one platinum-based regimen. Additional key eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, absence of Grade ≥2 pleural or pericardial effusion within 2 weeks prior to first dose of Rova-T, measurable disease per Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1, a minimum life expectancy of 12 weeks, adequate renal and hepatic function, and stable CNS metastases.

Patients received Rova-T (0.2 or 0.3 mg/kg) by intravenous infusion on Day (D) 1 of each 6-week cycle for 2 doses and dexamethasone (8 mg BID oral) on D-1, D1, and D2 of each 6-week cycle. Retreatment with Rova-T was permitted for patients who tolerated their initial doses and then progressed after disease control (defined as stable disease or better) was observed for at least 12 weeks after their last dose of Rova-T.

This study was conducted in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki. The human investigations were performed after approval by an institutional review board. All patients provided written informed consent before participation in the trial.

2.2. Assessments

The primary objective was to assess safety and tolerability. Safety assessments included adverse events (AEs), lab tests, physical exam, vital signs, electrocardiogram, echocardiograms, and ECOG performance status.

Dose-limiting toxicities (DLTs) and AEs were reported according to the U.S. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and were evaluated during the first 3 weeks of treatment. Adverse events were assessed until 70 days after final administration of Rova-T. DLTs were defined as any of the following events: thrombocytopenia requiring platelet transfusion or Grade 4 thrombocytopenia lasting more than 7 days; neutropenia requiring hematopoietic growth factor rescue; Grade 4 neutropenia lasting more than 7 days, or any febrile neutropenia; anemia requiring transfusion or Grade 4 anemia unrelated to underlying disease; clinically significant Grade 3 or 4 non-hematologic laboratory abnormality that did not resolve to Grade 0/1 within 7 days; Grade 3 or 4 non-laboratory adverse event (except fatigue, asthenia, nausea, manageable symptoms); and discontinuation of treatment due to toxicity.

The secondary objectives were pharmacokinetics and preliminary efficacy. The pharmacokinetics parameters analyzed included maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC), and elimination half-life ($t_{1/2}$). Blood samples for Rova-T concentrations were collected throughout the study. Noncompartmental pharmacokinetics parameters were calculated for Rova-T ADC and for Rova-T total antibody following administration of Rova-T at 0.2 mg/kg or 0.3 mg/kg in Cycle 1. The development of anti-therapeutic antibodies against Rova-T was monitored throughout the study. Radiographic tumor response per RECIST v1.1 was evaluated by the investigator and central reader every 6 weeks for 6 months, then every 12 weeks thereafter. Efficacy endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Expression of DLL3 in SCLC tissue and its relationship to clinical outcome was evaluated as an exploratory objective. Tumor tissue, consisting of a representative archived specimen or fresh tumor biopsy collected prior to treatment with Rova-T, was assessed retrospectively for expression of DLL3 by immunohistochemistry of formalin-fixed paraffin-embedded samples. DLL3 expression was measured retrospectively with the VENTANA DLL3 (SP347) rabbit monoclonal antibody (Ventana Medical Systems, Tucson, AZ, USA). DLL3 expression was categorized as high (≥75%), positive (≥25%), or negative (< 25%).

2.3. Statistical analysis

The safety analysis included all patients who received at least one dose of Rova-T. The DLT-evaluable set included all patients who were followed for the entire DLT evaluation period as well as those who experienced a DLT prior to the completion of the DLT window. The pharmacokinetics-evaluable set was all patients who received at least one dose of Rova-T and for whom a baseline measurement and at least one blood sample following a dose of study treatment were available. Tumor responses were evaluated in all patients who had at least one post-dose tumor assessment. Duration of response, progression-free survival, and overall survival were estimated using the Kaplan-Meier method. The OS by Kaplan-Meier method includes follow-up time, as it is one of the Life table method analyses (SAS Proc lifetest) that considers death or cut-off date. Efficacy was analyzed by DLL3 high (≥75%), DLL3 not high (< 75%), and all patients. A log-rank test was used to compare DLL3 high versus DLL3 not high patients for PFS and OS.

