Raludotatug deruxtecan (R-DXd) in Japanese patients with ovarian cancer: Subgroup analysis of a Phase 1 study

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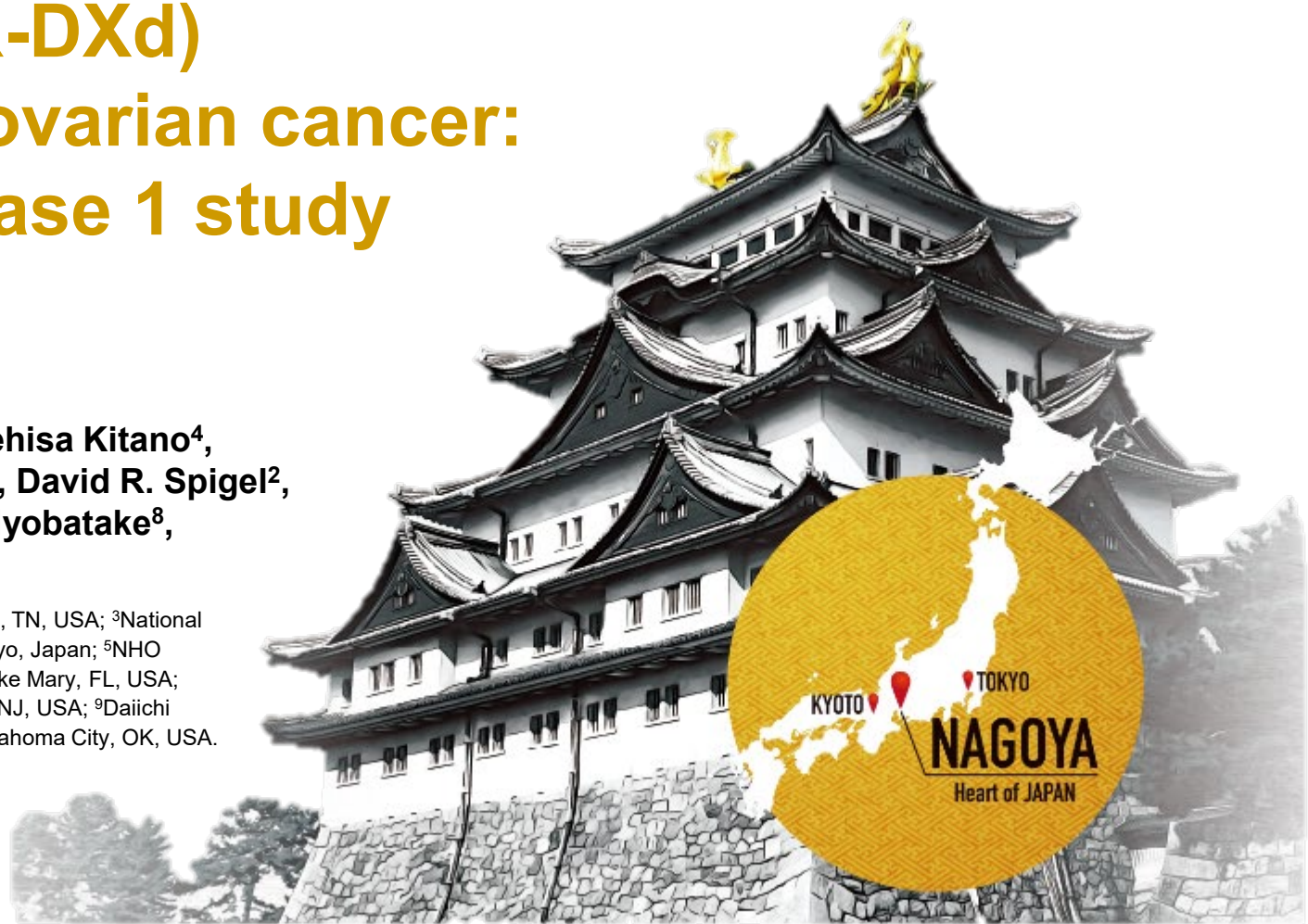


Presentation OS13-2

Declaration of interests

Research fund	□ scientific research fund □ contract □ donation □ other （ ） □ N/A	Sponsor	Daiichi Sankyo, Inc.
Name of lead presenter	**Kazuki Sudo**	**Institution or company/position**	**National Cancer Center Hospital, Tokyo, Japan**

