Raludotatug deruxtecan (R-DXd) monotherapy in patients with previously treated ovarian cancer: subgroup analysis of a first-in-human Phase 1 study

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ANNUAL MEETING
ON WOMEN'S CANCER
San Diego, CA • 2024

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Declaration of interests

Kathleen Moore

Research Grant: Verastem Oncology

Advisor: Novartis, OncXerna Therapeutics, Onconova Therapeutics, Panavance Therapeutics, VBL Therapeutics, Verastem Oncology, Zentalis, Regeneron, Exelixis, Gilead, GOG Partners

Invited Speaker: Research To Practice, OncLive, PRIME Therapeutics, PER, Great Debates and Updates

Principal Investigator: OncXerna Therapeutics

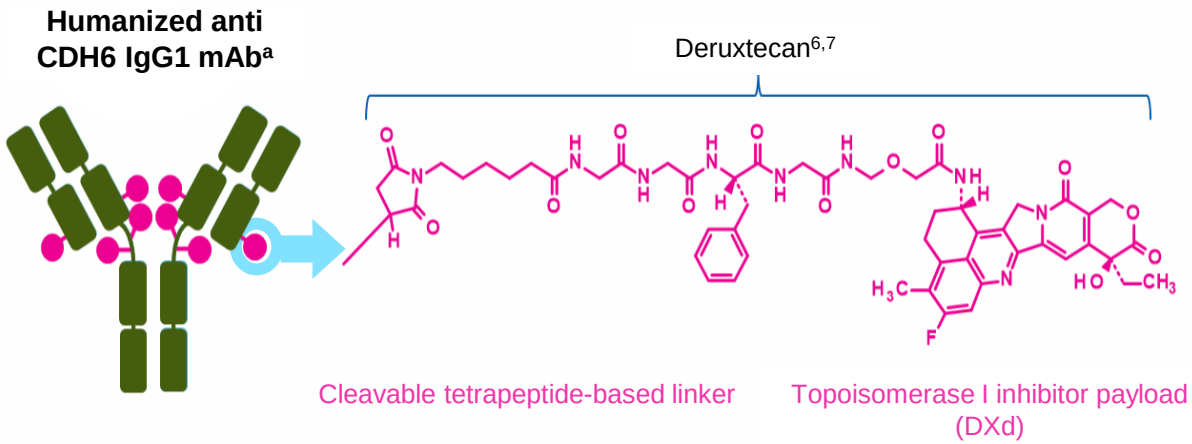
Board of Directors: ASCO, GOG Foundation

Funding: Daiichi Sankyo, Inc.

Background

- The emergence of platinum resistance in recurrent OVC is inevitable; these patients have a clear need for novel treatments[1]
- Expression of CDH6 is observed in ~65 to 85% of patients with OVC[2–4]
- Raludotatug deruxtecan (R-DXd) is an ADC comprising three parts: a humanized anti-CDH6 IgG1 mAb, covalently linked to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker[4,5]
- Early results from the ongoing Phase 1 trial (NCT04707248) demonstrated an acceptable safety profile and early efficacy signal for R-DXd in heavily pretreated patients with advanced OVC[6,7]

R-DXd was designed with 7 key attributes



Payload mechanism of action: topoisomerase I inhibitor[4,b]
High potency of payload[5,8,b]
High drug-to-antibody ratio of ≈8[4,b]
Payload with short systemic half-life[5,b,c]
Stable linker-payload[5,8,b]
Tumor-selective cleavable linker[4,5,8,b]
Bystander antitumor effect[4,b]

[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.
ADC, antibody–drug conjugate; CDH6, cadherin 6; DXd, exatecan derivative; IgG1, immunoglobulin G1; mAb, monoclonal antibody; OVC, ovarian cancer.

1. Richardson DL, et al. *JAMA Oncol.* 2023;9:851–859; 2. Bartolomé RA, et al. *Mol Oncol*. 2021;15:1849–1865; 3. Shintani D, et al. *Gynecol Oncol*. 2022;166(Suppl. 1):S116; 4. Suzuki H, et al. *Mol Cancer Ther*. 2024; 10.1158/1535-7163.MCT-23-0287. Online ahead of print; 5. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67:173–185; 6. Hamilton EP, et al. *J Clin Oncol.* 2022;40(16_suppl):3002-3002; 7. Moore KN, et al. *Ann Oncol.* 2023;34 (Suppl. 2): Abstr 745MO; 8. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097–5108.

