Raludotatug deruxtecan (R-DXd) in patients with platinum-resistant ovarian cancer: an updated analysis of efficacy and tolerability from the Phase 2 part of REJOICE-Ovarian01

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OBJECTIVE

- This is an updated analysis of patients with platinum-resistant OC included in the Phase 2 dose-optimization part of the Phase 2/3 REJOICE-Ovarian01 study. We report efficacy, tolerability, and PROs with an extended follow-up and a larger patient population than the primary analysis, with a focus on patients with CDH6 ≥1% TC (CDH6 ≥1% tumor cell membrane expression) who received R-DXd 5.6 mg/kg

CONCLUSIONS

- R-DXd demonstrated clinically meaningful antitumor activity across all doses, including a confirmed ORR of 50.0% (95% CI, 42.8–57.2) among response-evaluable patients with platinum-resistant OC
- In response-evaluable patients with CDH6 ≥1% TC who received R-DXd 5.6 mg/kg, confirmed ORR was 49.2% (95% CI, 36.4–62.1); responses were deep and durable, with a median DOR of 7.0 months and encouraging median PFS of 7.9 months
- The safety profile of R-DXd was manageable across all doses, and no new safety signals were identified
  - Three adjudicated treatment-related Grade ≥3 ILD/pneumonitis events were reported in this analysis: two Grade 5 events in the 6.4-mg/kg dose group and one Grade 3 event in the 4.8-mg/kg dose group
- In patients with CDH6 ≥1% TC who received R-DXd 5.6 mg/kg, patient-reported abdominal/GI symptoms and pain showed meaningful improvements from baseline to Week 12
  - Meaningful improvements from baseline were also observed across the all-treated population. A comprehensive analysis of PRO data in patients with platinum-resistant OC will be presented at a future congress
- OS data remain immature with a minimum follow-up of ~14 months; longer follow-up will be required to evaluate survival outcomes
- R-DXd 5.6 mg/kg continues to show the most favorable benefit–risk profile among the evaluated doses
- The ongoing Phase 3 part of the REJOICE-Ovarian01 trial is evaluating R-DXd 5.6 mg/kg vs treatment of physician's choice in patients with platinum-resistant OC

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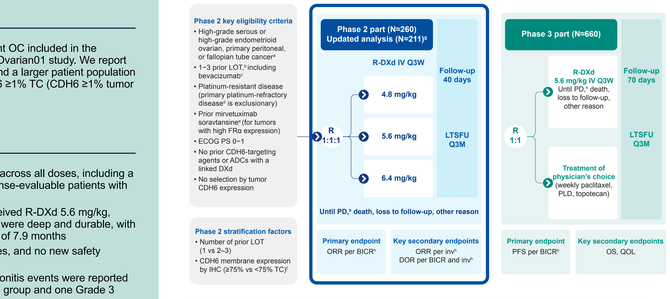
INTRODUCTION

- Platinum-resistant OC is associated with poor outcomes and a substantial symptom burden including abdominal/GI symptoms and pain[1,2]; there remains an unmet need for therapies that offer greater efficacy and improved tolerability[1]
- CDH6, a mediator of cell–cell adhesion, is expressed in up to 94% of OC tumors[3]
- Raludotatug deruxtecan (R-DXd) is a CDH6-directed ADC comprising a humanized anti-CDH6 IgG1 mAb attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker[4]
- REJOICE-Ovarian01 (NCT06161025) is a Phase 2/3 study evaluating R-DXd monotherapy in patients with platinum-resistant OC[5]; in the Phase 2 dose-optimization part, R-DXd showed promising efficacy and a manageable safety profile with 5.6 mg/kg identified as the optimal Phase 3 dose[3]
- We present results from all patients treated with R-DXd in the Phase 2 dose-optimization part of REJOICE-Ovarian01, with a minimum follow-up of ~14 months, and the first report of DOR, PFS, and PROs, including an analysis of efficacy in patients with CDH6 ≥1% TC