Table 1
Baseline characteristics of patients.

n, %	All patients (N = 29)
Age, years, median (range)	68 (47–86)
Age	
< 75 years	27 (93)
≥75 years	2 (7)
Gender	
Male	22 (76)
Female	7 (24)
ECOG Performance Status	
0	10 (35)
1	19 (65)
History of CNS metastasis	
Yes	7 (24)
No	22 (76)
Response to first-line treatment	
Sensitive*	13 (45)
Resistant†	8 (28)
Refractory‡	8 (28)
Prior lines of therapy	
2	9 (31)
3	13 (45)
≥4	7 (24)
Prior systemic treatments	
Amrubicin	29 (100)
Cisplatin	21 (72)
Carboplatin	15 (52)
Etoposide	22 (76)
Irinotecan	17 (59)
Topotecan	4 (14)
PD-1 inhibitor	1 (3)
Others	13 (45)
Tumor DLL3 expression[a]	
High (≥75%)	18 (64)
Positive (≥25%)	24 (86)
Negative (< 25%)	4 (14)
Unknown	1

ECOG, Eastern Cooperative Oncology Group.
Total number of patients across the tumor DLL3 expression categories does not add up to N = 29 because there are two overlapping categories. The DLL3 Positive category includes all patients with ≥25% DLL3 expression. The DLL3 High category includes all patients with ≥75% DLL3 expression (a subset of which are also counted in the DLL3 Positive category).

[a] Assessed retrospectively.

* Best response of stable disease (SD) or better to first-line (1 L) treatment, and treatment-free interval ≥90 days between 1 L and second-line (2 L) treatment.

† Best response of SD or better to 1 L treatment, and a treatment-free interval of < 90 days between 1 L and 2 L treatment.

‡ Defined as a best response of progressive disease (PD) to 1 L treatment.

3. Results

3.1. Participants

Between May 10, 2017 and August 20, 2018, 29 patients were enrolled, six patients were in the 0.2 mg/kg cohort and 23 patients were in the 0.3 mg/kg cohort (Fig. S1A). The median age of patients was 68 years (range: 47–86), 76% were male, and 69% had ≥3 prior lines of treatment (Table 1). Patients' tumor DLL3 expression overall was high (≥75%) in 64% of patients, and positive (≥25%) in 86% of patients.

3.2. DLT and safety

Allocation of patients to treatment during the study is summarized in Fig. S1A. Patients received Rova-T (0.2 or 0.3 mg/kg) by intravenous infusion on Day (D) 1 of each 6-week cycle for a total of 2 doses. In addition, retreatment was allowed if a patient met the criteria outlined in Fig. S1B. DLTs were not observed in the first three patients treated at the dose levels of 0.2 and 0.3 mg/kg. No MTD was determined; dose escalation was stopped at 0.3 mg/kg dose, same as utilized in global pivotal studies. The decision not to proceed with the enrollment of the 0.4 mg/kg dose cohort was made by the study sponsor since the RPTD was already established in prior clinical trials and the emerging pharmacokinetics and safety profiles for Japanese patients in the current study indicated similarity to these parameters in non-Japanese patients. Three patients were enrolled and received 0.2 mg/kg Rova-T treatment during the 0.3 mg/kg DLT evaluation period. After confirmation of tolerability at 0.3 mg/kg, 20 patients were enrolled in the 0.3 mg/kg expansion cohort. All 29 enrolled patients received at least one dose of Rova-T during the primary treatment period (prior to retreatment). Twelve patients (41%) received 2 cycles of Rova-T. One patient was retreated with Rova-T. Discontinuation of Rova-T treatment occurred in 17 patients (59%) with a primary reason for discontinuation due to progressive disease by RECIST v1.1 (11 patients [38%]), clinical progressive disease (2 patients [7%]), adverse events (2 patient [7%]), or other reasons (2 patients [7%]: 1 each: investigator decision and delayed administration more than 21 days).