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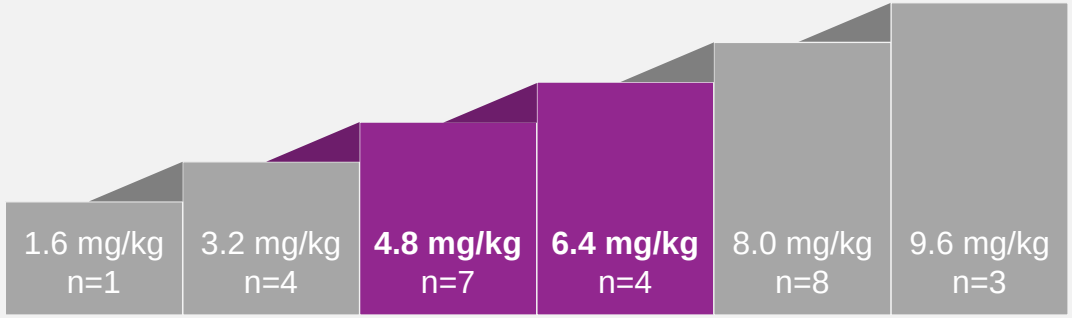
First-in-human Phase 1 study of R-DXd (NCT04707248)[1,2]

Part A | Dose escalation: R-DXd IV Q3W



Enrollment criteria:

- Advanced/metastatic OVC not amenable to SOC therapy
- ECOG PS 0–1
- Prior taxane and platinum-based chemotherapy
- No previous CDH6-targeting agents or ADCs with a linked topoisomerase I inhibitor
- Patients were not selected based on tumor CDH6 expression

Part B | Dose expansion: R-DXd IV Q3W[a]

OVC cohort: 4.8 mg/kg	OVC cohort: 5.6 mg/kg	OVC cohort: 6.4 mg/kg	OVC cohort: 8.0 mg/kg
n=6	n=8	n=20	n=7

Key primary objectives:

- Safety and tolerability
- Determine MTD and RDE
- ORR per RECIST 1.1 (dose expansion)

Key secondary objectives:

- PK: ADC, total anti-CDH6 antibody, and the DXd payload
- ORR per RECIST 1.1 (dose escalation)
- DOR, DCR, and CBR per RECIST 1.1
- Immunogenicity

We present an analysis of safety and preliminary efficacy in heavily pretreated patients with OVC receiving doses of 4.8–6.4 mg/kg (data cutoff: July 14, 2023), and a preliminary correlation analysis between CDH6 expression and efficacy

[a]4.8–8.0 mg/kg R-DXd dose cohorts were initially prioritized for dose expansion due to a favorable benefit/risk profile. As of October 2022, the 8.0 mg/kg cohort was closed due to a higher incidence of serious and Grade ≥3 TEAEs and lack of a favorable benefit/risk ratio (6/15 [40.0%] patients experienced serious and Grade ≥3 TEAEs).

ADC, antibody–drug conjugate; CBR, clinical benefit rate; CDH6, cadherin 6; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; ORR, objective response rate; OVC, ovarian cancer; PK, pharmacokinetics; Q3W, every 3 weeks; RDE, recommended doses for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SOC, standard-of-care.

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04707248. Accessed November 13, 2023; 2. Moore KN, et al. *Ann Oncol*. 2023;34 (Suppl. 2):Abstr 745MO.

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Baseline characteristics

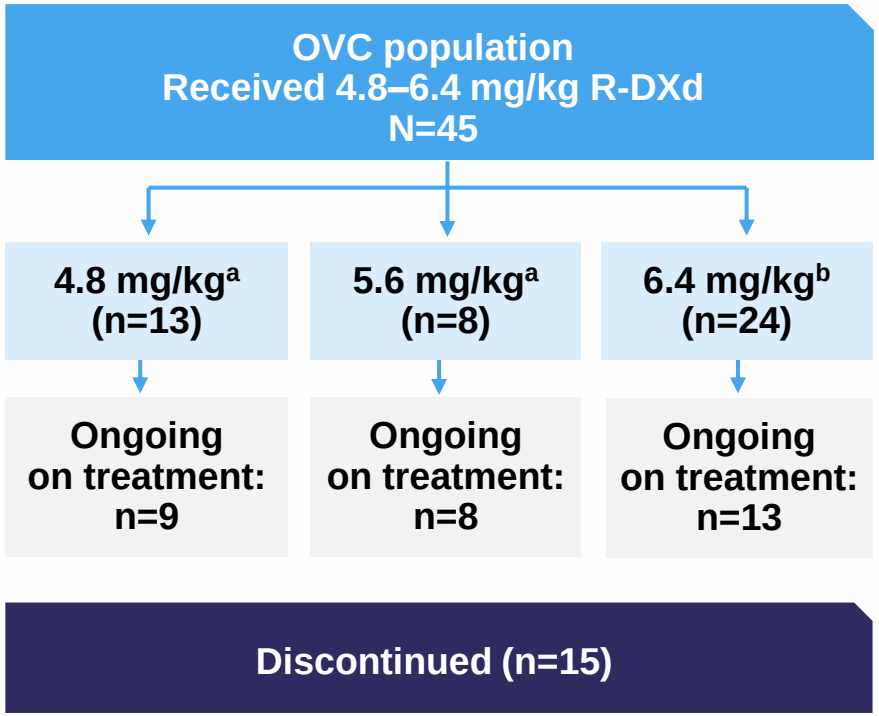
	4.8–6.4 mg/kg R-DXd[a] N=45
Age, years, median (range)	66 (42–82)
Age ≥65 years, n (%)	25 (55.6)
Country, n (%)	
United States	30 (66.7)
Japan	15 (33.3)
ECOG PS, n (%)	
0	18 (40.0)
1	27 (60.0)
Platinum-resistant disease,[b] n (%)	40 (88.9)
Number of prior systemic regimens, median (range)	4 (1–12)
Received prior systemic therapy, n (%)	
Bevacizumab	29 (64.4)
PARP inhibitor	29 (64.4)
Tumor CDH6 membrane positivity at any intensity %, median (range)	75 (0–99)

