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Raludotatug deruxtecan (R-DXd) in patients with platinum-resistant ovarian cancer: Primary analysis of the Phase 2, dose-optimization part of the REJOICE-Ovarian01 study

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Declaration of interests

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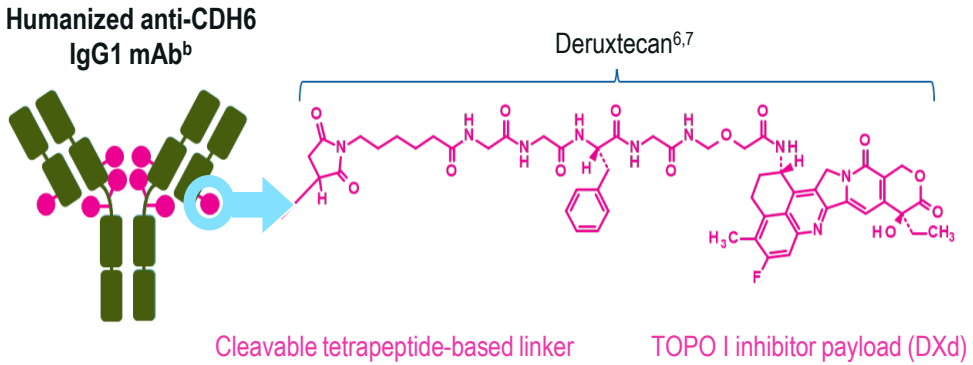
Background

- Platinum-resistant OC is associated with poor outcomes;[1,2] standard of care is single-agent non-platinum chemotherapy, which provides only a modest benefit; ORR is 10–15% and median OS is 10–12 months[1]
- Expression of CDH6 is observed in 65–85% of epithelial OC tumors[3–5]
- Raludotatug deruxtecan (R-DXd) is a CDH6-directed ADC comprising a humanized anti-CDH6 IgG1 mAb, covalently linked to a TOPO I inhibitor payload via a tetrapeptide-based cleavable linker[6,7]
- In the ongoing Phase 1 trial, R-DXd demonstrated a manageable safety profile and promising antitumor activity in 45 patients with heavily pretreated OC (89% had platinum-resistant OC)[8,a]
- R-DXd was administered at 4.8, 5.6, or 6.4 mg/kg IV Q3W. Across doses, 48.6% of patients achieved a confirmed objective response[8]

R-DXd was designed with 7 key attributes:



1	Payload mechanism of action: TOPO I inhibitor[7,c]
2	High potency of payload[6,7,c]
3	High drug-to-antibody ratio of ≈8[6,c]
4	Payload with short systemic half-life[7,c,d]
5	Plasma-stable linker-payload[6,7,c]
6	Tumor-selective cleavable linker[6,7,c]
7	Bystander antitumor effect[6,c]

[a]Defined as TFIp <6 months. [b]Image is for illustrative purposes only; actual drug positions may vary. [c]The clinical relevance of these features is under investigation. [d]Based on animal data.
ADC, antibody–drug conjugate; CDH6, cadherin 6; DXd, exatecan derivative; IgG1, immunoglobulin G1; IV, intravenous; mAb, monoclonal antibody; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; Q3W, every 3 weeks; TFIp, treatment-free interval from last platinum dose; TOPO I, topoisomerase I.
1. González-Martín A, et al. *Ann Oncol.* 2023;34:833–848. 2. Richardson DL, et al. *JAMA Oncol.* 2023;9:851–859; 3. Bartolomé RA, et al. *Mol Oncol.* 2021;15:1849–1865; 4. Shintani D, et al. Poster presentation at the European Society for Medical Oncology congress. October 20–24, 2023; Madrid, Spain. Presentation 777P. 5. Suzuki H, et al Poster presentation at the European Society for Medical Oncology congress. October 17–21, 2021; Virtual. Presentation #919. 6. Suzuki H, et al. *Mol Cancer Ther*. 2024;23:257–271.
7. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185. 8. Moore KN, et al. Oral presentation at the Society of Gynecologic Oncology 2024 Annual Meeting on Women's Cancer. March 16–18, 2024; San Diego, CA, USA.