	No	If yes, please specify the name of company, organization, your status.
Employee or adviser of company and/or profit-making organization	×	
Profit of stock	×	
Patent fee	×	
Lecturer fee	×	
Manuscript fee	×	
Research expenses from company	✓	NanoCarrier, Daiichi Sankyo, AstraZeneca, Pfizer, Amgen, PRA Health Sciences, Takeda, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA
Contributions or endowed chair	×	
Fees of testimony, judgment, comment, etc.	×	
Presents or other payment	×	
Representative of organization for clinical study receiving research expenses from company	×	

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 a humanized IgG1 antibody against CDH6, a stable linker selectively cleaved within tumor cells, and a membrane-permeable topoisomerase I inhibitor[4,5]
- Early results from the ongoing Phase 1 trial (NCT04707248) in Japanese and US patients demonstrated an acceptable safety profile and early efficacy signal for R-DXd in heavily treated advanced OVC[6,7]
- A subgroup analysis of Japanese patients with OVC is presented here (data cutoff: July 14, 2023)

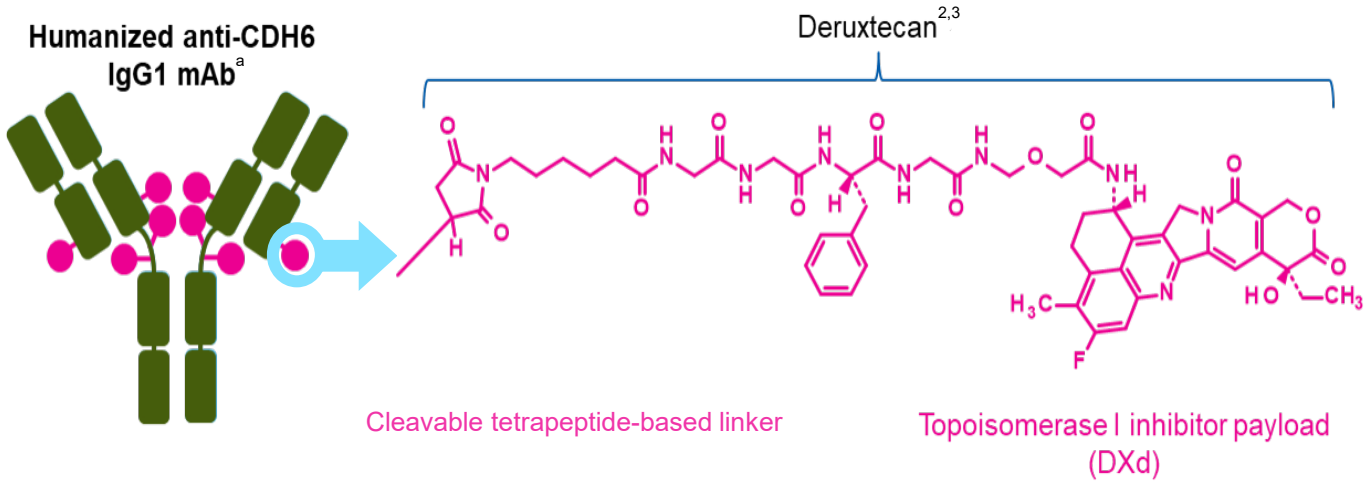
ADC, antibody–drug conjugate; CDH6, cadherin 6; IgG1, immunoglobulin G1; OVC, ovarian cancer.

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. 7. Moore KN, et al. *Ann Oncol*. 2023;34(Suppl. 2): Abstr 745MO.

R-DXd was designed with 7 key attributes

R-DXd is a CDH6-directed ADC composed of three parts:[1–5]

- Humanized anti-CDH6 IgG1 mAb
- Topoisomerase I inhibitor payload (an exatecan derivative, DXd)
- Tetrapeptide-based cleavable linker covalently bonds the above components



