Biomarker analysis of cadherin 6 (CDH6) and folate receptor alpha (FRα) expression, and raludotatug deruxtecan (R-DXd) antitumor activity by FRα status, in patients with platinum-resistant ovarian cancer from REJOICE-Ovarian01 and a first-in-human Phase 1 study of R-DXd

Kathleen Moore,[1] Isabelle Ray-Coquard,[2] Erika Hamilton,[3] Kosei Hasegawa,[4] Debra L Richardson,[5] Alexander Philipovskiy,[6] Kazuki Sudo,[7] Jung-Yun Lee,[8] Nicoletta Colombo,[9] David Garcia-Illescas,[10] Sany Hoxha,[11] Madan Gopal Kundu,[12] Yusuke Myobatake,[12] Connor Mailley,[12] Sandra Re,[12] Tsuyoshi Hirata,[12] Cynthia Turcotte,[12] Weiguo Feng,[12] Nanae Izumi[12]

[1]Fred and Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE, USA; [2]Centre Léon Bérard, University Claude Bernard and GINECO, Lyon, France; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; [5]Stephenson Cancer Center and Sarah Cannon Research Institute, University of Oklahoma Health Campus, Oklahoma City, OK, USA; [6]Florida Cancer Specialists/Sarah Cannon Research Institute, Lake Mary, FL, USA; [7]National Cancer Center Hospital, Tokyo, Japan; [8]Yonsei Cancer Center and Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [9]European Institute of Oncology, IRCCS, Milan, Italy; [10]Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [11]Merck & Co., Inc., Rahway, NJ, USA; [12]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA

#1591

SGO ANNUAL MEETING ON WOMEN'S CANCER

SAN JUAN, PR
APRIL 10-13, 2026

OBJECTIVES

- To evaluate CDH6 and FRα protein expression in baseline tumor samples from patients with platinum-resistant OC enrolled in either the Phase 1 DS6000-A-U101 dose-expansion study or the Phase 2 dose-optimization part of the Phase 2/3 REJOICE-Ovarian01 study
- To assess the impact of FRα status on the antitumor activity of R-DXd monotherapy at doses of 4.8–6.4 mg/kg

CONCLUSIONS

- Almost all platinum-resistant OC tumors were CDH6-positive; of 184 tumor samples, **93.5%** were positive for CDH6 expression at any intensity
- Among the tumor samples positive for CDH6 expression, 31.0% were FRα-positive and 62.5% were FRα-negative
- The level of CDH6 protein expression in the tumor cell membrane showed no correlation with FRα protein expression. This observation suggests that they are independent biomarkers in platinum-resistant OC
- R-DXd monotherapy (4.8–6.4 mg/kg IV Q3W) exhibited consistent efficacy in platinum-resistant OC tumors regardless of FRα expression level
  - **FRα-positive tumors:** ORR across doses was **59.3%** (95% CI, 45.0–72.4)
  - **FRα-negative tumors:** ORR across doses was **50.0%** (95% CI, 40.8–59.2)
- The Phase 3 part of the REJOICE-Ovarian01 study is evaluating R-DXd 5.6 mg/kg versus treatment of physician's choice in patients with platinum-resistant OC

Plain language summary
Poster

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INTRODUCTION

- Platinum-resistant OC is associated with poor clinical outcomes and a high unmet need, with standard-of-care non-platinum chemotherapy ± bevacizumab providing only modest benefit (median OS, 10–17 months)[1–4]
- The FRα-directed ADC mirvetuximab soravtansine has improved outcomes for some patients with platinum-resistant OC. However, only patients with FRα-positive tumors–approximately one-third of patients with platinum-resistant OC–are eligible for this treatment[5–8]
- CDH6, a mediator of cell–cell adhesion, is expressed in up to 94% of epithelial OC tumors[9]
- R-DXd is a CDH6-directed ADC comprising a humanized anti-CDH6 immunoglobulin G1 monoclonal antibody, linked to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker[10,11]
- In the Phase 1 first-in-human DS6000-A-U101 study, R-DXd demonstrated promising antitumor activity. Among patients with pretreated OC–89% of whom had platinum-resistant disease–treatment with R-DXd 4.8–6.4 mg/kg IV Q3W resulted in a confirmed ORR of 48.6% across doses[12]
- In the dose-optimization part of the ongoing Phase 2/3 REJOICE-Ovarian01 study, patients with platinum-resistant OC, who received R-DXd 4.8–6.4 mg/kg IV Q3W, achieved a confirmed ORR of 50.5% across doses[9]
- Here we report a retrospective exploratory biomarker analysis of CDH6 and FRα protein expression in platinum-resistant OC tumors and evaluate the impact of FRα expression on R-DXd efficacy