REJOICE-Ovarian01 study design

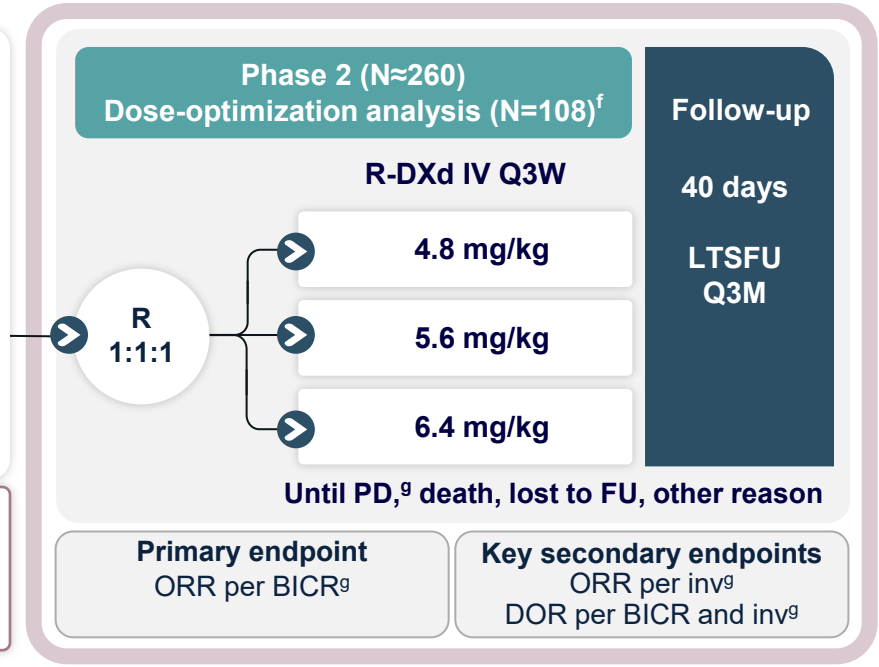
A Phase 2/3 multicenter, randomized study of R-DXd in patients with platinum-resistant, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer[1,2]

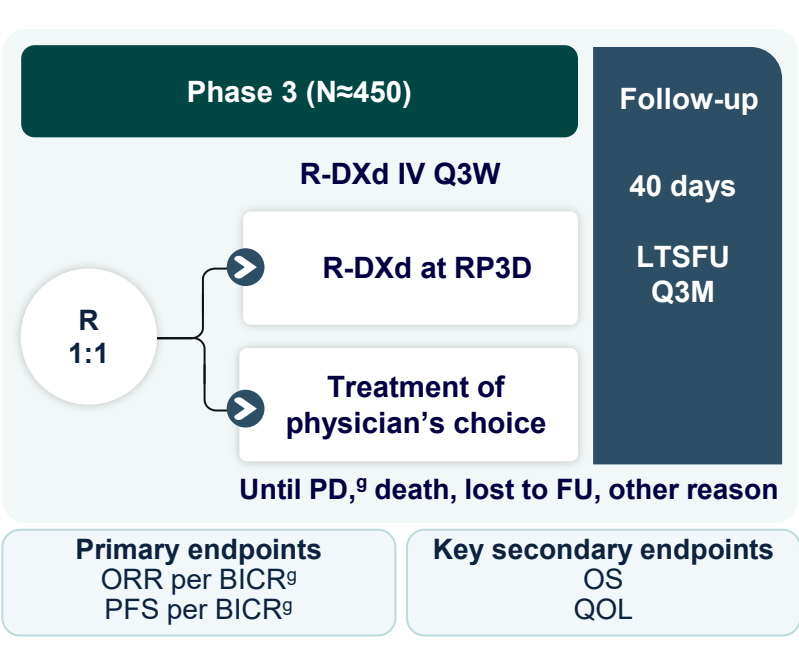
Key eligibility criteria

- High-grade serous or high-grade endometrioid ovarian, primary peritoneal, or fallopian tube cancer[a]
- 1−3 prior LOT, including bevacizumab[b]
- Platinum-resistant disease[c] (primary platinum-refractory disease is exclusionary)
- Prior mirvetuximab soravtansine[d] (for tumors with high FRα expression)
- ECOG PS 0−1
- No prior CDH6-targeting agents or ADCs with a linked DXd
- No selection by tumor CDH6 expression

Stratification factors

- Number of prior LOT (1 vs 2–3)
- CDH6 membrane expression by IHC (≥75% vs <75%)[e]
- TPC (paclitaxel vs other; Phase 3 only)





We present the primary analysis from the dose-optimization part of the Phase 2/3 REJOICE-Ovarian01 study, in 107 patients with platinum-resistant OC who had a follow-up of ≥18 weeks or discontinued treatment

[a]Patients must have ≥1 lesion not previously irradiated and amenable to biopsy; must consent 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]Unless ineligible. [c]Defined as 1 line of prior platinum therapy (≥4 cycles with best response of not PD) with radiologically documented progression >90 and ≤180 days following last dose of platinum therapy, or 2–3 lines of prior platinum therapy (≥2 cycles) with radiologically documented progression ≤180 days following the last dose of platinum. [d]Unless ineligible, not approved, or not available locally. [e]A stratification cutoff of 75% tumor cell membrane staining at any intensity was selected based on the median observed percentage tumor cell membrane staining (at any intensity) in the Phase 1 study population.[3] [f]Overall, 108 patients were randomized to receive R-DXd. One patient did not receive treatment, so 107 patients were treated and were included in the safety analysis set. [g]Per RECIST 1.1.
ADC, antibody–drug conjugate; BICR, blinded independent central review; CDH6, cadherin 6; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; FU, follow-up; IHC, immunohistochemistry; IV, intravenous; inv, investigator; LOT, lines of therapy; LTSFU, long-term survival follow up; ORR, objective response rate; OS, overall survival; RP3D, recommended phase 3 dose; PD, progressive disease; Q3M, every 3 months; Q3W, every 3 weeks; QOL, quality of life; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TPC, treatment of physician's choice.
1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06161025. Accessed October 7, 2025. 2. Ray-Coquard I, et al. Poster presentation at American Society of Clinical Oncology 2024; May 31–June 4; Chicago, IL, USA. Poster TPS5625. 3. Moore KN, et al. Oral presentation at the Society of Gynecologic Oncology 2024 Annual Meeting on Women's Cancer. March 16–18, 2024; San Diego, CA, USA.

