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Raludotatug deruxtecan (R-DXd) monotherapy in patients with heavily pretreated platinum-sensitive ovarian cancer: Subgroup analysis of a Phase 1 study

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Declaration of interests

Kathleen Moore

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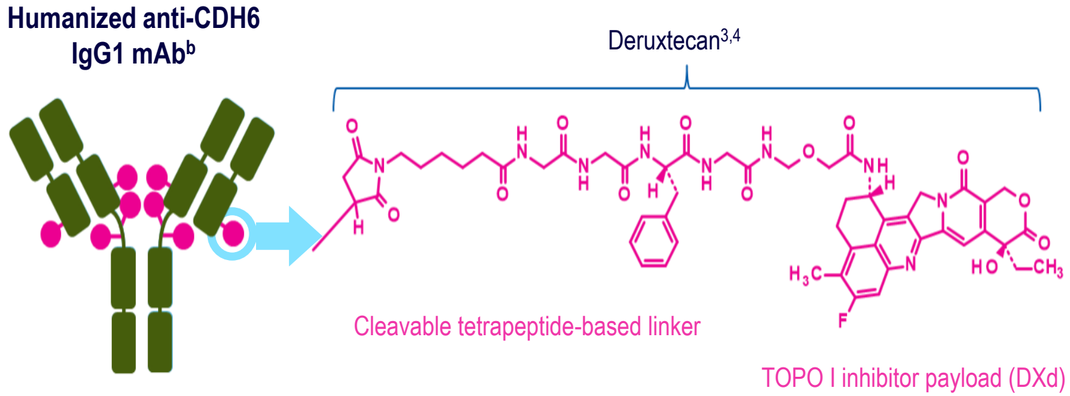
Background

- After surgery and/or first-line chemotherapy, ~70 to 80% of patients with advanced epithelial OC will experience disease relapse within 3 years[1,2]
- Raludotatug deruxtecan (R-DXd) is an ADC comprising a humanized anti-CDH6 IgG1 mAb covalently linked to a TOPO I inhibitor payload via a tetrapeptide-based cleavable linker[3,4]
- Expression of CDH6 is observed in 65 to 85% of patients with OC[5–7]
- In this ongoing Phase 1 trial (NCT04707248) in patients with pretreated OC not selected based on tumor CDH6 expression, R-DXd doses of 4.8, 5.6, or 6.4 mg/kg demonstrated a manageable safety profile and promising activity in a preliminary analysis; 48.6% of patients achieved a confirmed objective response[a]; 89% had platinum-resistant disease (defined as TFIp <6 months)[8,9]
- We present a subgroup analysis from this Phase 1 trial in patients with platinum-sensitive OC (PSOC; defined as TFIp ≥6 months)

R-DXd has 7 key attributes



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

[a]Confirmed objective response rate by investigator per RECIST 1.1. [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; IgG1, immunoglobulin G1; mAb, monoclonal antibody; OC, ovarian cancer; PSOC, platinum-sensitive OC; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TFIp, treatment-free interval from last platinum dose; TOPO I, topoisomerase I.

1. Pignata S, et al. *Ann Oncol*. 2017;9:28:viii51–viii56. 2. González-Martín A, et al. *Ann Oncol.* 2023;34:833–848. 3. Suzuki H, et al. *Mol Cancer Ther*. 2024;23:257–271. 4. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185. 5. Bartolomé RA, et al. *Mol Oncol*. 2021;15:1849–1865. 6. Shintani D, et al. Poster presentation at the European Society for Medical Oncology congress. October 20–24, 2023; Madrid, Spain. Presentation 777P. 7. Suzuki H, et al Poster presentation at the European Society for Medical Oncology congress. October 10–16, 2021; Virtual. Presentation #919. 8. Moore KN, et al. Oral presentation at the European Society for Medical Oncology congress. October 20–24, 2023; Madrid, Spain. Presentation 745MO. 9. 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.

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

Part A | Dose escalation: R-DXd IV Q3W

Enrollment criteria:

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

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

OC cohort: 4.8 mg/kg n=40	OC cohort: 5.6 mg/kg n=42	OC cohort: 6.4 mg/kg n=40	OC cohort: 8.0 mg/kg n=7

Key primary objectives:

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

Key secondary objectives:

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

18 patients with PSOC were enrolled across 3 dose levels (4.8, 5.6, and 6.4 mg/kg)

Data cutoff: January 10, 2025.