METHODS

- REJOICE-Ovarian01 (NCT06161025) is a Phase 2/3 global, multicenter, randomized, open-label study of R-DXd in patients with platinum-resistant, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer (**Figure 1**)
- Patients were enrolled regardless of their tumor CDH6 expression by IHC and randomized to receive R-DXd 4.8, 5.6, or 6.4 mg/kg IV Q3W until PD, death, loss to follow-up, or other reason
- Tumor response was analyzed in response-evaluable patients, defined as those who received R-DXd and had measurable disease at baseline by BICR; all other time-to-event endpoints were analyzed in all patients treated with R-DXd. Safety was analyzed in all treated patients
- PROs were assessed as an exploratory endpoint; abdominal/GI symptoms and pain were evaluated using MMRM analyses of the EORTC QLQ-OV28 abdominal/GI symptoms subscale and the EORTC QLQ-C30 pain subscale, respectively

Figure 1: REJOICE-Ovarian01 study design (NCT06161025)[3,5]



[a]Patients must have had ≥1 lesion not previously irradiated and amenable to biopsy; must have consented to provide a pretreatment biopsy and, in Phase 2 only, an on-treatment biopsy tissue sample and have ≥1 measurable lesion per RECIST 1.1. [b]In the Phase 3 part, patients with 1–4 prior LOT are eligible. [c]Unless ineligible. [d]Defined as disease that has progressed on or within ≤90 days of the last dose of first line platinum-based chemotherapy. [e]Unless ineligible, not approved, or not available locally. [f]A CDH6 stratification cutoff of 75% TC membrane expression was selected based on the observed median of CDH6 expression in the DS6000A-A1101 Phase 1 study population. [g]Overall, 211 patients were randomized to receive R-DXd. One patient did not receive treatment, so 210 patients were treated and were included in the updated analysis. [h]Per RECIST 1.1.

RESULTS

Patient characteristics and treatment exposure

- At the February 2, 2026 data cutoff, 211 patients had been randomized to receive R-DXd at doses of 4.8, 5.6, or 6.4 mg/kg, of whom 210 had received ≥1 dose of R-DXd; minimum follow-up was ~14 months. Patient baseline characteristics are presented in **Table 1**
- At the data cutoff, across all doses, 23 patients (11.0%) remained on study treatment, and 187 patients (89.0%) had discontinued R-DXd: 145 patients (69.0%) discontinued due to PD, 12 (5.7%) due to clinical progression, 18 (8.6%) due to adverse events, 11 (5.2%) due to death, 1 (0.5%) due to patient's decision
  - In the 5.6-mg/kg dose group, 6 patients (8.7%) remained on study treatment, and 63 (91.3%) had discontinued R-DXd: 49 patients (71.0%) discontinued due to PD, 4 (5.8%) due to clinical progression, 5 (7.2%) due to adverse events, and 5 (7.2%) due to death

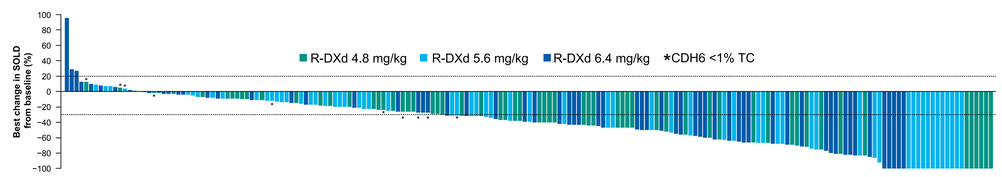
Table 1: Baseline demographic and clinical characteristics

	R-DXd 4.8–6.4 mg/kg[a] N=210	R-DXd 5.6 mg/kg[a] n=69
Age, median (range), years	61.0 (23–82)	60.0 (34–82)
Age ≥65 years, n (%)	81 (38.6)	24 (34.8)
Region, n (%)		
Europe	140 (66.7)	50 (72.5)
Asia	65 (31.0)	17 (24.6)
North America	4 (1.9)	2 (2.9)
Australia	1 (0.5)	0
ECOG PS, n (%)		
0	125 (59.5)	39 (56.5)
1	85 (40.5)	30 (43.5)
Cancer type, n (%)		
Ovarian	183 (87.1)	64 (92.8)
Fallopian tube	20 (9.5)	5 (7.2)
Peritoneal	7 (3.3)	0
Number of prior LOTs, n (%)		
1	18 (8.6)	5 (7.2)
2	86 (41.0)	32 (46.4)
3	106 (50.5)	32 (46.4)
Received prior therapy, n (%)		
Bevacizumab	178 (84.8)	55 (79.7)
PARP inhibitor	144 (68.6)	50 (72.5)
Immunotherapy	9 (4.3)	5 (7.2)
Mirvetuximab soravtansine	5 (2.4)	1 (1.4)
Last platinum-free interval, n (%)		
<3 months	89 (42.4)	34 (49.3)
3–6 months	121 (57.6)	35 (50.7)
CDH6 ≥1% TC,[b] n (%)	195 (94.7)[c]	64 (92.8)
Patient-reported symptom scores, n; mean (standard deviation)		
Abdominal/GI symptoms (EORTC QLQ-OV28)	n=200; 25.1 (21.9)	n=65; 28.7 (24.3)
Pain (EORTC QLQ-C30)	n=201; 26.5 (25.8)	n=64; 30.7 (27.4)

