Preliminary Safety and Efficacy of Rovalpituzumab Tesirine in Patients With Delta-Like Protein 3-Expressing Advanced Solid Tumors

Rahul Aggarwal[1], Aaron Mansfield[2], Himisha Beltran[3], Anna F. Farago[4], Christine L. Hann[5], Frederic Kaye[6], Karl Lewis[7], Jiaxin Niu[8], Stephen Richey[9], David Smith[10], Heloisa P. Soares[11], Alexander Spira[12], Matthew Taylor[13], Saiama N. Waqar[14], Satwant Lally[15], Michael Rossi[15], Laura Saunders[15], Scott J. Dylla[15], Edward Kavalerchik[15], Yan Luo[16], Lowell Anthony[17]

[1]University of California at San Francisco, San Francisco, CA, USA; [2]Mayo Clinic, Rochester, MN, USA; [3]Weill Cornell Medical College, New York, NY, USA; [4]Massachusetts General Hospital, Boston, MA, USA; [5]Johns Hopkins University, Baltimore, MD, USA; [6]University of Florida, Gainesville, FL, USA; [7]University of Colorado, Denver, CO, USA; [8]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [9]Texas Oncology, Ft. Worth, TX, USA; [10]Compass Oncology, Vancouver, WA, USA; [11]Moffitt Cancer Center, Tampa, FL, USA; [12]Virginia Cancer Specialists, Fairfax, VA, USA; [13]Oregon Health and Science University, Portland, OR, USA; [14]Washington University School of Medicine, St. Louis, MO, USA; [15]AbbVie Stemcentrx LLC, South San Francisco, CA, USA; [16]AbbVie Inc., North Chicago, IL, USA; [17]University of Kentucky Chandler Medical Center, Lexington, KY, USA

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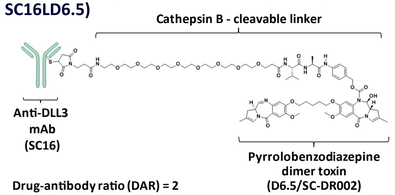
OBJECTIVES

- To determine the safety, tolerability, and antitumor activity of rovalpituzumab tesirine (Rova-T™) in patients with delta-like protein 3 (DLL3)-expressing advanced solid tumors

BACKGROUND

- Delta-like protein 3 (DLL3) is an atypical Notch receptor family ligand expressed in high-grade neuroendocrine carcinomas (NECs), with minimal to no expression in normal tissue[1]
  - DLL3 has a role in development and cell fate decisions[1,2]
  - DLL3 protein is expressed on the cell surface, making it accessible to monoclonal antibodies[1]
- Rova-T is an antibody-drug conjugate (ADC) targeting DLL3
  - It is composed of a DLL3-targeting IgG1 monoclonal antibody tethered to the DNA cross-linking pyrrolobenzodiazepine (PBD) agent SC-DR002 (D6.5) via a protease-cleavable linker[1] (**Figure 1**)

Figure 1. Rovalpituzumab Tesirine (Rova-T, SC16LD6.5)



DLL3, delta-like protein 3; mAb, monoclonal antibody.

- The primary mechanism of action of Rova-T is binding of the ADC to DLL3 on target-expressing cells; internalization of the complex; and release of the cytotoxin via proteolytic cleavage in late endosomes, leading to interstrand DNA crosslinks and cell death[1]
- A Phase 1 study of Rova-T monotherapy in small cell lung cancer (SCLC) showed encouraging antitumor activity in patients with DLL3 expression, a manageable safety profile, and was well-tolerated[3]
  - Improved efficacy in high DLL3-expressing tumors suggests that DLL3 expression may help identify patients who are more likely to benefit from treatment
  - Rova-T is currently being evaluated for efficacy and safety in patients with extensive stage SCLC in multiple Phase 2/3 studies

BACKGROUND (CONTINUED)

- Preclinical studies have shown that in addition to SCLC, DLL3 is expressed in neuroendocrine tumors such as those arising from the prostate, pancreas, and gallbladder[4]
  - DLL3 expression was also observed in metastatic melanoma, medullary thyroid cancer (MTC), and glioblastoma (GBM)[4]
  - In patient-derived xenograft models of several of these tumor types, Rova-T has shown effective and durable responses[4]
- Here, we present preliminary safety and efficacy of Rova-T in a "basket" trial across a number of solid tumors expressing DLL3