All patients experienced ≥1 treatment-emergent AE (TEAE) of any grade. The most frequent hematological adverse events (any grade) related to Rova-T occurring in ≥30% of patients were platelet count decreased in 22 patients (76%), white blood cell count decreased in 10 patients (35%), and neutrophil count decreased in 9 patients (31%). Non-hematological adverse events related to Rova-T occurring in ≥10% of patients included pleural effusion in 15 patients (52%), pericardial effusion in 7 patients (24%), edema in 13 patients (45%), peripheral edema in 12 patients (41%), aspartate aminotransferase (AST) increased in 12 patients (42%), alanine aminotransferase (ALT) increased in 9 patients (31%), hypoalbuminaemia in 9 patients (31%), and decreased appetite in 8 patients (27%) (Table 2). The most frequent Grade 3 or 4 treatment-related adverse events in > 10% of patients were platelet count decreased in 9 patients (31%) and neutrophil count decreased in 5 patients (17%), increased AST and hypoalbuminaemia in 4 patients (14% each) (Table 2). Three patients (10%) experienced Grade 4 platelet count decreased and concomitant Grade 1 epistaxis and received platelet transfusions. One of these patients also experienced Grade 1 hematuria and Grade 1 gastrointestinal hemorrhage. Serious adverse events occurred in 13 patients (45%), and in 5 patients (17%) were related to Rova-T treatment (Table S1).

Adverse events leading to Rova-T dose delay occurred in 5 patients (17%). The most frequent adverse event leading to Rova-T dose delay was Grade 2 pleural effusion in 3 patients (10%). Adverse events leading to Rova-T dose reduction occurred in 3 patients (10%); two patients had neutropenia (one patient each: Grade 3 and Grade 4) one of which also had Grade 3 AST increased, and one patient had Grade 3 platelet count decreased. Adverse events leading to Rova-T discontinuation, including secondary reasons where multiple reasons were provided for discontinuation, occurred in 4 patients in the primary treatment period (14%) whose adverse events were pleural effusion in two patients (one patient each: Grade 2 and Grade 3), Grade 2 anemia, and Grade 2 malaise.

3.3. Pharmacokinetics

Maximum Rova-T total antibody serum concentrations were observed approximately 30 min after the end of Rova-T infusion in most patients. The pharmacokinetic parameters such as C_{max}, AUC_t and AUC_{inf} for ADC and total antibody were dose-proportional from 0.2 mg/kg to 0.3 mg/kg. The harmonic mean terminal elimination half-life in Cycle 1 was 11.3 and 15.2 days for 0.3 and 0.2 mg/kg doses respectively for ADC (Table 3). Total antibody C_{max} was similar to that of ADC

Table 2
Treatment-emergent adverse events* related to Rova-T (in ≥10% of patients).

n, %	Grade 1–2	Grade 3	Grade 4
Any AE related to Rova-T	14 (48)	11 (38)	4 (14)
Hematological AEs			
Platelet count decreased[a]	13 (45)	6 (21)	3 (10)
White blood cell count decreased	7 (24)	3 (10)	0
Anemia[b]	6 (21)	3 (10)	0
Neutrophil count decreased	4 (14)	4 (14)	1 (3)
Lymphocyte count decreased	1 (3)	3 (10)	0
Non Hematological AEs: Respiratory/thoracic/cardiac AEs			
Pleural effusion	12 (41)	3 (10)	0
Pericardial effusion	7 (24)	0	0
General disorders			
Edema	11 (38)	2 (7)	0
Peripheral edema	11 (38)	1 (3)	0
Fatigue	3 (10)	1 (3)	0
Metabolism and nutrition disorders			
Hypoalbuminaemia	5 (17)	4 (14)	0
Malaise	5 (17)	0	0
Decreased appetite	7 (24)	1 (3)	0
Gastrointestinal disorders			
Nausea	4 (14)	0	0
Constipation	3 (10)	0	0
Skin disorders			
Maculopapular rash	4 (14)	0	0
Photosensitivity reaction	3 (10)	0	0
Investigations			
AST increased	8 (28)	4 (14)	0
ALT increased	7 (24)	2 (7)	0
ALP increased	4 (14)	1 (3)	0
Lipase increased	2 (7)	1 (3)	0

* By MedDRA 20.1 preferred term.
[a] Includes thrombocytopenia.
[b] Includes hemoglobin decreased. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

species, $t_{1/2}$ was slightly longer at 12.8 and 18.5 days for 0.3 and 0.2 mg/kg dose levels, respectively, and AUC_{inf} was higher as well (Table 3). No anti-therapeutic antibodies were detected against Rova-T in any patient in the present study.