[a]Only patients treated with ≥1 dose were included in this analysis and made up the safety analysis cohort. [b]CDH6 ≥1% TC was defined as CDH6 ≥1% tumor cell membrane expression as determined using the clinical trial assay for CDH6 (SP450) (Roche Diagnostics). [c]Percentage calculated after excluding 4 patients whose samples were of insufficient quality to determine CDH6 membrane expression.

RESULTS

Figure 2: Antitumor activity of R-DXd across all doses (n=191)[a]



[a]Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan, both by BICR, were included in the waterfall plot (n=191). Twelve patients did not have measurable disease at baseline (R-DXd 4.8 mg/kg, n=7; 5.6 mg/kg, n=1; 6.4 mg/kg, n=4), and 7 patients had no adequate post-baseline tumor assessment (R-DXd 5.6 mg/kg, n=3; 6.4 mg/kg, n=4).

Tumor response and PROs

- Antitumor activity in patients with platinum-resistant OC across all doses of R-DXd, and in patients with CDH6 ≥1% TC who received R-DXd 5.6 mg/kg (the selected Phase 3 dose), is presented in **Table 2**
  - Among 198 response-evaluable patients, regardless of tumor CDH6 expression and across all doses, confirmed ORR was 50.0% (95% CI, 42.8–57.2), including 15 CRs and 84 PRs
  - Among 63 response-evaluable patients with CDH6 ≥1% TC who received R-DXd 5.6 mg/kg, confirmed ORR was 49.2% (95% CI, 36.4–62.1), including 7 CRs and 24 PRs
- Clinically meaningful tumor responses were seen irrespective of dose (**Figure 2**)
- R-DXd treatment was associated with deep and durable responses in patients with CDH6 ≥1% TC in the 5.6-mg/kg dose group (**Figure 3**)
- Patient-reported abdominal/GI symptoms and pain improved from baseline to Week 12 (EORTC QLQ-OV28 and QLQ-C30; MMRM) (**Figure 4**)

Table 2: Summary of efficacy endpoints[a]

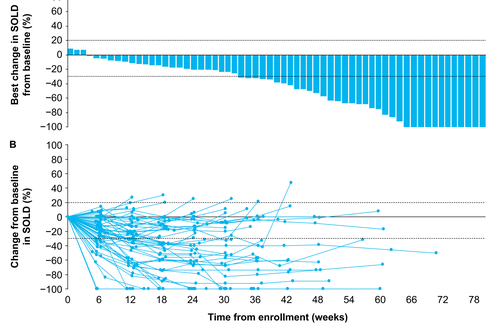
Efficacy outcomes by BICR per RECIST 1.1	R-DXd 4.8–6.4 mg/kg All treated patients N=210	R-DXd 5.6 mg/kg CDH6 ≥1% TC n=64
ORR in response-evaluable patients,[b] % (n/N; 95% CI)	50.0 (99/198; 42.8–57.2)	49.2 (31/63; 36.4–62.1)
BOR[c] in response-evaluable patients,n (%)	n=198	n=63
CR	15 (7.6)	7 (11.1)
PR	84 (42.4)	24 (38.1)
SD	78 (39.4)	28 (44.4)
PD	14 (7.1)	2 (3.2)
Not evaluable	7 (3.5)[c]	2 (3.2)[c]
DCR[c] in response-evaluable patients, %, (n/N; 95% CI)	78.8 (156/198; 72.4–84.3)	84.1 (53/63; 72.7–92.1)
DOR, median (95% CI), months	6.9 (5.6–8.3)	7.0 (4.3–10.3)
PFS, median (95% CI), months	6.9 (5.7–7.2)	7.9 (5.6–8.3)