Data cutoff: July 14, 2023.

[a]Only patients treated with ≥1 dose of R-DXd 4.8–6.4 mg/kg were included in this analysis and defined as the safety analysis cohort. [b]Defined as tumor progression during or <6 months after completion of prior platinum therapy.

CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; PARP, poly (adenosine diphosphate [ADP]-ribose) polymerase.

Patient disposition



Treatment status	OVC population 4.8–6.4 mg/kg R-DXd N=45
Ongoing study treatment, n (%)	30 (66.7)
Discontinued from the study, n (%)	15 (33.3)
Progression[c]	8 (17.8)
Adverse events	5 (11.1)
Other	2 (4.4)[d]
Duration on study treatment, weeks, median (range)	17.9 (3.0–114.9)
Treatment duration, n (%)	
≥6 months	10 (22.2)
≥12 months	1 (2.2)

Data cutoff: July 14, 2023.

[a]Enrollment ongoing. [b]Enrollment completed. [c]Progressive disease per RECIST 1.1. [d]Death (n=1) and informed consent withdrawn (n=1). One patient died following CTCAE Grade 5 stroke not related to treatment.
CTCAE, Common Terminology Criteria for Adverse Events; OVC, ovarian cancer; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

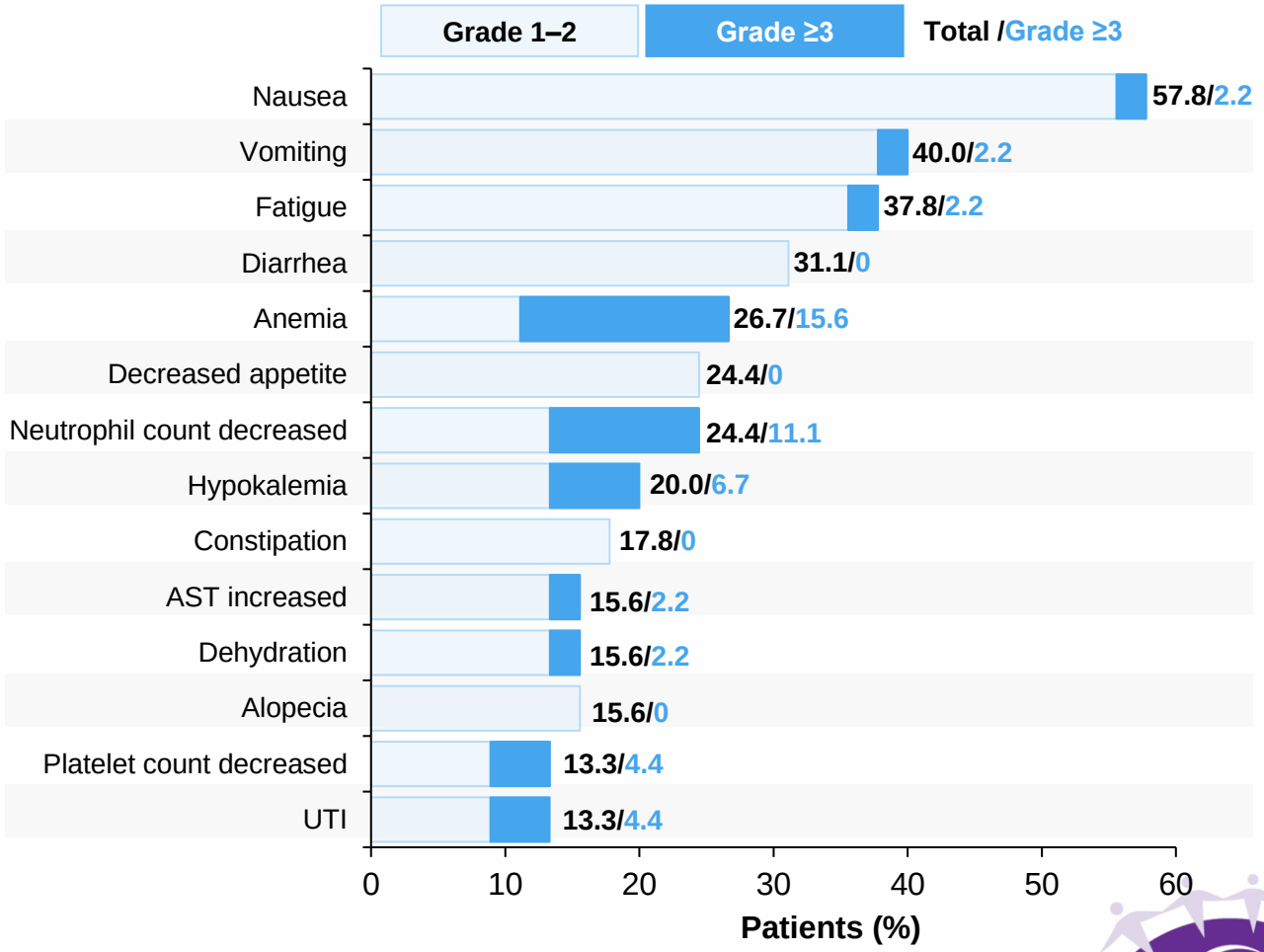
Safety summary: the AE profile of R-DXd appears to be manageable