3.4. Efficacy

Among 29 patients, confirmed partial responses (PR) were observed in 3 patients (10%) and stable disease (SD) occurred in 12 patients (41%) by investigator assessment regardless of DLL3 expression (Table 4). One patient who achieved a confirmed objective response (PR) and subsequently progressed was retreated with one dose of Rova-T and achieved a second partial response prior to study discontinuation without confirmatory scans. Disease control rate was 55% (95% CI 36, 74) for all patients. Among 18 DLL3 high patients, confirmed PR and SD were observed in 3 patients (17%) and 7 patients (39%), respectively. Disease control rate was 56% (95% CI 31, 79) in DLL3 high patients. Of the 27 patients with measurable target lesions post-baseline, 16 patients (59%) had a reduction from baseline in the sum diameter of their target lesions, including 11 of 18 (61%) DLL3 high patients (Fig. 1). Central assessment of response is summarized in Table S2. By central assessment of all 29 patients regardless of DLL3 expression, a confirmed objective response (PR) was observed in one patient (3%), and the disease control rate was 62% (95% CI 42, 79). Among 18 DLL3 high patients with central assessment, one patient (6%) had a confirmed PR.

Median duration of response (95% CI) was 3.0 months (2.9, 4.1) for all patients. Median progression-free survival (mPFS) (95% CI) was 2.2 months (1.2, 3.0) for all patients and 2.9 months (1.2, 3.6) for DLL3 high patients (Fig. 2A). Median overall survival (mOS) (95% CI) was 5.8 months (4.1, 9.2) for all patients and 7.4 months (4.1, 11.9) for DLL3 high patients (Fig. 2B). Per protocol, mOS time is equal to median follow-up time.

By central assessment, the median duration of response (95% CI) was 4.1 months for all patients, and the mPFS (95% CI) was 2.7 months (1.2, 3.6) for all patients and was 3.2 months (1.2, 4.2) for DLL3 high patients (Fig. S2). The difference in PFS for DLL3 high versus DLL3 not high was P = 0.082 per Investigator, and P = 0.157 by central review (Log-Rank test). The difference in OS for DLL3 high versus DLL3 not high was P = 0.346.

Table 4
ORR, DCR, DOR, PFS, and OS by Investigator Assessment.

n, (%)	DLL3 high[a] patients (N = 18)	DLL3 not high[b] patients (N = 10)	All patients[c] (N = 29)
Objective Response Rate[d]	3 (17%)	0	3 (10%)
Disease Control Rate[e]	10 (56%)	6 (60%)	16 (55%)
DOR, median (months)	3.0	–	3.0
[95% CI]	[2.9, 4.1]		[2.9, 4.1]
PFS, median (months)	2.9	2.0	2.2
[95% CI]	[1.2, 3.6]	[0.7, 2.7]	[1.2, 3.0]
OS, median (months)	7.4	5.1	5.8
[95% CI]	[4.1, 11.9]	[1.8, 7.8]	[4.1, 9.2]

DCR, disease control rate; DOR, duration of objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[a] DLL3 high expression was ≥75%.
[b] DLL3 not high includes patients with positive (25–74%) and negative (< 25%) tumor DLL3 expression.
[c] One of the 29 patients had unknown tumor DLL3 expression.
[d] Confirmed complete response plus confirmed partial response per RECISTv1.1.
[e] CR + PR + SD.

Table 3
Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of Rova-T ADC and Total Antibody in Cycle 1.

Pharmacokinetic Parameters (units)	ADC		Total Antibody	
	0.2 mg/kg (N = 6)	0.3 mg/kg (N = 23)	0.2 mg/kg (N = 6)	0.3 mg/kg (N = 23)
C_{max} (μg/mL)	4.58 (4.61, 14)	7.08 (7.16, 15)	4.24 (4.25, 7)	7.08 (7.17, 15)
T_{max} (hour)[a]	0.5 (0.5 - 2.0)	0.5 (0.5 - 4.0)	1.3 (0.5 - 2.0)	0.5 (0.5 - 2.0)
AUC_t (μg d/mL)	32.4 (32.5, 10)	49.1 (51.1, 29)	36.0 (36.2, 11)	54.7 (57.0, 29)
AUC_{inf} (μg d/mL)	44.0 (44.5, 17)	62.0 (65.8, 36)	54.9 (56.0, 22)	73.8 (78.7. 37)
$t_{1/2}$ (days)[b]	17.63 (35.29)	13.58 (36.15)	26.45 (71.09)	16.83 (42.69)

Abbreviations: C_{max}, maximum observed plasma concentration; T_{max}, time to maximum observed plasma concentration; AUC_t, area under the plasma concentration-time curve over the dosing interval; AUC_{inf}, AUC from time 0 to infinity; $t_{1/2}$, elimination half-life.
[a] Median (minimum – maximum).
[b] Arithmetic mean (CV%).