Baseline characteristics and prior systemic therapies

Patient and tumor characteristics	R-DXd 4.8–6.4 mg/kg[a] N=107
Age, median (range), years	60 (34–81)
Age >70 years, n (%)	17 (15.9)
Region, n (%)	
Asia	45 (42.1)
Europe	61 (57.0)
Australia	1 (0.9)
ECOG PS, n (%)	
0	61 (57.0)
1	46 (43.0)
Cancer type, n (%)	
Ovarian	91 (85.0)
Peritoneal	4 (3.7)
Fallopian tube	12 (11.2)
Tumor FIGO stage at initial diagnosis, n (%)	
I–II	11 (10.3)
III	53 (49.5)
IV	39 (36.4)
Unknown	4 (3.7)

Tumor characteristics and prior therapies	R-DXd 4.8–6.4 mg/kg[a] N=107
Number of prior lines of systemic therapy, n (%)	
1	10 (9.3)
2	42 (39.3)
3	55 (51.4)
Received prior therapy, n (%)	
Bevacizumab	89 (83.2)
PARP inhibitor	75 (70.1)
Mirvetuximab soravtansine	3 (2.8)
Last platinum-free interval, n (%)	
<3 months	47 (43.9)
3–6 months	60 (56.1)
Tumor CDH6 membrane positivity at any intensity at baseline,[b] n (%)	n=101[c]
Any positivity	**95 (94.1)**
<75% positive	41 (40.6)
≥75% positive[d]	60 (59.4)

Data cutoff: February 26, 2025. Study was initiated on February 27, 2024.

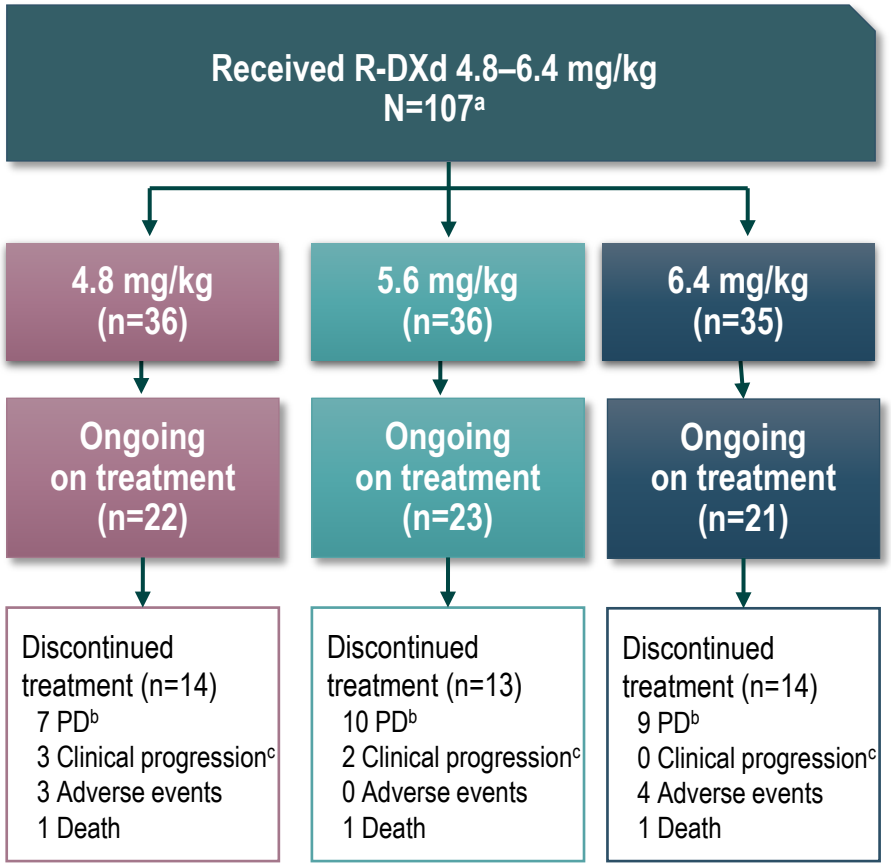
[a]Only patients treated with ≥1 dose were included in this analysis and made up the safety analysis cohort. [b]Tumor CDH6 positivity was defined as the percentage of viable tumor cells positive for CDH6 membrane staining at any intensity (1+/2+/3+) determined by CDH6 clinical trial assay (SP450; Roche Diagnostics). [c]Six tumor samples were of insufficient quality to determine CDH6 membrane positivity. [d]A stratification cutoff of 75% tumor cell membrane staining at any intensity was selected based on the median observed percentage tumor cell membrane staining (at any intensity) in the Phase 1 study population.[1]

CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; PARP, poly (adenosine diphosphate [ADP]-ribose) polymerase; PD, progressive disease.