[a]The median follow-up for OS in the 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg dose groups was 15.4 months (95% CI, 15.1–15.9), 15.2 months (95% CI, 15.0–15.9), and 15.2 months (95% CI, 15.0–15.8), respectively; OS data were immature at the time of data cut-off. [b]Response-evaluable patients defined as those who received R-DXd and had measurable disease at baseline by BICR. [c]BOR was defined as the best response across all therapy, from the start of study treatment until the end of last anticancer therapy, prior to progression, PR, SD patients and patients with CDH6 ≥1% TC membrane expression (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 following treatment initiation (not meeting criteria for CR, PR, or SD). [c]Patients had no adequate post-baseline tumor assessment by BICR. [c]DCR was defined as percentage of patients with BOR of CR, PR, or SD ≥77 days (per RECIST 1.1).

Safety

- Across all doses, any-grade TRAEs were reported in 200 patients (95.2%) and Grade ≥3 TRAEs in 86 patients (41.0%); in the 5.6-mg/kg dose group, any-grade TRAEs were reported in 68 patients (98.6%) and Grade ≥3 TRAEs were reported in 27 patients (39.1%; **Table 3**)
- TRAEs led to R-DXd discontinuation in 14 patients (6.7%) across all doses, and in 5 patients (7.2%) in the 5.6-mg/kg dose group
- Any-grade adjudicated treatment-related ILD/pneumonitis was reported in 16 patients (7.6%) across all doses. Grade ≥3 events comprised two Grade 5 events in the 6.4-mg/kg dose group and one Grade 3 event in the 4.8-mg/kg dose group
  - In the 5.6-mg/kg dose group, adjudicated treatment-related ILD/pneumonitis was reported in 4 patients (5.8%) (Grade 1, n=1; Grade 2, n=3); no Grade 5 events were reported
- Febrile neutropenia was reported in 3 patients (1.4%) across all doses, including 2 patients (2.9%) in the 5.6-mg/kg dose group (Grade 3, n=1; Grade 4, n=1) and 1 (1.4%) patient in the 6.4-mg/kg dose group (Grade 3, n=1)
- The most common TEAEs reported in the 5.6-mg/kg dose group are presented in **Figure 5**

Figure 3: Tumor response in patients with CDH6 ≥1% TC who received R-DXd 5.6 mg/kg (n=61)[a] (A) best change in SOLD and (B) depth and durability of response



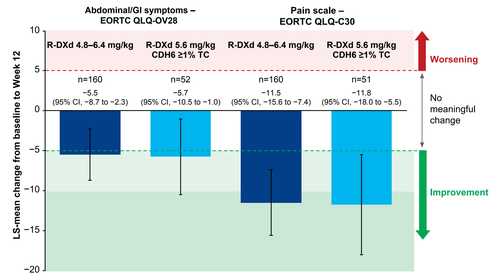
[a]Tumor response was assessed by BICR per RECIST 1.1; only patients with measurable disease at baseline by BICR and ≥1 post-baseline tumor scan were included in each of the waterfall and spider plots (n=61). One patient did not have measurable disease at baseline by BICR, and 2 patients had no adequate post-baseline tumor assessment by BICR.

Table 3: Safety summary[a]

	R-DXd 4.8–6.4 mg/kg N=210	R-DXd 5.6 mg/kg n=69
Any TEAE, n (%)	210 (100)	69 (100)
Grade ≥3	127 (60.5)	43 (62.3)
Any TRAE, n (%)	200 (95.2)	68 (98.6)
Grade ≥3	86 (41.0)	27 (39.1)
Grade 5	2 (1.0)[b]	0
Any SAE, n (%)	80 (38.1)	24 (34.8)
Grade ≥3	70 (33.3)	22 (31.9)
Grade 5	20 (9.5)	7 (10.1)
Any treatment-related SAE, n (%)	24 (11.4)	6 (8.7)
Grade ≥3	22 (10.5)	6 (8.7)
Grade 5	2 (1.0)[b]	0
Dose modifications due to TRAEs, n (%)		
Drug discontinuation	14 (6.7)	5 (7.2)
Dose reduction	43 (20.5)	12 (17.4)
Dose delay	52 (24.8)	15 (21.7)
Adjudicated treatment-related ILD/pneumonitis,[c] n (%)		
Any grade	16 (7.6)	4 (5.8)
Grade ≥3	3 (1.4)	0
Grade 5	2 (1.0)[c]	0