Overall safety summary

	4.8–6.4 mg/kg R-DXd N=45
Any TEAE, n (%)	42 (93.3)
Grade ≥3	20 (44.4)
Treatment-related TEAE, n (%)	41 (91.1)
Grade ≥3	12 (26.7)
Grade 5	0
Any SAE, n (%)	11 (24.4)
Grade ≥3	10 (22.2)
Treatment-related SAE, n (%)	4 (8.9)
Grade ≥3	3 (6.7)
Grade 5	0
Dose modifications,[a] n (%)	
Drug discontinuation	5 (11.1)
Dose interruption	14 (31.1)
Dose reduction	7 (15.6)

- Drug-related ILD/pneumonitis was reported in 2 patients, who received a starting dose of 6.4 mg/kg. Both cases were Grade 2

Most common TEAEs (≥10%)



Data cutoff: July 14, 2023.

[a]Dose modifications associated with TEAE.

Patients received R-DXd at doses of 4.8 mg/kg (n=13), 5.4 mg/kg (n=8) and 6.4 mg/kg (n=24).

AE, adverse event; AST, aspartate aminotransferase; ILD, interstitial lung disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

Preliminary antitumor activity of R-DXd is promising in heavily pretreated patients with OVC receiving doses of 4.8–6.4 mg/kg

Confirmed ORR:[a]

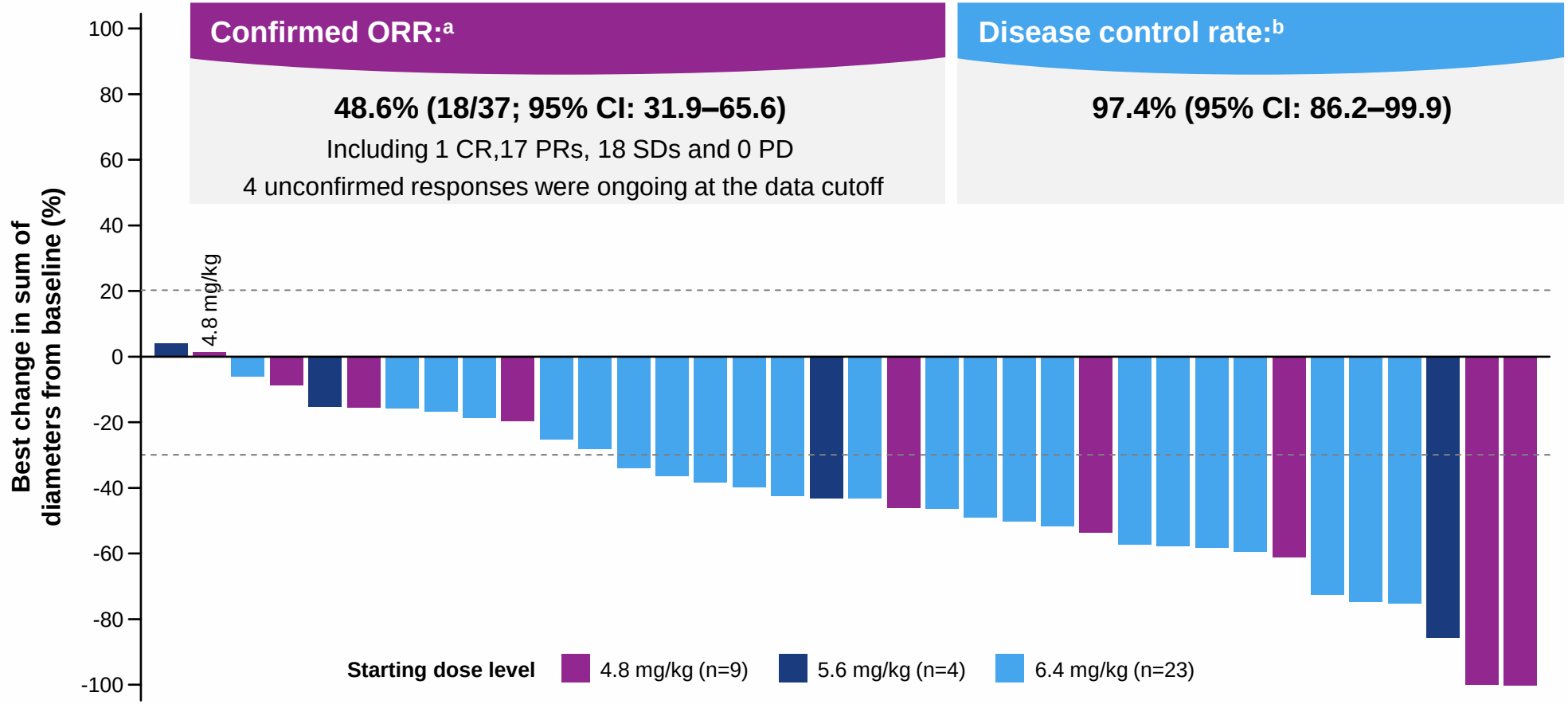
48.6% (18/37; 95% CI: 31.9–65.6)