[a]The 4.8- to 8.0-mg/kg R-DXd dose cohorts were initially prioritized for dose expansion due to a favorable risk–benefit 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 risk–benefit 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; OC, ovarian cancer; ORR, objective response rate; PSOC, platinum-sensitive OC; Q3W, every 3 weeks; RDE, recommended dose for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SOC, standard-of-care; TEAE, treatment-emergent adverse event; TOPO I, topoisomerase I.

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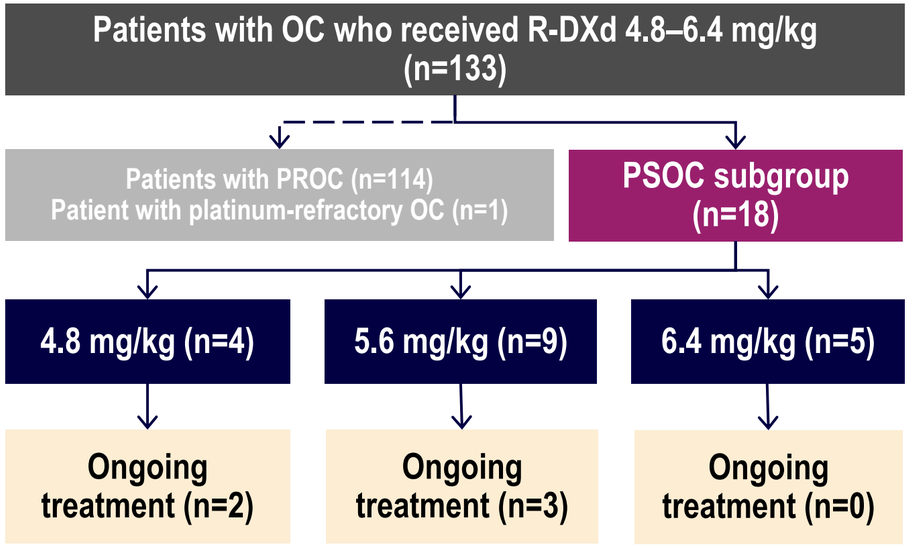
Patient baseline characteristics and disposition

	PSOC subgroup 4.8–6.4 mg/kg[a] n=18
Age, years, median (range)	65 (50–81)
Age ≥65 years, n (%)	9 (50.0)
Country, n (%)	
United States	14 (77.8)
Japan	4 (22.2)
ECOG PS, n (%)	
0	4 (22.2)
1	14 (77.8)
Number of prior systemic regimens, median (range)	4 (2–6)
Received prior bevacizumab treatment, n (%)	14 (77.8)
Received prior PARP inhibitor treatment, n (%)	15 (83.3)
Disease progression on PARP inhibitor,[b] n/N (%)	12/15 (80.0)
Tumor CDH6 membrane positivity,[c] median % (range)	67.5 (20–100)