1. Moore KN, et al. Oral presentation at the Society of Gynecologic Oncology 2024 Annual Meeting on Women's Cancer. March 16–18, 2024; San Diego, CA, USA.

Patient disposition and treatment exposure

Data cutoff: February 26, 2025



	R-DXd 4.8–6.4 mg/kg N=107[a]
Ongoing on study treatment, n (%)	66 (61.7)
Discontinued from study treatment, n (%)	41 (38.3)
PD[b]	26 (24.3)
Adverse events	7 (6.5)
Death	3 (2.8)
Clinical progression[c]	5 (4.7)
Duration on study treatment, median (range), months	5.5 (0.7–9.7)
Relative dose intensity,[d] %, median (range)	97.3 (62.4–108.0)

Patients included in the dose-optimization analysis had completed ≥18 weeks of follow-up or discontinued treatment due to an adverse event, PD or death

The median follow-up for 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg cohorts was 5.6 months (95% CI, 4.7–6.3), 5.6 months (95% CI, 4.6–5.8), and 5.2 months (95% CI, 4.9–5.8), respectively.

[a]Only patients treated with ≥1 dose were included in this analysis and made up the safety analysis cohort. [b]Per RECIST 1.1. [c]Clinical progression was defined as definitive clinical signs of PD but the most recent radiographic assessment did not meet the criteria for PD according to RECIST 1.1. [d]Relative dose intensity was defined as the administered dose intensity (mg/kg/cycle) expressed as a percentage of the planned dose intensity (mg/kg/cycle).

CI, confidence interval; PD, progressive disease; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1.

R-DXd monotherapy demonstrated promising antitumor activity at all doses in patients with platinum-resistant OC

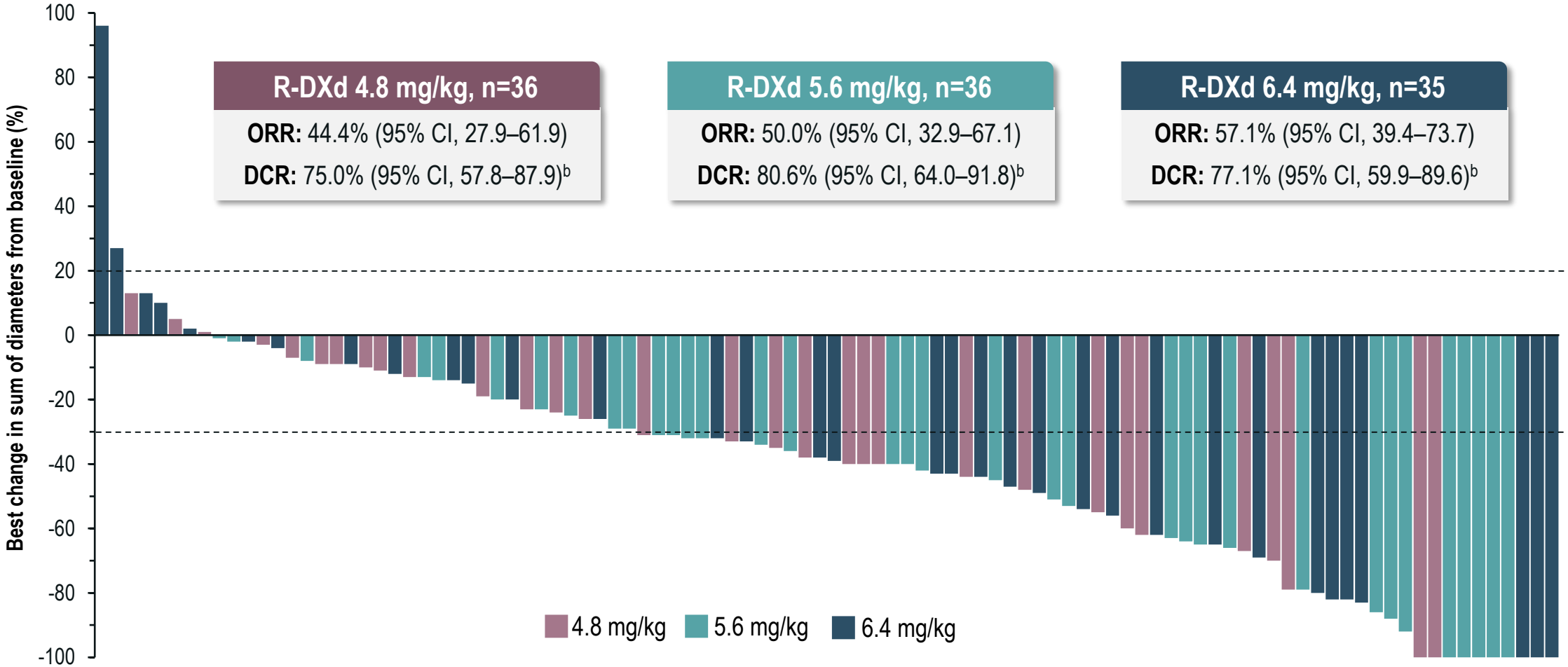
Confirmed response by BICR[a]	R-DXd 4.8 mg/kg n=36	R-DXd 5.6 mg/kg n=36	R-DXd 6.4 mg/kg n=35	R-DXd 4.8–6.4 mg/kg N=107
ORR, % (95% CI)	44.4 (27.9–61.9)	50.0 (32.9–67.1)	57.1 (39.4–73.7)	50.5 (40.6–60.3)
BOR,[b] n (%)				
CR	1 (2.8)	2 (5.6)	0	3 (2.8)
PR	15 (41.7)	16 (44.4)	20 (57.1)	51 (47.7)
SD	17 (47.2)	15 (41.7)	10 (28.6)	42 (39.3)
PD	2 (5.6)	2 (5.6)	4 (11.4)	8 (7.5)
Not evaluable	1 (2.8)[c]	1 (2.8)[d]	1 (2.9)[c]	3 (2.8)
DCR,[e] % (95% CI)	75.0 (57.8–87.9)	80.6 (64.0–91.8)	77.1 (59.9–89.6)	77.6 (68.5–85.1)
TTR, median (range), weeks	7.1 (5.4–18.7)	6.6 (5.1–18.3)	7.2 (5.3–19.1)	7.1 (5.1–19.1)