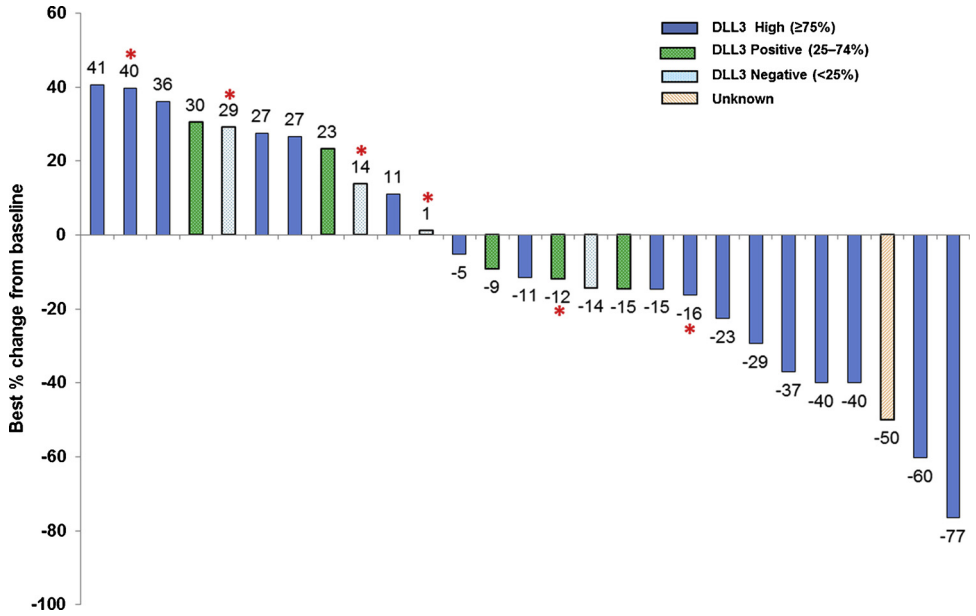

Fig. 1. Best Percent Change from Baseline in Tumor Size Per Investigator.
Six patients who received 0.2 mg/kg Rova-T are denoted with a red asterisk.

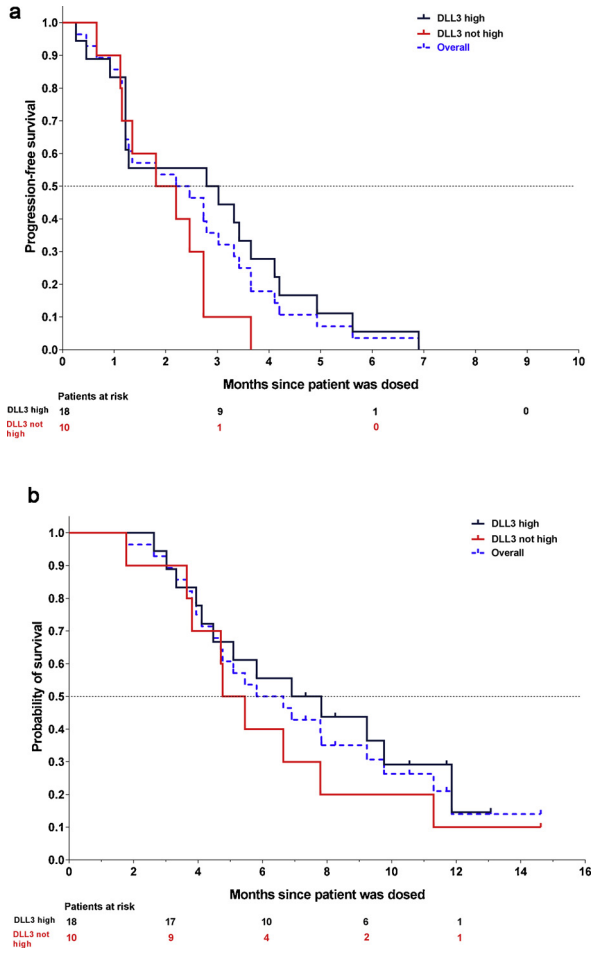

Fig. 2. (A) PFS by Investigator Assessment and (B) OS for DLL3 High and Not High Patients.