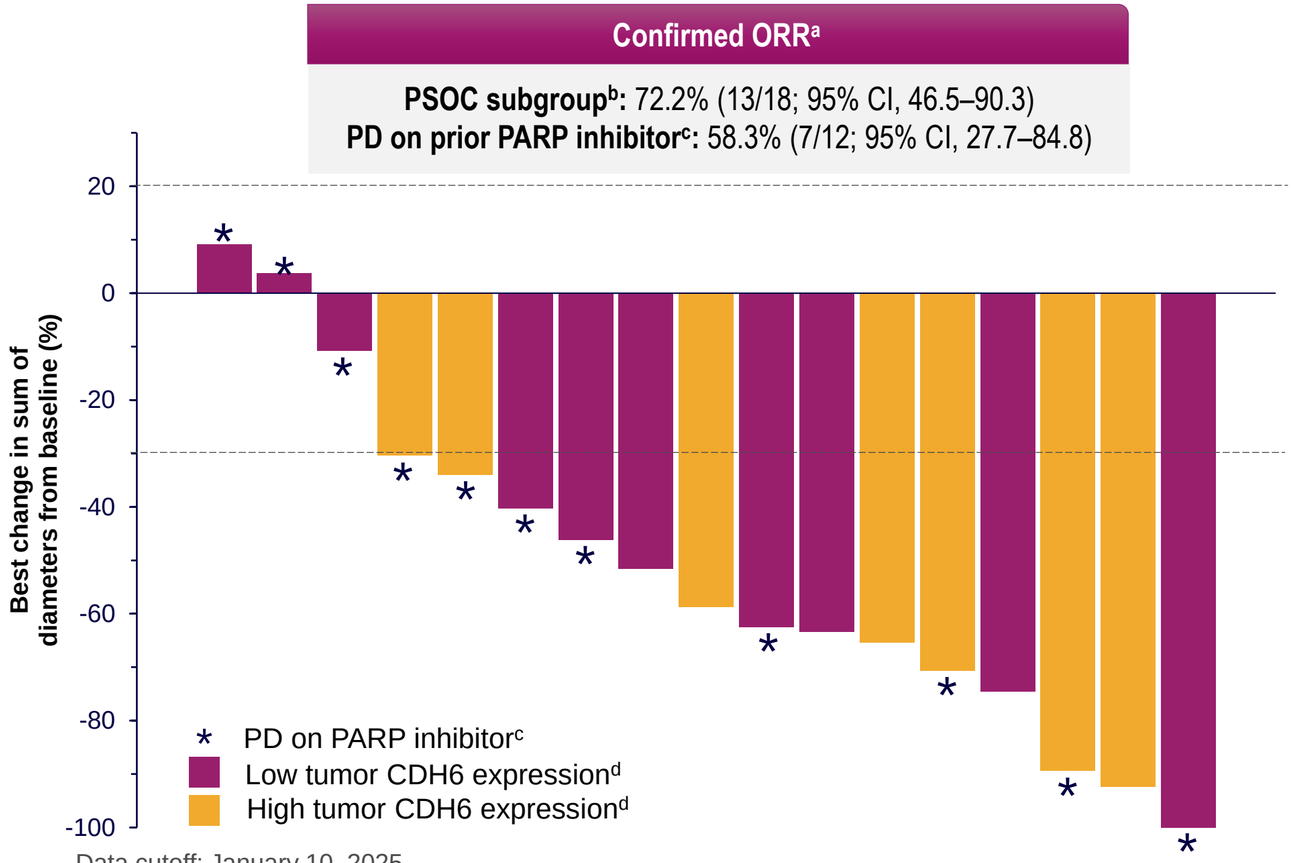
- In total, 13 patients (72.2%) have discontinued study treatment, including:
  - 9 patients (50.0%) with PD[d]
  - 3 patients (16.7%) with adverse events[e]
  - 1 patient (5.6%) with clinical progression
- The median duration on study treatment was 6.9 months (range, 0.7–12.2)

Data cutoff: January 10, 2025.

[a]Only patients with PSOC (TFIp ≥6 months) and treated with ≥1 dose of R-DXd 4.8–6.4 mg/kg were included in the PSOC subgroup analysis. [b]PD on or within ≤30 days of prior PARP inhibitor treatment . [c]Total positive staining for CDH6 membrane expression is determined by clinical trial assay for CDH6 (SP450; Roche Diagnostics). [d]Per RECIST 1.1. [e]Discontinuations due to adverse events were due to increased ALT and AST (n=1), cardiac arrest (n=1), and ILD (n=1).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; OC, ovarian cancer; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PROC, platinum-resistant OC; PSOC, platinum-sensitive OC; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TFIp, treatment-free interval from last platinum dose.

Efficacy summary: Preliminary efficacy is promising in patients with PSOC



	PSOC subgroup 4.8–6.4 mg/kg n=18	PD on PARP inhibitor[c] n=12
Best overall response,[e] n (%)		
CR	0	0
PR	13 (72.2)	7 (58.3)
SD	3 (16.7)	3 (25.0)
PD	1 (5.6)	1 (8.3)
Not evaluable	1 (5.6)	1 (8.3)
Disease control rate,[f] % (95% CI)	88.9 (65.3–98.6)	83.3 (51.6–97.9)
Clinical benefit rate,[g] % (95% CI)	77.8 (52.4–93.6)	66.7 (34.9–90.1)
Median TTR, months, (95% CI)	1.4 (1.2–2.7)	1.4 (1.2–NE)
Median DOR, months, (95% CI)	5.7 (4.2–NE)	5.1 (2.8–NE)
Median follow-up, months (range)	6.9 (1.6–10.5)	6.9 (1.6–6.9)
Median PFS, months, (95% CI)	8.1 (4.1–NE)	7.1 (2.8–NE)
Median follow-up, months (range)	8.3 (0–11.7)	8.3 (0–11.4)

Data cutoff: January 10, 2025.