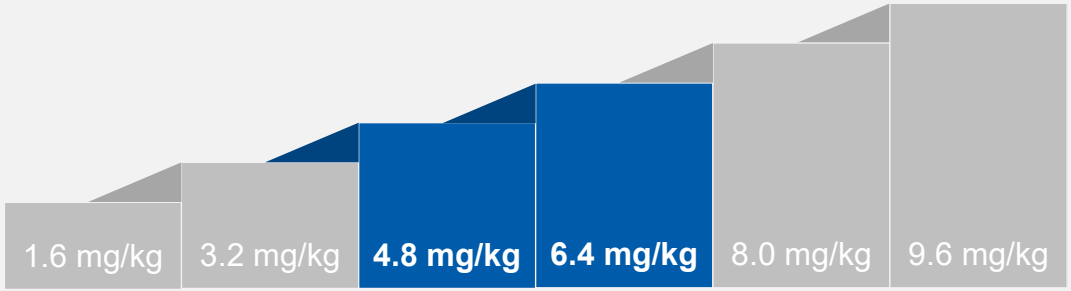
Payload mechanism of action: topoisomerase I inhibitor[1,b]
High potency of payload[4,5,b]
High drug-to-antibody ratio of ≈8[1,b]
Payload with short systemic half-life[4,b,c]
Stable linker-payload[4,5,b]
Tumor-selective cleavable linker[1,4,5,b]
Bystander antitumor effect[1,b]

[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.

1. Suzuki H, et al. *Mol Cancer Ther*. 2024; 10.1158/1535-7163.MCT-23-0287. Online ahead of print; 2. Hamilton EP, et al. *J Clin Oncol*. 2022;40(16 Suppl.):3002; 3. Moore KN, et al. *Ann Oncol*. 2023;34 (Suppl. 2): Abstr 745MO; 4. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185; 5. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108.

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: 6.4 mg/kg** | **OVC cohort: 5.6 mg/kg** | **OVC cohort: 8.0 mg/kg**

Key primary objectives:

- Safety and tolerability
- Determine MTD and RDE
- ORR per RECIST v1.1 (dose expansion)

Key secondary objectives:

- PK: ADC, total anti-CDH6 antibody, and the DXd payload
- ORR per RECIST v1.1 (dose escalation)
- DOR, DCR, and CBR per RECIST v1.1
- Immunogenicity

This analysis included Japanese patients with OVC who received R-DXd at 4.8, 5.6, and 6.4 mg/kg[a]

[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.