METHODS

- This analysis used baseline tumor samples from patients with platinum-resistant OC, enrolled in either the dose-expansion part of the Phase 1 DS6000-A-U101 study (NCT04707248) or in the Phase 2 dose-optimization part of the REJOICE-Ovarian01 study (NCT06161025)
- Samples were analyzed by immunohistochemistry:
  - CDH6 expression was analyzed using the CDH6 clinical trial assay (SP450; Roche Diagnostics)
  - FRα expression was analyzed using the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (Roche Diagnostics)
- CDH6 protein expression was scored using both H-score and according to an exploratory classification for CDH6-positive expression:
  - **CDH6-positive:** ≥1% of viable tumor cells positive for CDH6 membrane staining at any intensity (1+/2+/3+)
- FRα protein expression was scored using both H-score for the exploratory analysis and samples were also categorized according to the mirvetuximab soravtansine eligibility criteria[5,6]:
  - **FRα-positive (high):** ≥75% of viable tumor cells with 2+/3+ membrane staining
  - **FRα-negative (low):** <75% of viable tumor cells with 2+/3+ membrane staining
- The correlation between CDH6 expression and FRα expression was assessed using Pearson's correlation coefficient (*r*), calculated using the *cor.test* function in R
- The tumor response analysis included patients with available CDH6 and FRα expression data who were treated with R-DXd monotherapy (4.8–6.4 mg/kg IV Q3W). The responder analysis was further restricted to patients with measurable disease at baseline assessed by BICR per RECIST 1.1.
  - The data cutoff dates for the analysis were July 3, 2025 for the DS6000-A-U101 study, and May 29, 2025 for the REJOICE-Ovarian01 study

RESULTS

CDH6 and FRα expression in platinum-resistant OC

- Baseline tumor samples from 95 patients with platinum-resistant OC enrolled in the DS6000-A-U101 study and from 89 patients with platinum-resistant OC enrolled in the REJOICE-Ovarian01 study were available and of sufficient tissue quality for analysis of both CDH6 and FRα expression by immunohistochemistry
- Among all tumor samples analyzed (N=184):
  - 93.5% (n=172) of samples were CDH6-positive; the median CDH6 expression on the tumor cell membrane was 77.0% (range, 0–100) (**Figures 1A and 1C**)
  - 31.0% (n=57) of samples were FRα-positive; the median FRα expression on the tumor cell membrane was 35.0% (range, 0–100) (**Figures 1B and 1C**)
  - 6.5% (n=12) were both CDH6-negative and FRα-negative (**Figure 1C**)
- Among the CDH6-positive samples (n=172), 31.0% (n=57) were FRα-positive and 62.5% (n=115) were FRα-negative (**Figure 1C**)
- There was no correlation between CDH6 and FRα expression on the tumor cell membrane evaluated by H-score (r=0.11; *P*=0.13) (**Figure 2**)

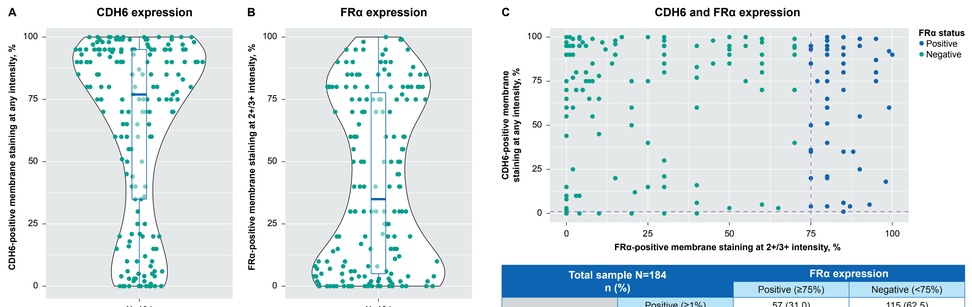
Patient baseline and disease characteristics