METHODS

- This is a Phase 1, open-label, multicenter study (NCT02709889) of Rova-T in 8 cohorts: malignant melanoma, MTC, GBM, large cell NEC (LCNEC) of the lung, neuroendocrine prostate cancer (NEPC), high-grade gastroenteropancreatic NEC (GEP NEC), other NECs, and other solid tumors
- The study opened for enrollment in September 2016
- A 3+3 dose escalation is used in each cohort, at doses 0.2-0.4 mg/kg of Rova-T administered intravenously on Day 1 of each 42-day cycle, and proceeding until a maximum tolerated dose (MTD) is determined
- Expansion cohorts will be conducted with the recommended Phase 2 dose (RPTD)
- Eligibility criteria are summarized in **Table 1**

Table 1. Key Patient Eligibility Criteria

Key inclusion criteria
Histologically confirmed, unresectable, DLL3-expressing advanced solid tumor with measurable disease, relapsed/refractory (R/R) to standard therapy
Life expectancy ≥ 12 weeks
ECOG performance score 0-1
Adequate hematologic, hepatic, and renal function
Recovery to Grade 1 of any clinically significant toxicity (excluding alopecia) prior to initiation of study drug
For prostate cancer patients: cancer of predominantly small cell NEC and/or intermediate atypical carcinoma histologic differentiation; progressive disease by PCWG3, RECIST v1.1, or both during or within 4 weeks following completion of ≥ 1 prior systemic therapy; surgically/medically castrated
Key exclusion criteria
Prior exposure to a pyrrolobenzodiazepine (PBD)-based drug, prior participation in a Rova-T clinical trial, or known hypersensitivity to Rova-T or excipient
Recent or serious ongoing infection
Documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with NYHA Class III-IV within 6 months prior to first dose of study drug
Women who are pregnant or breastfeeding

DLL3, delta-like protein 3; ECOG, Eastern Cooperative Oncology Group; mAb, monoclonal antibody; ADC, antibody-drug conjugage; NEC, neuroendocrine carcinoma; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors; NYHA, New York Heart Association.

RESULTS

PATIENT DISPOSITION AND DOSING

- As of 30 June 2017, 63 treated patients had data available (**Tables 2 and 3**)
- The last cleared dose was 0.3 mg/kg Rova-T and the MTD has not been reached

Table 2. Patient Demographics

Characteristics	N = 63
Gender, n (%)	
Female	21 (33)
Male	41 (65)
Unknown/missing	1 (2)
Median age (range)	62 (28-80)
Baseline ECOG PS	
0	9 (14)
1	52 (83)
2	1 (2)
Missing	1 (2)
Tumor type, n (%)	
Melanoma	5 (8)
MTC	2 (3)
GBM	4 (6)
LCNEC-lung	7 (11)
NEPC	7 (11)
GEP NEC	8 (13)
Other NEC	17 (27)
Other solid tumor	13 (21)
Stage at study entry, n (%)	
IIIa	3 (5)
IIIb	2 (3)
IV	57 (91)
Missing	1 (2)
Prior lines of therapy	
1	13 (21)
2	14 (22)
3	14 (22)
≥ 4	19 (30)
Missing	3 (5)

ECOG PS, Eastern Cooperative Oncology Group performance score; MTC, medullary thyroid cancer; GBM, glioblastoma; LCNEC-lung, large cell neuroendocrine carcinoma of the lung; NEPC, neuroendocrine prostate cancer; GEP NEC, high-grade gastroenteropancreatic neuroendocrine carcinoma; NEC, neuroendocrine carcinoma.

Table 3. Dosing Cohorts

Rova-T (mg/kg)	N = 63 n (%)	Cycles completed 1	2	≥ 3	Mean no. cycles (+/- SD)
0.2	39 (62)	25	7	7	1.6 (1.0)
0.3	21 (33)	15	5	1	1.3 (0.6)
0.4	3 (5)	3	0	0	1.0 (0)

No., number; SD, standard deviation.

SAFETY

- An adverse event (AE) overview is shown in **Table 4**
- Overall, 57 patients (91%) had at least one AE (**Table 5**)

Table 4. Overview of AEs

AEs	Rova-T dose (mg/kg) 0.2 N = 39 n	0.3 N = 21 n	0.4 N = 3 n	Total N = 63 n (%)
All AEs	36	18	3	57 (91)
Drug-related	27	16	2	45 (71)
Grade 3/4 AEs	24	9	2	35 (56)
Drug-related	12	6	1	19 (30)
Serious AEs	16	9	1	26 (41)
Drug-related	2	7	0	9 (14)
AEs leading to treatment discontinuation	6	4	0	10 (16)
Grade 5 AE (Death)	2	2	0	4 (6)