JSMO2024 February 22 (Thu) - 24 (Sat), 2024

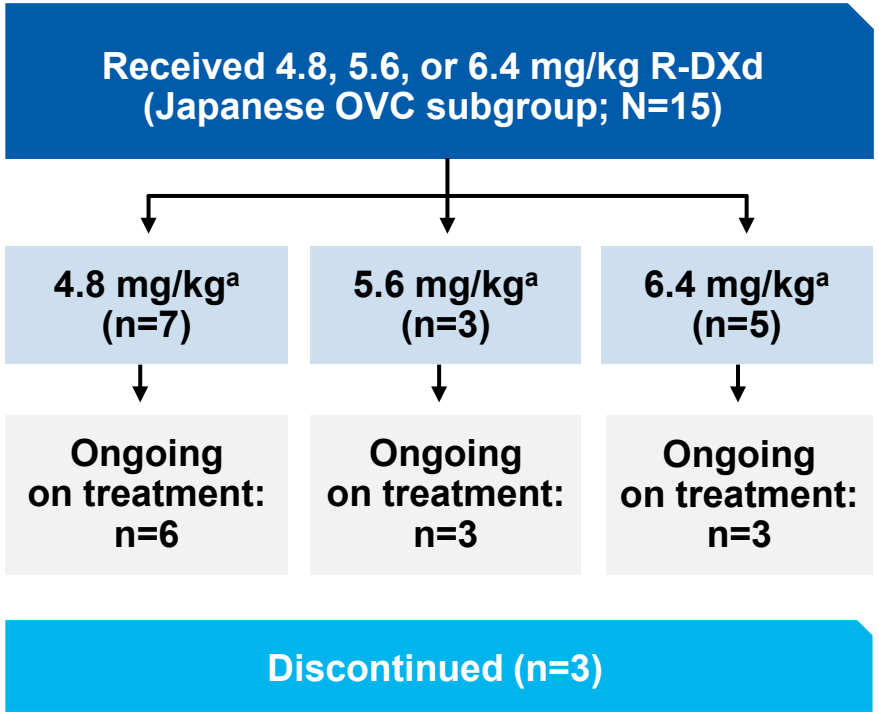
Baseline characteristics

	Overall[a] N=45	Japanese n=15
Age, years, median (range)	66 (42–82)	60 (42−76)
Age ≥65 years, n (%)	25 (55.6)	5 (33.3)
Country, n (%)		
Japan	15 (33.3)	15 (100.0)
United States	30 (66.7)	0
ECOG PS, n (%)		
0	18 (40.0)	8 (53.3)
1	27 (60.0)	7 (46.7)
Platinum-resistant disease[b], n (%)	40 (88.9)	13 (86.7)
Number of prior systemic regimens, median (range)	4 (1–12)	4 (2−8)
Received prior systemic therapy, n (%)		
Bevacizumab	29 (64.4)	9 (60.0)
PARP inhibitor	29 (64.4)	11 (73.3)
Tumor CDH6 expression H-score, median (range)	140.5 (0–250)	155.0 (0–213)

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

Data cutoff: July 14, 2023



Treatment status	Overall N=45	Japanese n=15
Ongoing study treatment, n (%)	30 (66.7)	12 (80.0)
Discontinued from the study, n (%)	15 (33.3)	3 (20.0)
Progression[b]	8 (17.8)	1 (6.7)
Adverse events	5 (11.1)	2 (13.3)
Other	2 (4.4)[c]	0
Duration on study treatment, weeks, median (range)	17.9 (3.0–114.9)	13.0 (3.0–54.6)
Treatment duration, n (%)		
≥6 months	10 (22.2)	3 (20.0)
≥12 months	1 (2.2)	1 (6.7)

Data cutoff: July 14, 2023.
[a]Enrollment ongoing. [b]Progressive disease per RECIST 1.1. [c]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.

Efficacy of R-DXd

Confirmed ORR by RECIST v1.1 in Japanese patients with OVC was 50%, similar to the response reported in the overall cohort

	Overall n=38	Japanese n=12
Confirmed ORR, % (95% CI) [n/N]	48.6 (31.9, 65.6) [18/37][e]	50 (21.2, 78.9) [6/12]
Best overall response[a], n (%)		
CR	1 (2.6)	1 (8.3)
PR	17(44.7)	5 (41.7)
SD	18 (47.4)	6 (50.0)
Non-CR/non-PD	1 (2.6)[e]	0
Not evaluable	1 (2.6)[f]	0
Disease control rate[b], % (95% CI)	97.4 (86.2, 99.9)	100.0 (73.5, 100)
Clinical benefit rate[c], % (95% CI)	50.0 (33.4, 66.6)	50.0 (21.1, 78.9)
Median time to response, weeks (95% CI)	5.7 (5.3, 11.4)	5.9 (5.1, NE)
Median DOR, months, (95% CI)	11.2 (3.1, NE)	11.2 (2.4, NE)
Median follow-up, months (range)	6.7 (1.4–16.8)	8.1 (2.4–11.2)
CA-125 response rate[d], % (95% CI) [n/N]	46.7 (28.3, 65.7) [14/30]	44.4 (13.7, 78.8) [4/9]
Median PFS[g], months, (95% CI)	8.1 (5.3, NE)	12.4 (5.3, NE)
Median follow-up, months (range)	4.0 (0–25.1)	2.8 (0–12.4)

Data cutoff: July 14, 2023.

[a]BOR of CR or PR (per RECIST V1.1) must be confirmed and maintained ≥28 days. [b]CR + PR + SD (per RECIST V1.1) ≥5 weeks. [c]CR + PR + SD (per RECIST V1.1) ≥180 days. [d]CA-125 response is defined as ≥50% reduction in CA-125 levels from baseline confirmed and maintained ≥28 days (evaluable patients had baseline level ≥2x ULN ≤2 weeks prior to starting treatment). [e]One patient with no target lesion at baseline was excluded from the ORR dataset. [f]One patient discontinued and did not have a post-baseline assessment. [g]Evaluable population: Japanese subgroup, n=15 and overall cohort, N=45. The evaluable population for PFS included patients who received ≥1 dose of study treatment.

BOR, best objective response; CA-125, cancer antigen 125; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; ORR, objective response rate; OVC, ovarian cancer; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; ULN, upper limit of normal.