Including 1 CR,17 PRs, 18 SDs and 0 PD

4 unconfirmed responses were ongoing at the data cutoff

Disease control rate:[b]

97.4% (95% CI: 86.2–99.9)

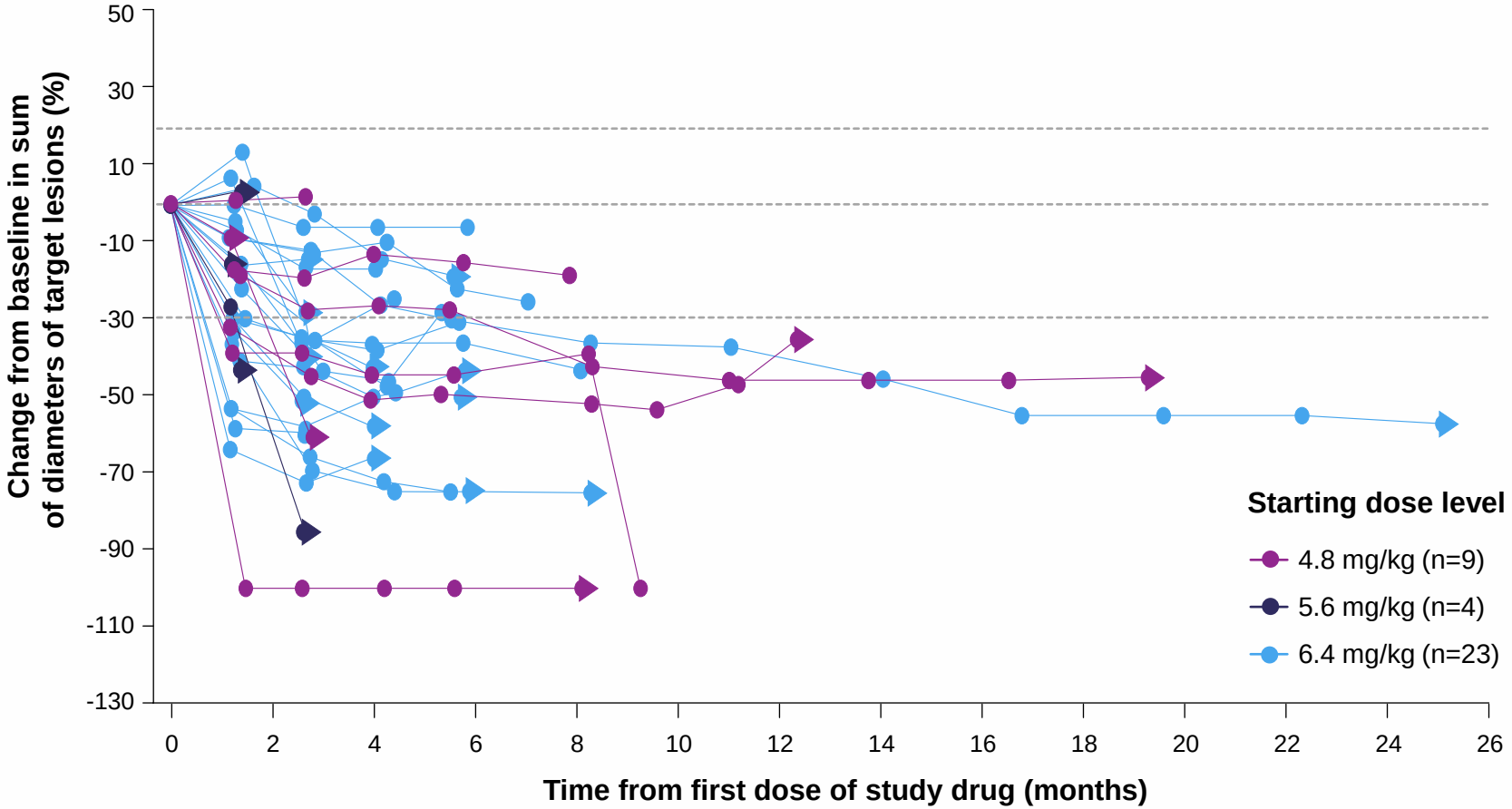


Data cutoff: July 14, 2023.

[a]The evaluable population (n=37) included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason prior to the first post-baseline tumor assessment with change from baseline in target tumor size assessed per RECIST 1.1; one patient with no target lesion at baseline was excluded from the ORR dataset. [b]CR + PR + SD (per RECIST 1.1) ≥5 weeks. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan were included in the waterfall plot: 7 patients had