4. Discussion

Rova-T has demonstrated promising efficacy and tolerability in both second-line and third-line SCLC patients in the FIH study [14]. The recommended phase II dose and schedule was established as 0.3 mg/kg every 6 weeks, and Rova-T was subsequently investigated in the phase II TRINITY study as a potentially important therapeutic option in patients with DLL3-expressing SCLC after progression following at least 2 prior systemic regimens [16]. However, Japanese patients were not enrolled in these studies. Therefore, this was the first study to explore the safety, tolerability, pharmacokinetics, and antitumor activity of Rova-T in Japanese SCLC patients.

Compared to the FIH study [14], where patients received doses of Rova-T ranging from 0.05 mg/kg to 0.8 mg/kg every three or six weeks, similar types of treatment-associated adverse events were seen in this study of Japanese patients.

Platelet count decreased/thrombocytopenia was the most frequent hematological adverse event, with a median time to onset of 15.5 days and a median duration of 8 days. These decreases were not associated with any significant clinical adverse events of bleeding. Decreased neutrophil count was observed less frequently, did not require treatment with growth factors, and was not associated with fever.

Pleural and pericardial effusions were frequently observed events, with median times to onset of 56 days and 43 days after first dose, respectively. Most patients with pleural effusions were managed with drainage and/or systemic corticosteroids. No Grade ≥3 pericardial effusions were observed in this study, and none of the patients required drainage procedures. No cases of cardiac tamponade were observed, and none of the effusion events were fatal. Peripheral edema events had a median time to onset of 66 days and were managed by treatment with diuretics, with or without the addition of a systemic corticosteroid. Overall, these effusion-related adverse events were manageable.

The pharmacokinetic parameters assessed for both ADC and total antibody species inJapanese patients were similar to previous observations in non-Japanese patients with SCLC at both the 0.2 mg/kg and 0.3 mg/kg dose levels [14].

We examined DLL3 expression in SCLC samples from Japanese patients. Eighty-six percent were positive for DLL3 expression, with 64% expressing high levels of DLL3. In the FIH study, 88% of patients' tumors were DLL3 positive, with 67% expressing high levels of DLL3.

Tanaka et al. have reported DLL3 positive expression in 83% of Japanese SCLC patients and 32% DLL3 high expression using the same mouse monoclonal antibody as the FIH study [17]. In contrast, our study used a rabbit monoclonal antibody to analyse DLL3 expression. Although different antibodies were used, the DLL3 expression distribution in this study was consistent with the FIH study.

Rova-T demonstrated anti-tumor activity in Japanese patients with relapsed SCLC who received at least two prior lines of chemotherapy; 17% of DLL3 high patients had an objective response and 56% achieved disease control per investigator assessment. All responders received 0.3 mg/kg Rova-T and had tumors with high DLL3 expression. In addition, mOS increased by more than two months in DLL3 high patients (7.4 months) compared to DLL3 not high patients (5.1 months). Similarly, Rova-T appeared to be more active in DLL3 high patients in the significantly larger TRINITY study [16]. However, this trend thus far observed should be confirmed in larger studies (phase III MERU and TAHOE).

Currently two randomized Rova-T phase III studies are ongoing: TAHOE, evaluating Rova-T vs. topotecan in second-line SCLC patients, and MERU evaluating Rova-T in maintenance following 4 cycles of platinum doublet front-line chemotherapy. The enrollment into the TAHOE (NCT03061812) study has been discontinued following The Independent Data Monitoring Committee recommendation based on the shorter overall survival in the Rova-T arm compared with the topotecan control arm.

In conclusion, data from this study of Rova-T in Japanese patients with SCLC was generally consistent with data reported in studies of non-Japanese patients. Given the significant unmet medical need and limited treatment options, Rova-T provides patients with DLL3-expressing relapsed SCLC a meaningful clinical benefit and a manageable safety profile that supports further investigation and inclusion of Japanese patients in an ongoing phase III MERU study (NCT03033511).

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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), as well as 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.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). 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.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.07.025.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424, https://doi.org/10.3322/caac.21492.