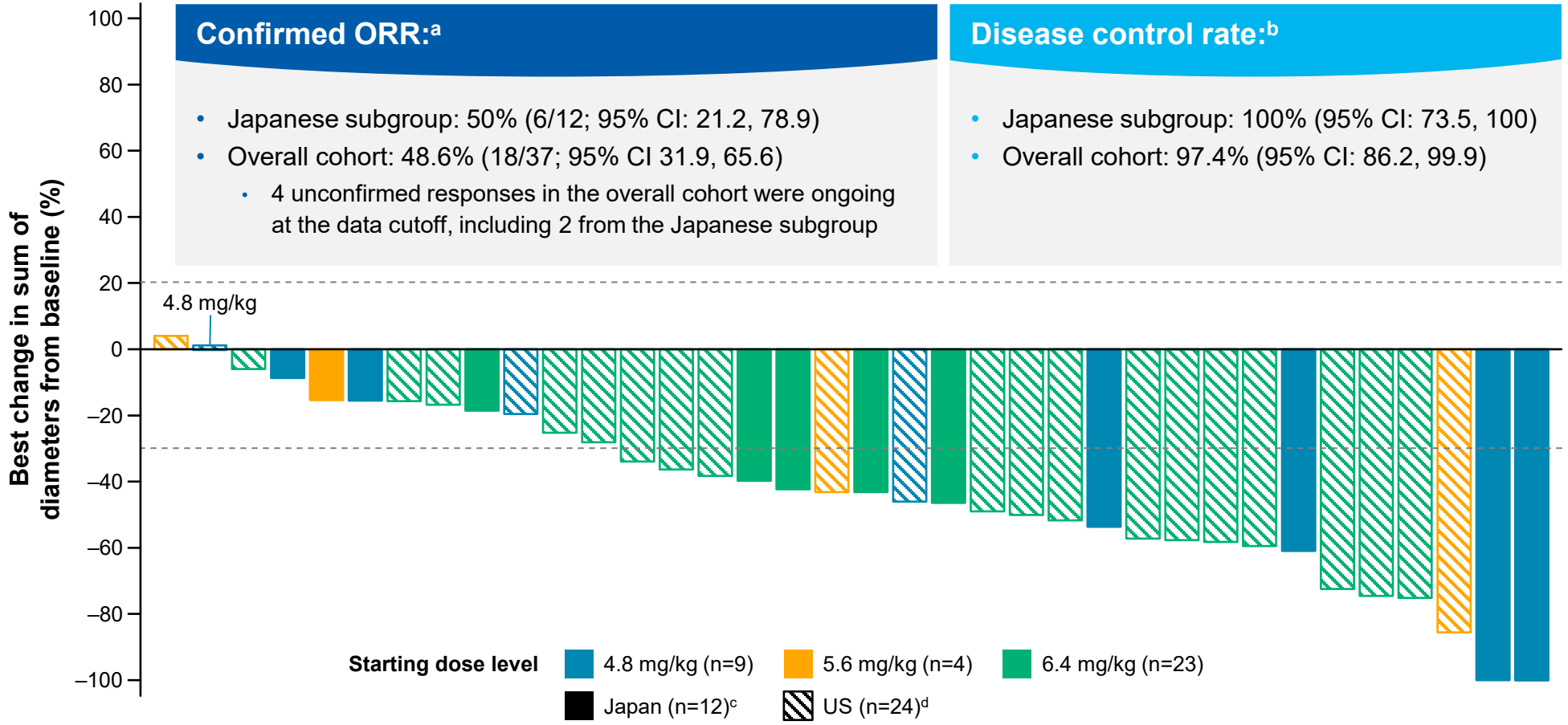
Preliminary antitumor activity of R-DXd is promising in heavily pretreated patients with OVC

Confirmed ORR:[a]

- Japanese subgroup: 50% (6/12; 95% CI: 21.2, 78.9)
- Overall cohort: 48.6% (18/37; 95% CI 31.9, 65.6)
  - 4 unconfirmed responses in the overall cohort were ongoing at the data cutoff, including 2 from the Japanese subgroup

Disease control rate:[b]

- Japanese subgroup: 100% (95% CI: 73.5, 100)
- Overall cohort: 97.4% (95% CI: 86.2, 99.9)