no post-baseline scans to date; 1 patient had no measurable lesions at baseline; 1 patient discontinued treatment and had no post-baseline scan.

CI, confidence interval; CR, complete response; OVC, ovarian cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Preliminary antitumor activity of R-DXd is promising in heavily pretreated patients with OVC receiving doses of 4.8–6.4 mg/kg



Median DOR:[a]

11.2 months (95% CI: 3.1–NE)

Median (range) FU: 6.7 months (1.4–16.8)

Median TTR:[a]

5.7 weeks (95% CI: 5.3–11.4)

Median PFS:[b]

8.1 months (95% CI: 5.3–NE)

Median (range) FU: 4.0 months (0–25.1)

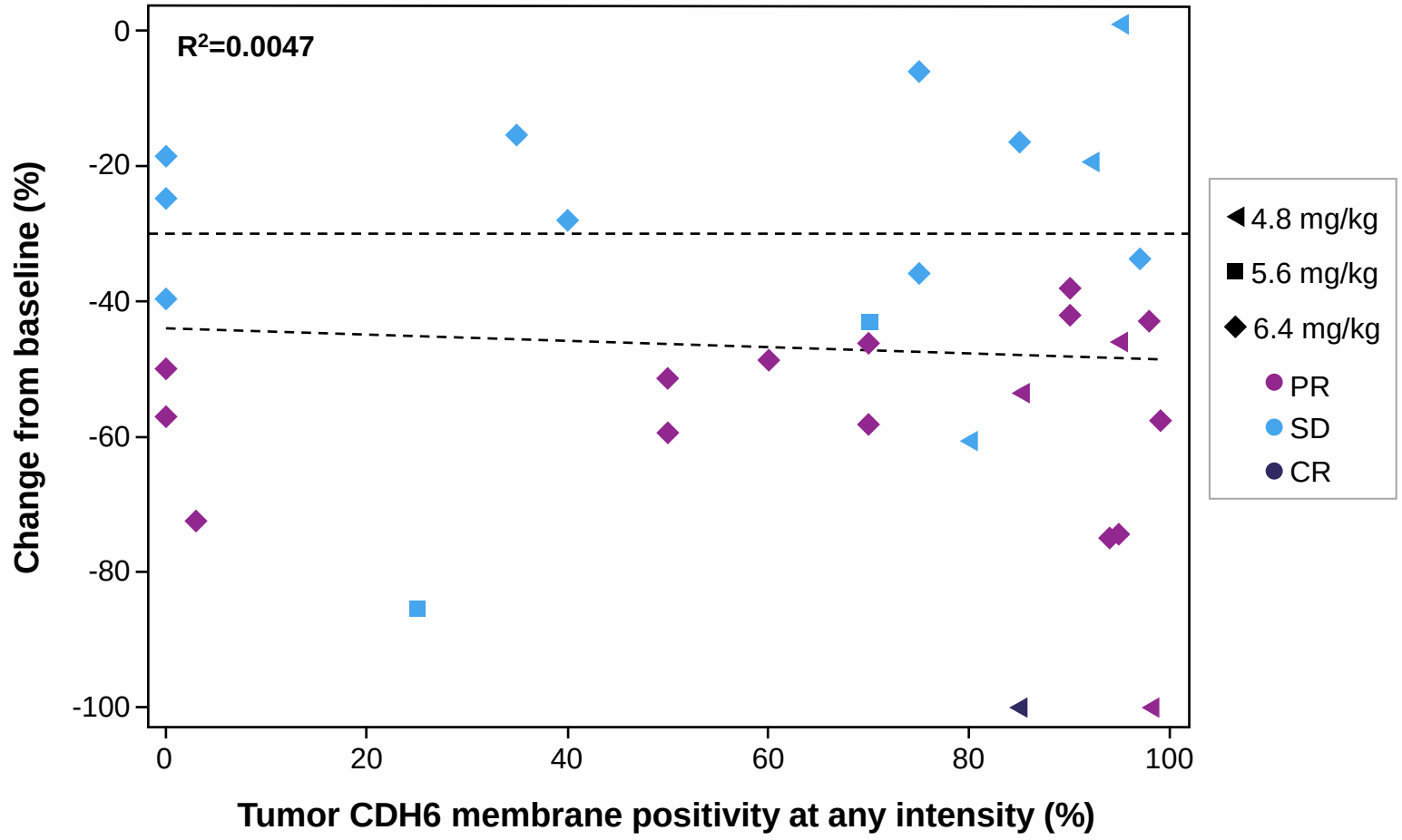
Data cutoff: July 14, 2023.