Data cutoff: February 26, 2025. The median follow-up for 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg cohorts was 5.6 months (95% CI, 4.7–6.3), 5.6 months (95% CI, 4.6–5.8), and 5.2 months (95% CI, 4.9–5.8), respectively.

[a]Per RECIST 1.1. [b]BOR 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]Patient had no baseline tumor assessment by BICR. [d]Patient had no adequate post-baseline tumor assessment by BICR. [e]DCR was defined as percentage of patients with BOR of CR, PR, or SD (per RECIST 1.1).

BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; OC, ovarian cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; TTR, time to response.

Clinically meaningful tumor responses were seen irrespective of dose[a]

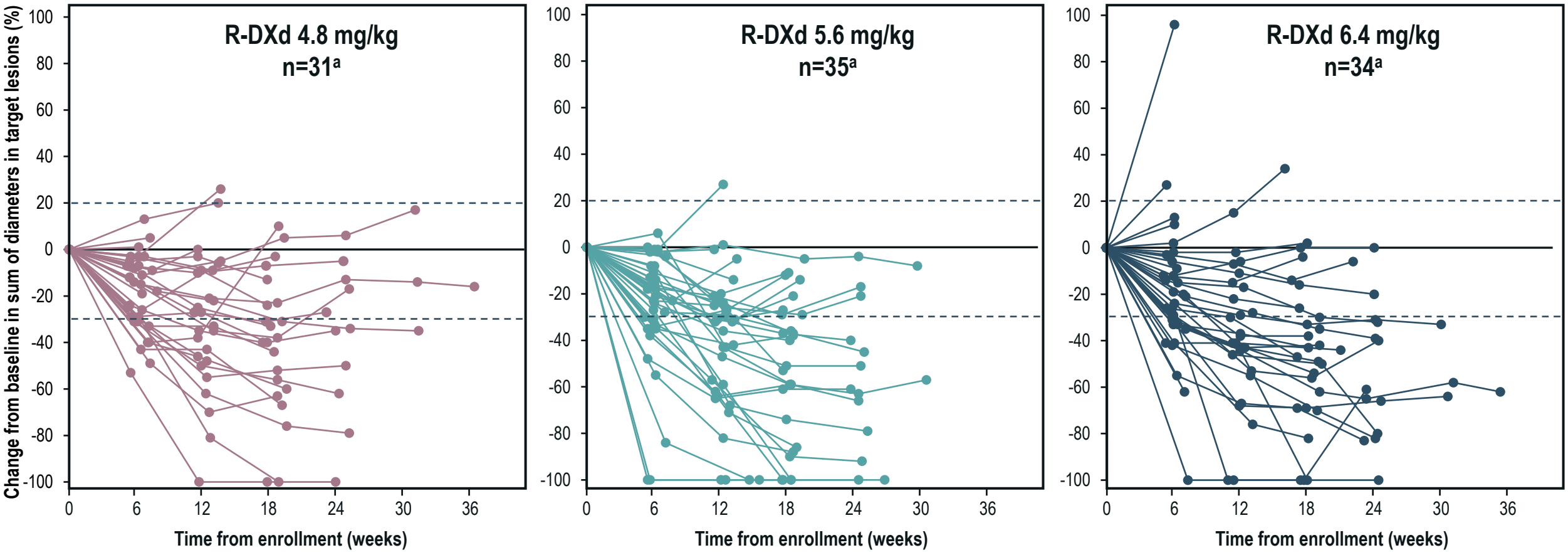


Data cutoff: February 26, 2025. The median follow-up for 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg cohorts was 5.6 months (95% CI, 4.7–6.3), 5.6 months (95% CI, 4.6–5.8), and 5.2 months (95% CI, 4.9–5.8), respectively.