Table 5. Overall AEs

AEs ≥15% total patients	Rova-T dose (mg/kg) 0.2 N = 39 n	0.3 N = 21 n	0.4 N = 3 n	Total N = 63 n (%)
All AEs	36	18	3	57 (91)
Fatigue	19	7	3	29 (46)
Nausea	9	8	1	18 (29)
Thrombocytopenia	8	5	2	15 (24)
Vomiting	9	5	0	14 (22)
Abdominal pain	7	5	0	12 (19)
AST increased[a]	7	5	0	12 (19)
Diarrhea	6	5	0	11 (18)
Dyspnoea	7	4	0	11 (18)
Blood alk phos increased	5	4	1	10 (16)
Photosensitivity	8	2	0	10 (16)

AST, aspartate aminotransferase; alk phos, alkaline phosphatase.
[a]Eight of 12 patients with elevated AST had liver lesions.

- The most common drug-related AEs were:
  - Fatigue; 17 patients (27%)
  - Thrombocytopenia; 12 patients (19%)
  - Increased AST levels; 10 patients (16%)
- The most common drug-related Grade 3/4 AEs were:
  - Fatigue; 4 patients (6%)
  - Increased AST levels, increased ALT (alanine aminotransferase) levels, anemia, thrombocytopenia; 3 patients (5%) each
  - Increased blood alkaline phosphatase levels, vomiting, nausea, pericardial effusion; 2 patients (3%) each
- Twenty-six patients (41%) had a serious AE (**Table 6**)
  - Drug-related serious AEs that occurred in ≥ 2 patients included: 2 patients (3%) each with pleural effusion and vomiting

Table 6. Serious AEs

Serious AEs > 1 patient overall	Rova-T dose (mg/kg), n 0.2 N = 39	0.3 N = 21	0.4 N = 3	Total N = 63 n (%)
Overall serious AEs	**16**	**9**	**1**	**26 (41)**
Dehydration	1	2	0	3 (5)
Pneumonia	2	1	0	3 (5)
Vomiting	1	2	0	3 (5)
Pleural effusion	1	1	0	2 (3)
Respiratory failure	1	1	0	2 (3)

- Four patients died while on study
- Three patients died while on study, which were not drug-related (progressive GBM and hypovolemia, both in the 0.2 mg/kg cohort, catheter-related infection in the 0.3 mg/kg cohort)
- One patient with an atypical thymic carcinoid tumor ("other NEC" cohort) received 0.3 mg/kg Rova-T and had a dose-limiting toxicity of acute respiratory failure, resulting in death

PRELIMINARY EFFICACY

- Efficacy was assessed with the majority of patients early in dose escalation and receiving 1 dose of Rova-T (**Table 3**)
- Clinical case studies in melanoma and small cell tumor of mediastinum (**Table 7**) demonstrate preliminary efficacy in DLL3-expressing tumors (both in the 0.2 mg/kg cohort) beyond SCLC
- Patient 1 achieved PR and maintained PR through post-Cycle 3 (C3) assessment thus far
  - Perinephric lesion at baseline and post-C3 assessment is shown (**Figure 2**)
- Patient 2 achieved PR and maintained PR through post-C4 assessment thus far
  - Liver metastasis lesion at baseline and post-C4 assessment is shown (**Figure 3**)

Table 7. Characteristics of Exemplary Patients

Patient	Age/ Sex	Tumor type	Initial diagnosis	Prior lines of therapy	Cycles completed
1	68/F	Stage IV extensive melanoma	June 2015	1	3
2	35/F	Stage IV high grade neuroendocrine/ small cell of mediastinum (other NEC)	Sept 2015	2	4

Figure 2. Patient with Melanoma Demonstrating PR and Decreased Perinephric Metastases

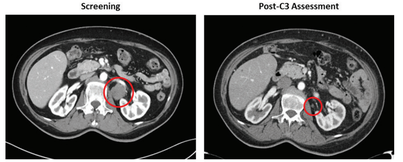
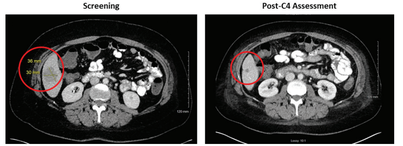


Figure 3. Patient with Small Cell Tumor of Mediastinum Demonstrating PR and Decreased Liver Metastases



CONCLUSIONS

- Rova-T is tolerated at the doses tested so far and the safety profile is consistent with the Phase 1 study of Rova-T in SCLC
- The MTD has not been reached in any disease cohorts and dose escalation is ongoing
- Reduction in tumor burden and confirmed responses have been observed for Rova-T in DLL3-expressing, advanced solid tumors beyond SCLC
- Preliminary safety and efficacy data of Rova-T warrant continued study in these disease populations

Corresponding author email: rahul.aggarwal@ucsf.edu

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