[a]The evaluable population included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason prior to the first post-baseline tumor assessment, with change from baseline in target tumor size assessed per RECIST 1.1. [b]Evaluable population, N=45. The evaluable population for PFS included patients who received ≥1 dose of study treatment. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan were included in the spider plot: 7 patients had no post-baseline scans to date; 1 patient had no measurable lesions at baseline; 1 patient discontinued treatment and had no post-baseline scan.

CI, confidence interval; DOR, duration of response; FU, follow-up; NE, not estimable; OVC, ovarian cancer; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TTR, time to response.

Preliminary biomarker assessment: Patients with a wide range of CDH6 expression show antitumor activity

CDH6 level by percent change from baseline for evaluable patients (n=32)[a,b]



Best overall response

CR: 1
PR: 17
SD: 14

Tumor samples from patients at baseline

Archival samples: 18
Freshly collected biopsies: 14

Data cutoff: July 14, 2023.

[a]Immunohistochemical data from patients at baseline (prior to R-DXd treatment). Doses included 4.8 mg/kg (n=7), 5.6 mg/kg (n=2) and 6.4 mg/kg (n=23). [b]One patient with no target lesion at baseline was excluded from the ORR dataset and 1 patient discontinued and did not have a post-baseline assessment.

BOR, best overall response; CDH6, cadherin 6; CR, complete response; ORR, objective response rate; PR partial response; SD, stable disease.

Conclusions

- R-DXd is the first CDH6-directed ADC to demonstrate promising efficacy in heavily pretreated patients with OVC who were not selected based on tumor CDH6 expression
  - In patients with OVC, the ORR achieved with R-DXd was 48.6% including one CR and 17 PRs
  - Median DOR was 11.2 months[a]
  - Median PFS was 8.1 months[b]
- Preliminary biomarker assessment indicates that antitumor activity is observed in tumors harboring a wide range of CDH6 expression, with no correlation between CDH6 expression and response has been observed to date. Correlation analyses will continue to be evaluated
- The safety profile of R-DXd appears to be manageable and comparable to the safety profiles of other DXd ADCs[1,2]
- These data support further clinical evaluation of R-DXd in patients with OVC
- A Phase 2/3 study of R-DXd in patients with platinum-resistant OVC, REJOICE-Ovarian01 (NCT06161025), has been initiated globally

Data cutoff: July 14, 2023.

[a]Median follow-up for DOR: 6.7 months (range, 1.4–16.8). [b]Median follow-up for PFS: 4.0 months (range, 0–25.1).

ADC, antibody–drug conjugate; CDH6, cadherin 6; CR, complete response; DOR, duration of response; DXd, exatecan derivative; ORR, objective response rate; OVC, ovarian cancer; PFS, progression-free survival; PR, partial response.