Only patients with measurable disease at baseline and ≥1 postbaseline tumor scan were included in the waterfall plot. One patient who received R-DXd 6.4 mg/kg had a target lesion at baseline but no postbaseline scan, so was not evaluable.
[a]ORR by investigator is shown. [b]Efficacy-evaluable population (n=18) includes all patients with PSOC who received ≥1 dose of R-DXd and have completed ≥1 postbaseline tumor assessment or discontinued from treatment due to AE, PD, or death prior to the first postbaseline tumor assessment. [c]PD during or ≤30 days following completion of PARP inhibitor treatment. [d]Tumor CDH6 expression is defined as <75% (low) or ≥75% (high); total tumor cells positive for CDH6 membrane staining is determined by clinical trial assay for CDH6 (SP450; Roche Diagnostics). [e]Best overall response of CR or PR (per RECIST 1.1) must be confirmed and maintained ≥28 days. [f]CR + PR + SD (per RECIST 1.1) ≥5 weeks. [g]CR + PR + SD (per RECIST 1.1) ≥180 days.
AE, adverse event; CDH6, cadherin 6; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; ORR, objective response rate; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PR, partial response; PSOC, platinum-sensitive ovarian cancer; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; TTR, time to response.

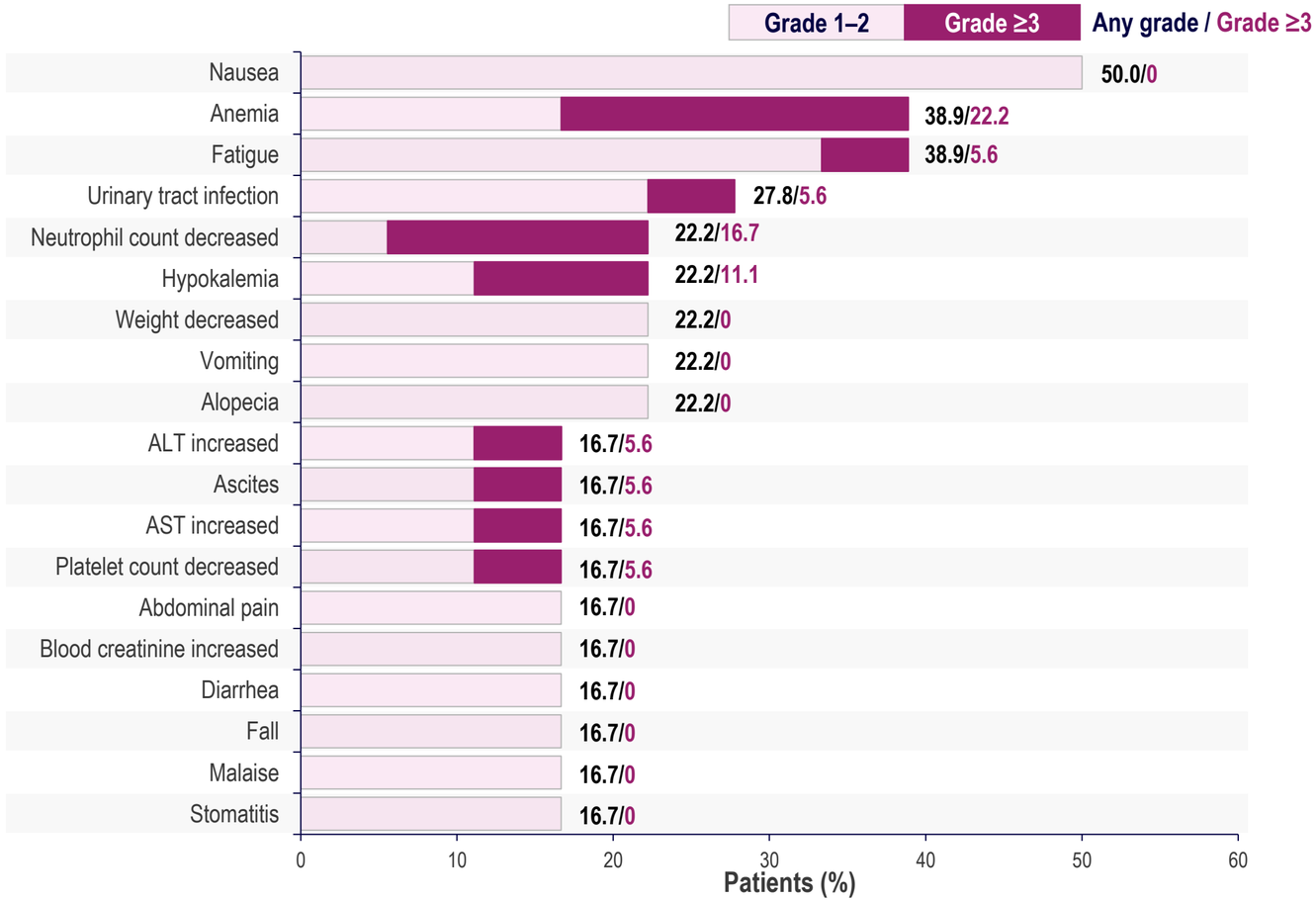
Safety summary: The safety profile of R-DXd is manageable