- Baseline characteristics of patients in this exploratory biomarker analysis who had available CDH6 and FRα expression data are shown in **Table 1**
  - Baseline characteristics of the R-DXd 5.6-mg/kg cohort were consistent with those observed in the pooled R-DXd 4.8–6.4 mg/kg dose group, regardless of FRα expression

Association between FRα expression and tumor response

- Patients treated with R-DXd monotherapy (4.8–6.4 mg/kg IV Q3W) exhibited clinically meaningful tumor responses regardless of tumor FRα status (**Table 2**)
- Across all doses, the confirmed ORR was 59.3% (95% CI, 45.0–72.4) in patients with FRα-positive tumors and 50.0% (95% CI, 40.8–59.2) in patients with FRα-negative tumors
- Among patients treated with R-DXd 5.6 mg/kg, the dose selected for Phase 3 evaluation, the confirmed ORR was 47.4% (95% CI, 24.4–71.1) in patients with FRα-positive tumors and 52.4% (95% CI, 36.4–68.0) in patients with FRα-negative tumors

Figure 1. Distribution of CDH6 (A) and FRα (B) expression and their association (C) in platinum-resistant OC tumors



Total sample N=184 n (%)		FRα expression	
		Positive (≥75%)	Negative (<75%)
CDH6 expression	Positive (≥1%)	57 (31.0)	115 (62.5)
	Negative (<1%)	0	12 (6.5)

Figure 2. Correlation between CDH6 and FRα protein expression

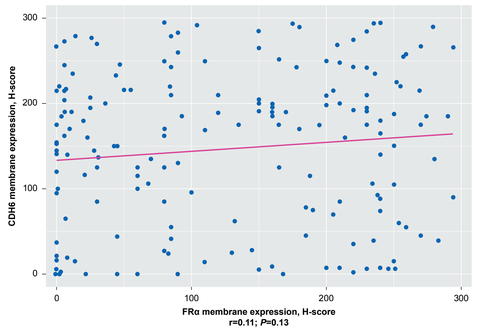


Table 1: Baseline characteristics for pooled R-DXd 4.8–6.4 mg/kg dose cohorts by FRα expression

	FRα-positive (n=57)	FRα-negative (n=127)	All patients (N=184)
Age, years, median (range)	62.0 (44–79)	62.0 (34–84)	62.0 (34–84)
ECOG PS, n (%)			
0	33 (57.9)	71 (55.9)	104 (56.5)
1	24 (42.1)	56 (44.1)	80 (43.5)
Cancer type, n (%)			
Ovarian	44 (77.2)	104 (81.9)	148 (80.4)
Peritoneal	6 (10.5)	11 (8.7)	17 (9.2)
Fallopian tube	7 (12.3)	12 (9.4)	19 (10.3)
Number of prior LOTs, n (%)			
1	6 (10.5)	8 (6.3)	14 (7.6)
2	15 (26.3)	35 (27.6)	50 (27.2)
3	23 (40.4)	43 (33.9)	66 (35.9)
≥4	13 (22.8)	41 (32.3)	54 (29.3)
Last platinum-free interval, n (%)			
<3 months	28 (49.1)	65 (51.2)	93 (50.5)
3–6 months	29 (50.9)	62 (48.8)	91 (49.5)
Prior therapy, n (%)			
Bevacizumab	42 (73.7)	96 (75.6)	138 (75.0)
PARP inhibitor	42 (73.7)	97 (76.4)	139 (75.5)
Mirvetuximab soravtansine	0	7 (5.5)	7 (3.8)

Table 2. Summary of tumor response for pooled R-DXd 4.8–6.4 mg/kg dose cohorts and the R-DXd 5.6-mg/kg cohort