1. Guo Z, et al. *J Clin Pharm Ther*. 2022;47:1837–1844; 2. Jänne PA, et al. *Cancer Discov*. 2022;12:74–89.

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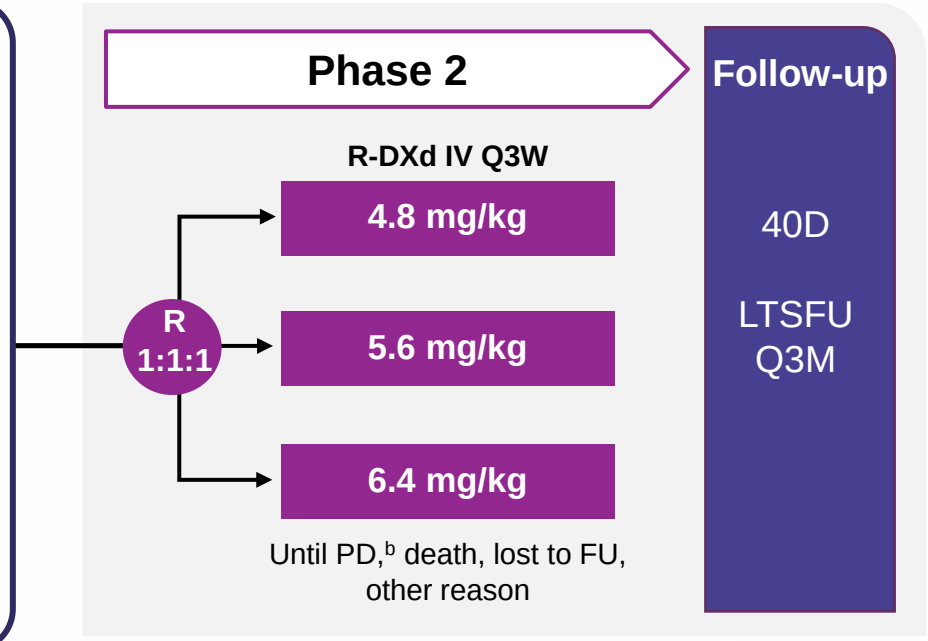
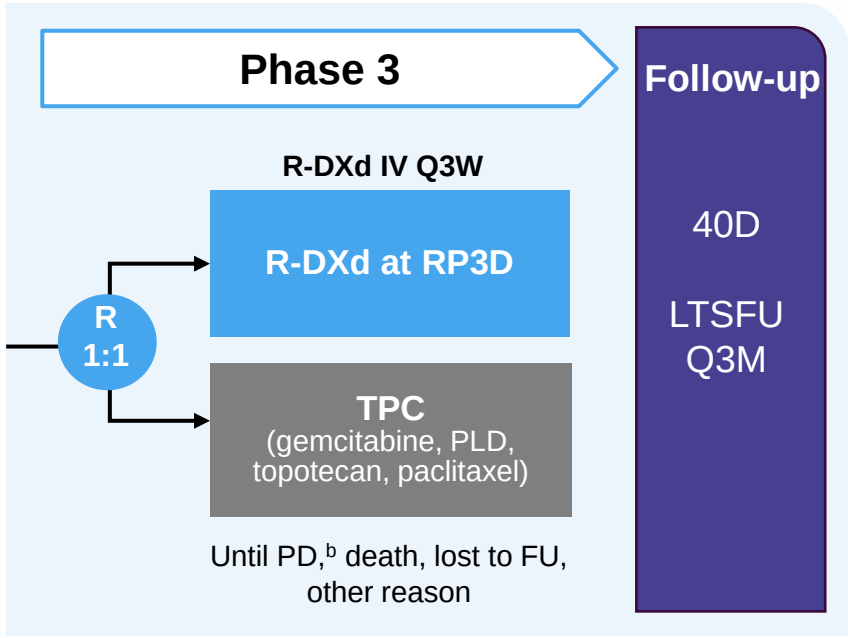
REJOICE-Ovarian01: Phase 2/3 randomized study of R-DXd in platinum-resistant OVC (NCT06161025)

Key eligibility criteria:

- High-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer
- 1−3 prior LOT (inc. bevacizumab)
- Platinum-resistant disease
- Prior MIRV if high FRα[a]
- ECOG PS 0−1
- No prior CDH6-targeting agents or ADCs with linked TOPO I inhibitor
- Patients with primary platinum-refractory disease are not eligible





Stratification:

- Number of prior LOT (1 vs 2/3)
- CDH6 expression (high vs low)
- TPC (paclitaxel vs others; *Ph 3 only*)

Primary endpoints:
- ORR per BICR[b]

Key secondary endpoints:
- ORR per inv[b]
- DOR

Primary endpoints:
- ORR per BICR[b]
- PFS per BICR[b]

Key secondary endpoints:
- OS
- QOL

[a]Unless ineligible, not approved or available locally. [b]Per RECIST 1.1. ADC, antibody–drug conjugate; BICR, blinded independent central review; CDH6, cadherin 6; D, days; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; FU, follow-up; inv, investigator; IV, intravenous; LOT, lines of therapy; LTSFU, long-term survival follow up; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; OVC, ovarian cancer; RP3D, recommended phase 3 dose; PD, progressive disease; PLD, pegylated liposomal doxorubicin; Q3M, every 3 months; QOL, quality of life; Q3W, every 3 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TEAEs, treatment-emergent adverse events; TOPO I, topoisomerase I; TPC, treatment of physician's choice.

ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06161025.

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