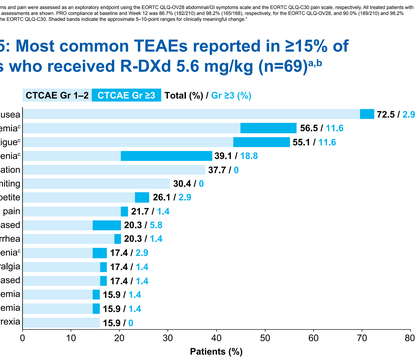
[a]Reported safety events are defined using MedDRA Preferred Terms and CTCAE criteria. [b]Grade 5 events were ILD/pneumonitis (n=2), both in the 6.4-mg/kg dose group. [c]All suspected ILD/pneumonitis events were adjudicated by an independent ILD adjudication committee. [c]Both events were in the 6.4-mg/kg dose group.

Figure 4: Patient-reported GI symptoms and pain: MMRM LS-mean change from baseline to Week 12[a]



[a]Patient-reported GI symptoms and pain were assessed as an exploratory endpoint using the EORTC QLQ-OV28 abdominal/GI symptoms scale and the EORTC QLQ-C30 pain scale, respectively. All treated patients with baseline and Week 12 PRO assessments are shown. PRO compliance at baseline and Week 12 was 86.7% (182/210) and 98.2% (165/168), respectively, for the EORTC QLQ-OV28, and 90.0% (189/210) and 98.2% (165/168), respectively, for the EORTC QLQ-C30. Shaded bands indicate the approximate 5–10-point ranges for clinically meaningful change.[7]

Figure 5: Most common TEAEs reported in ≥15% of patients who received R-DXd 5.6 mg/kg (n=69)[a,b]



[a]Reported safety events are defined using MedDRA Preferred Terms and CTCAE criteria. [b]Grade 4 hematologic TEAEs reported at 5.6 mg/kg: neutropenia (n=2), thrombocytopenia (n=2), leukopenia (n=1). No Grade 5 hematologic TEAEs were reported at any dose. Grade ≥3 febrile neutropenia was reported in 3 patients, 2 in the R-DXd 5.6-mg/kg dose group (1 Grade 3 and 1 Grade 4), and 1 in the 6.4-mg/kg dose group (Grade 3). [c]Grouped preferred terms were counted with a maximum of one event per patient per grouped event. Anemia included anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased; fatigue included fatigue, asthenia, malaise, and lethargy; neutropenia included neutropenia and neutrophil count decreased; and leukopenia included leukopenia and white blood cell count decreased.

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ABBREVIATIONS

ADC, antibody–drug conjugate; **AST**, aspartate aminotransferase; **BICR**, blinded independent central review; **BOR**, best overall response; **CDH6**, cadherin 6; **CI**, confidence interval; **CR**, complete response; **CTCAE**, Common Terminology Criteria for Adverse Events; **DCR**, disease control rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EORTC QLQ-C30**, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; **EORTC QLQ-OV28**, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module; **FRα**, folate receptor alpha; **GGT**, gamma-glutamyl transferase; **GI**, gastrointestinal; **Gr**, Grade; **IgG1**, immunoglobulin G1; **IHC**, immunohistochemistry; **IV**, intravenous; **LOT**, line of therapy; **LS**, long-term stable follow-up; **mAb**, monoclonal antibody; **MedDRA**, Medical Dictionary for Regulatory Activities; **MMRM**, mixed model for repeated measures; **ORR**, objective response rate; **OS**, overall survival; **PARP**, poly (ADP-ribose) polymerase; **PD**, progressive disease; **PFS**, progression-free survival; **PLD**, pegylated liposomal doxorubicin; **PR**, partial response; **PRO**, patient-reported outcome; **Q3M**, every 3 months; **Q3W**, every 3 weeks; **QOL**, quality of life; **R**, randomized; **R-DXd**, raludotatug deruxtecan; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SAE**, serious adverse event; **SD**, stable disease; **SOLD**, sum of longest diameters of target lesions; **TC**, tumor cell; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment-related adverse event.

DISCLOSURES

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