[a]Antitumor response assessed by BICR per RECIST 1.1. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan, both by BICR, were included in the waterfall plot (n=100). Six patients (R-DXd 4.8 mg/kg [n=5]; 6.4 mg/kg [n=1]) did not have measurable disease at baseline and one patient (R-DXd 5.6 mg/kg) had no adequate post-baseline tumor assessment. [b]DCR was defined as percentage of patients with BOR of CR, PR, or SD (per RECIST 1.1).

BICR, blinded independent central review; CI, confidence interval; DCR, disease control rate; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1.

R-DXd treatment was associated with rapid responses at all doses



Median TTR:[b] 7.1 weeks (range, 5.4–18.7)

Median TTR:[b] 6.6 weeks (range, 5.1–18.3)

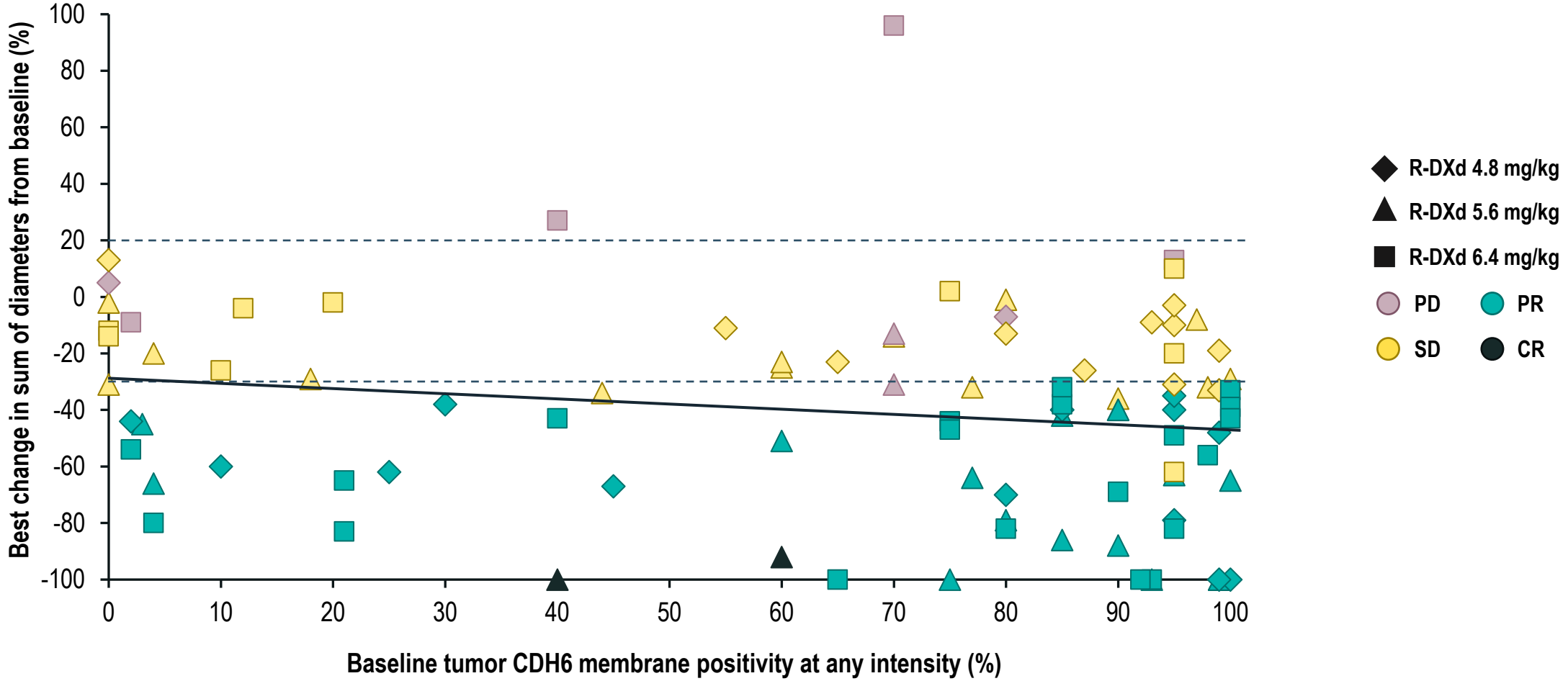
Median TTR:[b] 7.2 weeks (range, 5.3–19.1)

Data cutoff: February 26, 2025. The median follow-up for 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg cohorts was 5.6 months (95% CI, 4.7–6.3), 5.6 months (95% CI, 4.6–5.8), and 5.2 months (95% CI, 4.9–5.8), respectively.

[a]Antitumor response assessed by BICR per RECIST 1.1. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan, both by BICR, were included in the spider plots (n=100). Six patients (R-DXd 4.8 mg/kg [n=5]; 6.4 mg/kg [n=1]) did not have measurable disease at baseline and one patient (R-DXd 5.6 mg/kg) had no adequate post-baseline tumor assessment. [b]By BICR per RECIST 1.1. Overall median TTR was 7.1 weeks (range, 5.1–19.1).

BICR, blinded independent central review; CI, confidence interval; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TTR, time to response.