[2] L.A. Torre, F. Bray, R.L. Siegel, et al., Global cancer statistics, 2012, CA Cancer J. Clin. 65 (2015) 87–108, https://doi.org/10.3322/caac.21262.

[3] S. Cheng, W.K. Evans, D. Stys-Norman, et al., Chemotherapy for relapsed small cell lung cancer: a systematic review and practice guideline, J. Thorac. Oncol. 2 (2007) 348–354, https://doi.org/10.1097/01.JTO.0000263720.15062.51.

[4] N. Asai, Y. Ohkuni, N. Kaneko, et al., Relapsed small cell lung cancer: treatment options and latest developments, Ther. Adv. Med. Oncol. 6 (2014) 69–82, https://doi.org/10.1177/1758834013517413.

[5] A.G. Nicholson, K. Chansky, J. Crowley, et al., The international association for the study of lung cancer lung cancer staging project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer, J. Thorac. Oncol. 11 (2016) 300–311, https://doi.org/10.1016/j.jtho.2015.10.008.

[6] Guidelines for Clinical Practice of Lung Cancer, Japan, (2019) Accessed at https://www.haigan.gr.jp/modules/guideline/index.php.

[7] NCCN: NCCN Guidelines Version 1.2019: Small Cell Lung Cancer, (2018) Oct 10.

[8] D. Simos, G. Sajjady, M. Sergi, et al., Third-line chemotherapy in small-cell lung cancer: an international analysis, Clin. Lung Cancer 15 (2014) 110–118, https://doi.org/10.1016/j.cllc.2013.11.003.

[9] K. Saruwatari, S. Umemura, S. Nomura, et al., Prognostic factor analysis in patients with small-cell lung cancer treated with third-line chemotherapy, Clin. Lung Cancer 17 (2016) 581–587, https://doi.org/10.1016/j.cllc.2016.05.022.

[10] G. Chapman, D.B. Sparrow, E. Kremmer, et al., Notch inhibition by the ligand DELTA-LIKE 3 defines the mechanism of abnormal vertebral segmentation in spondylocostal dysostosis, Hum. Mol. Genet. 20 (2011) 905–916, https://doi.org/10.1093/hmg/ddq529.

[11] L.R. Saunders, A.J. Bankovich, W.C. Anderson, et al., A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo, Sci. Transl. Med. 7 (2015) 302ra136, , https://doi.org/10.1126/scitranslmed.aac9459.

[12] J.A. Hartley, V.J. Spanswick, N. Brooks, et al., SJG-136 (NSC 694501), a novelrationally designed DNA minor groove interstrand cross-linking agent with potent and broad spectrum antitumor activity: part 1: cellular pharmacology, in vitro and initial in vivo antitumor activity, Cancer Res. 64 (2004) 6693–6699, https://doi.org/10.1158/0008-5472.CAN-03-2941.

[13] P.H. Clingen, I.U. De Silva, P.J. McHugh, et al., The XPF-ERCC1 endonuclease and homologous recombination contribute to the repair of minor groove DNA interstrand crosslinks in mammalian cells produced by the pyrrolo[2,1-c][1,4]benzodiazepine dimer SJG-136, Nucleic Acids Res. 33 (2005) 3283–3291, https://doi.org/10.1093/nar/gki639.

[14] C.M. Rudin, M.C. Pietanza, T.M. Bauer, 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. 18 (2017) 42–51, https://doi.org/10.1016/S1470-2045(16)30565-4.

[15] R.A. Soo, E.C.A. Stone, K.M. Cummings, et al., Scientific advances in thoracic oncology 2016, J. Thorac. Oncol. 12 (2017) 1183–1209, https://doi.org/10.1016/j.jtho.2017.05.019.

[16] D.P. Carbone, D. Morgensztern, S. Le Moulec, et al., Efficacy and safety of rovalpituzumab tesirine in patients with DLL3-expressing, ≥ 3rd line small cell lung cancer: results from the phase 2 TRINITY study, J. Clin. Oncol. 36 (15_suppl) (2018), https://doi.org/10.1200/JCO.2018.36.15_suppl.8507 8507–8507.

[17] K. Tanaka, K. Isse, T. Fujihira, et al., Prevalence of Delta-like protein 3 expression in patients with small cell lung cancer, Lung Cancer 115 (2018) 116–120, https://doi.org/10.1016/j.lungcan.2017.11.018.