Overall safety summary

	PSOC subgroup[a] 4.8–6.4 mg/kg n=18
Any TEAE, n (%)	18 (100)
Grade ≥3	14 (77.8)
Treatment-related TEAE, n (%)	16 (88.9)
Grade ≥3	9 (50.0)
Grade 5 (fatal)	0
Any SAE, n (%)	5 (27.8)
Grade ≥3	5 (27.8)
Treatment-related SAE, n (%)	0
Dose modifications,[b] n (%)	
Drug discontinuation	2 (11.1)
Dose interruption	7 (38.9)
Dose reduction	4 (22.2)

- Drug-related ILD/pneumonitis (Grade 2) was reported in 1 patient, who received a starting dose of R-DXd 6.4 mg/kg
- The safety profile in the subgroup of patients with PSOC was comparable to that in the overall study population[1,2]

Most common all-cause TEAEs[c] (any grade, ≥15%)



Data cutoff: January 10, 2025.

[a]Patients received R-DXd at doses of 4.8 mg/kg (n=4), 5.6 mg/kg (n=9) and 6.4 mg/kg (n=5). [b]Dose modifications associated with treatment-related TEAE. [c]Reported safety events are defined by MedDRA preferred terminology.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; PSOC, platinum-sensitive ovarian cancer; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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Conclusions

- In this subgroup of 18 patients with PSOC who had received multiple prior treatments, R-DXd demonstrated promising efficacy:
  - In total, 72.2% (13/18; 95% CI, 46.5–90.3) of patients achieved an objective response; the clinical benefit rate was 77.8% (95% CI, 52.4–93.6)
  - Median DOR in the PSOC subgroup was 5.7 months (95% CI, 4.2–NE)[a]
- Of the 12 patients who experienced PD on or within ≤30 days of prior PARP inhibitor treatment, 58.3% (7/12; 95% CI, 27.7–84.8) achieved an objective response
- The safety profile of R-DXd in patients with PSOC was manageable and consistent with previous reports in patients with advanced OC[1,2]
  - The most common all-cause, any-grade TEAEs were nausea (50.0%), anemia (38.9%), and fatigue (38.9%)
- These encouraging results of treatment with R-DXd 4.8 to 6.4 mg/kg in patients with PSOC, many with PD following PARP inhibitor treatment, support further investigation of R-DXd in this patient population

Data cutoff: January 10, 2025.

[a]Median follow-up for DOR: 6.9 months (range, 1.6–10.5).

CI, confidence interval; DOR, duration of response; NE, not estimable; OC, ovarian cancer; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PSOC, platinum-sensitive OC; TEAE, treatment-emergent adverse event.

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