Clinically meaningful tumor responses were observed across a range of CDH6 expression levels



Data cutoff: February 26, 2025. The median follow-up for 4.8-mg/kg, 5.6-mg/kg, and 6.4-mg/kg cohorts was 5.6 months (95% CI, 4.7–6.3), 5.6 months (95% CI, 4.6–5.8), and 5.2 months (95% CI, 4.9–5.8), respectively.
Patients with available baseline tumor CDH6 expression data, who had measurable disease at baseline and ≥1 post-baseline tumor scan (assessed by BICR), were included in the scatter plot (n=94). Tumor CDH6 positivity was defined as the percentage of viable tumor cells positive for CDH6 membrane staining at any intensity (1+/2+/3+) determined by CDH6 clinical trial assay (SP450; Roche Diagnostics).
BICR, blinded independent central review; CDH6, cadherin 6; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease.

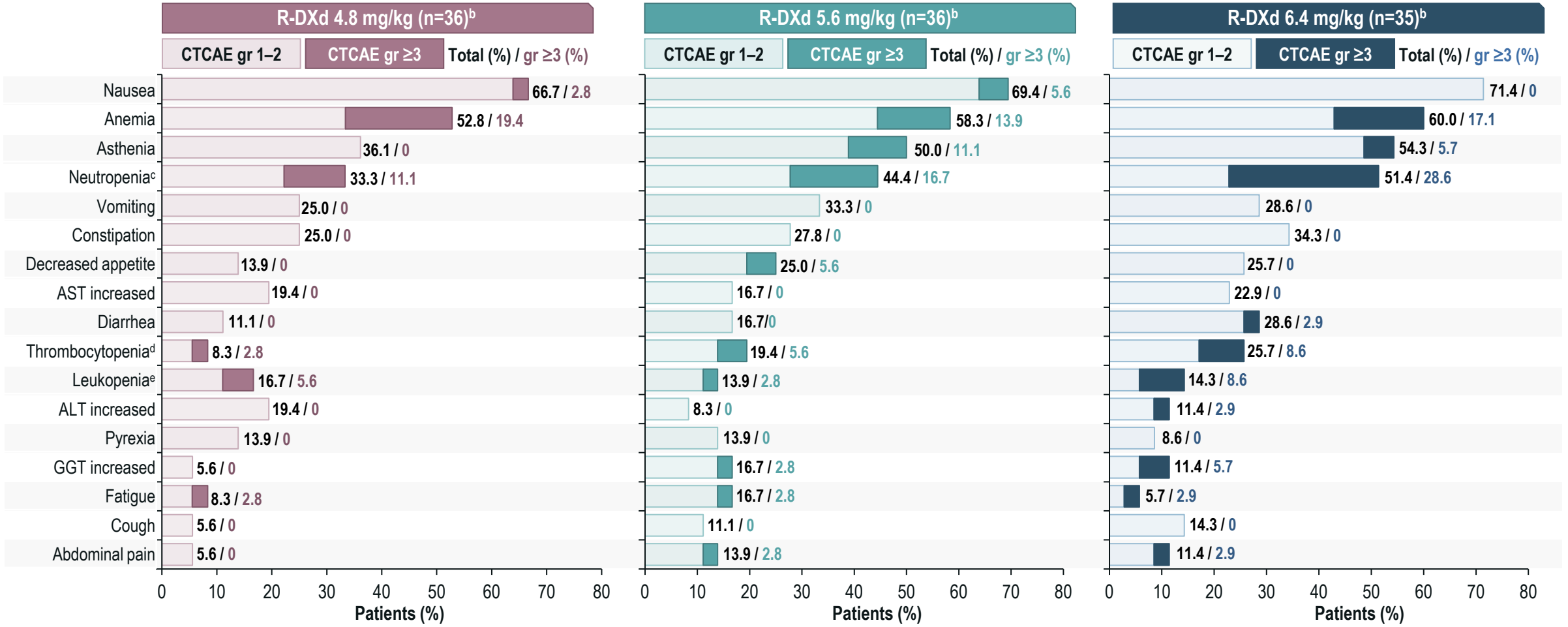
The 5.6-mg/kg dose provided the optimal benefit–risk profile

	R-DXd 4.8 mg/kg n=36	R-DXd 5.6 mg/kg n=36	R-DXd 6.4 mg/kg n=35	R-DXd 4.8–6.4 mg/kg N=107
Any TEAE, n (%)	35 (97.2)	36 (100)	35 (100)	106 (99.1)
Grade ≥3	16 (44.4)	20 (55.6)	20 (57.1)	56 (52.3)
Any treatment-related TEAE, n (%)	32 (88.9)	34 (94.4)	34 (97.1)	100 (93.5)
Grade ≥3	10 (27.8)	11 (30.6)	17 (48.6)	38 (35.5)
Grade 5	0	0	0	0
Any SAE, n (%)	14 (38.9)	12 (33.3)	14 (40.0)	40 (37.4)
Grade ≥3	13 (36.1)	10 (27.8)	11 (31.4)	34 (31.8)
Grade 5	3 (8.3)[a]	2 (5.6)[b]	1 (2.9)[c]	6 (5.6)
Any treatment-related SAE, n (%)	3 (8.3)	3 (8.3)	7 (20.0)	13 (12.1)
Grade ≥3	3 (8.3)	3 (8.3)	5 (14.3)	11 (10.3)
Grade 5	0	0	0	0
Dose modifications associated with treatment-related TEAEs,[d] n (%)				
Drug discontinuation	3 (8.3)	0	3 (8.6)	6 (5.6)
Dose reduction	5 (13.9)	4 (11.1)	11 (31.4)	20 (18.7)
Dose delay	8 (22.2)	7 (19.4)	10 (28.6)	25 (23.4)
ILD/pneumonitis adjudicated as treatment related,[e] n (%)				
Any grade	1 (2.8)	1 (2.8)	2 (5.7)	4 (3.7)
Grade ≥3	1 (2.8)[f]	0	0	1 (0.9)
Grade 5	0	0	0	0