Response by BICR[a]	R-DXd 4.8–6.4 mg/kg			R-DXd 5.6 mg/kg		
	FRα-positive (n=54)	FRα-negative (n=122)	All patients (n=176)	FRα-positive (n=19)	FRα-negative (n=42)	All patients (n=61)
Confirmed ORR, % (95% CI)	59.3 (45.0–72.4)	50.0 (40.8–59.2)	52.8 (45.2–60.4)	47.4 (24.4–71.1)	52.4 (36.4–68.0)	50.8 (37.7–63.9)
Best overall response,[b] n (%)						
CR	3 (5.6)	12 (9.8)	15 (8.5)	1 (5.3)	3 (7.1)	4 (6.6)
PR	29 (53.7)	49 (40.2)	78 (44.3)	8 (42.1)	19 (45.2)	27 (44.3)
SD	20 (37.0)	49 (40.2)	69 (39.2)	9 (47.4)	15 (35.7)	24 (39.3)
PD	1 (1.9)	10 (8.2)	11 (6.3)	1 (5.3)	3 (7.1)	4 (6.6)
Not evaluable	1 (1.9)	2 (1.6)	3 (1.7)	0	2 (4.8)	2 (3.3)
Disease control rate,[c] % (95% CI)	85.2 (72.9–93.4)	77.9 (69.5–84.9)	80.1 (73.4–85.7)	78.9 (54.4–93.9)	83.3 (68.6–93.0)	82.0 (70.0–90.6)

[a]The responder analysis included patients with available FRα and CDH6 expression data and who had measurable disease at baseline assessed by BICR per RECIST 1.1. [b]Best overall response was defined as the best response across all timepoints; CR, ≥2 assessments of CR ≥4 weeks apart, prior to progression; PR, ≥2 assessments of PR (or CR) ≥4 weeks apart, prior to progression (not meeting criteria for CR); SD, ≥1 assessment of SD (or better) ≥5 weeks following treatment initiation, and before progression (not meeting criteria for CR or PR); PD, progression ≥12 weeks following treatment initiation (not meeting criteria for CR, PR, or SD). [c]Disease control rate was defined as percentage of patients with BOR of CR, PR, or SD ≥77 days.

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ABBREVIATIONS

ADC, antibody–drug conjugate; **BICR**, blinded independent central review; **CDH6**, cadherin 6; **CI**, confidence interval; **CR**, complete response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **FDA**, United States Food and Drug Administration; **FRα**, folate receptor alpha; **IV**, intravenous; **LOT**, line of therapy; **OC**, ovarian cancer; **ORR**, objective response rate; **OS**, overall survival; **PARP**, poly (ADP-ribose) polymerase; **PD**, progressive disease; **PR**, partial response; **Q3W**, every 3 weeks; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SD**, stable disease.

DECLARATION OF INTERESTS

Kathleen Moore

Research grant from Verastem Oncology; Advisor for Novartis, OncXerna Therapeutics, Onconova Therapeutics, Panavance Therapeutics, VBL Therapeutics, Verastem Oncology, Zentalis, Regeneron, Exelixis, Gilead, GOG Partners; Invited Speaker for Research to Practice, OncLive, PRIME Therapeutics, PER, Great Debates and Updates; Principal Investigator for OncXerna Therapeutics; Board of Directors for ASCO and GOG Foundation; and funding from Daiichi Sankyo, Inc.

ACKNOWLEDGMENTS

We thank the patients, their families, and their caregivers for study participation, and the study staff for their contributions.

This study is sponsored by Daiichi Sankyo, Inc. In October 2023, Daiichi Sankyo entered into a global development and commercialization collaboration agreement with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) for raludotatug deruxtecan (R-DXd).

Medical writing support was provided by Anna Atkinson, PhD, of BOLDSCIENCE, Inc., and was funded by Daiichi Sankyo, Inc. Editorial support was provided in accordance with Good Publication Practice guidelines (https://www.ismpp.org/gpp-2022).

Presented at The Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; April 10–13, 2026; San Juan, PR, USA

katmoore@unmc.edu

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