The safety profile of the 4.8 and 5.6 mg/kg cohorts were similar.
Treatment-related TEAEs occurred more frequently in the 6.4 mg/kg cohort (vs 4.8 and 5.6 mg/kg cohorts)

Data cutoff: February 26, 2025.
Reported safety events are defined using MedDRA Preferred Terms and CTCAE criteria.
[a]Grade 5 events were hepatic failure, ovarian cancer, and malignant neoplasm progression. [b]Grade 5 events were ovarian cancer and aspiration. [c]Grade 5 event was influenza infection. [d]Dose modifications associated with treatment-related TEAEs defined as: dose discontinuation, no subsequent administration of R-DXd; dose reduction, R-DXd dose was reduced at next administration; dose delay, study drug was not administered at the next scheduled cycle but was administered at a later date. [e]ILD/pneumonitis events were adjudicated by an independent ILD adjudication committee. [f]ILD/pneumonitis Grade ≥3 event (adjudicated as treatment related) was grade 3.
CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Most common TEAEs (≥10% of overall population)[a]



Nausea, anemia, asthenia and neutropenia were the most common TEAEs across all doses

Data cutoff: February 26, 2025.

[a]TEAEs reported in ≥10% of all patients who received R-DXd 4.8–6.4 mg/kg. Reported safety events are defined by MedDRA preferred terminology. [b]Grade 4 hematologic TEAEs reported at 4.8 mg/kg: neutropenia[c] (n=2), thrombocytopenia[d] (n=1); at 5.6 mg/kg: neutropenia[c] (n=2), thrombocytopenia[d] (n=1), leukopenia[e] (n=1); at 6.4 mg/kg: neutropenia[c] (n=3), thrombocytopenia[d] (n=1), lymphopenia (n=1). No grade 5 hematologic TEAEs were reported at any dose. Grade 3 febrile neutropenia was reported in 2 patients, one each in the R-DXd 5.6 and 6.4 mg/kg cohorts. [c]Neutropenia was defined as the grouped incidence of events reported under the preferred terms '*neutropenia*' and '*neutrophil count decreased*', with a maximum of one event per patient per grouped preferred term. [d]Thrombocytopenia was defined as the grouped incidence of events reported under the preferred terms '*thrombocytopenia*' and '*platelet count decreased*', with a maximum of one event per patient per grouped preferred term. [e]Leukopenia was defined as the preferred term '*white blood cell count decreased.*'

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma-glutamyltransferase; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Conclusions

- In this dose-optimization analysis, 107 patients with platinum-resistant OC received R-DXd at doses of 4.8–6.4 mg/kg
  - In total, 94.1% of tumors demonstrated positive CDH6 membrane expression by IHC
- After a minimum of 18 weeks of follow-up, R-DXd demonstrated promising efficacy across all evaluated doses:
  - The confirmed ORR was 50.5%, including three CRs (2.8%)
  - Clinically meaningful tumor responses were observed across a range of CDH6 expression levels
  - Further follow-up is required to obtain mature data on DOR and PFS
- The safety profile of R-DXd appears manageable and is consistent with the safety findings reported in the Phase 1 study[1,2]
  - One adjudicated treatment-related Grade ≥3 ILD event (Grade 3) was reported in this analysis
- Based on these efficacy and safety results, as well as PK and ER data,[3] R-DXd 5.6 mg/kg provided a positive benefit–risk profile and was considered the optimal dose
- The Phase 3 part of the REJOICE-Ovarian01 study will evaluate R-DXd 5.6 mg/kg versus treatment of physician's choice in patients with platinum-resistant OC

Data cutoff: February 26, 2025.

CR, complete response; DOR, duration of response; ER, exposure–response; IHC. immunohistochemistry; ORR, objective response rate; OC, ovarian cancer; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response.

1. Moore KN, et al. Oral presentation at the European Society for Medical Oncology congress. October 20–24, 2023; Madrid, Spain. Presentation 745MO. 2. Moore KN, et al. Oral presentation at the Society of Gynecologic Oncology 2024 Annual Meeting on Women's Cancer. March 16–18, 2024; San Diego, CA, USA. 3. Daiichi Sankyo, Inc. Data on file.

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