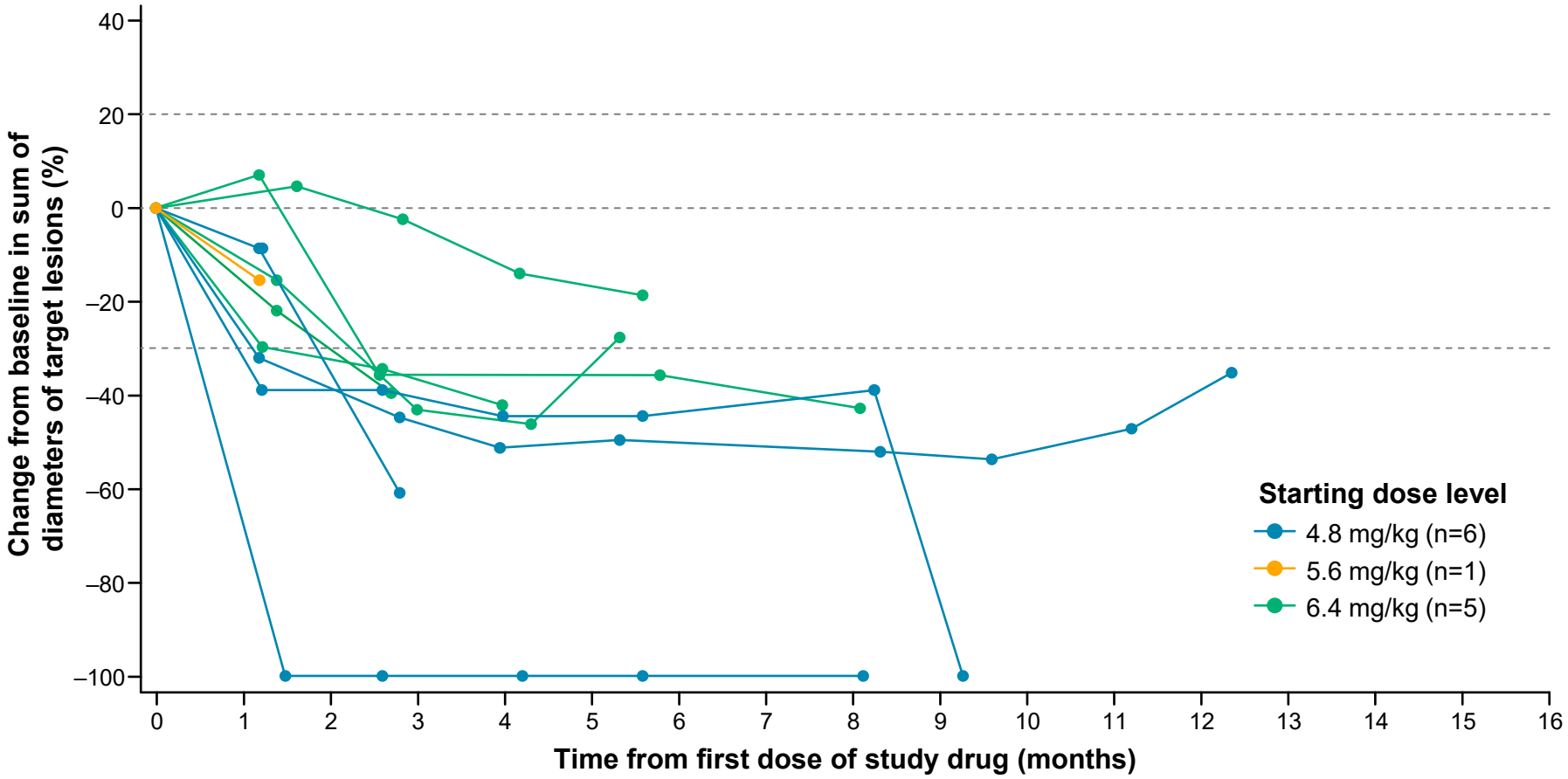


Data cutoff: July 14, 2023.

[a]The efficacy-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. Change from baseline in target tumor size was assessed per RECIST v1.1. [b]CR + PR + SD (per RECIST V1.1) ≥5 weeks. [c]In the Japanese subgroup, 3 patients were recently enrolled and did not have any post-baseline scans to date. [d]In the US subgroup, 1 patient had no measurable lesions at baseline; 1 patient discontinued treatment and had no post-baseline scan; and 4 patients had no post-baseline scans. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan were included in the waterfall plot.

CI, confidence interval; CR, complete response; OVC, ovarian cancer; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Preliminary antitumor activity of R-DXd is promising in heavily pretreated Japanese patients with OVC



Median DOR:[a]

- Japanese subgroup: 11.2 months (95% CI: 2.4, NE)
- Overall cohort: 11.2 months (95% CI 3.1, NE)

Median TTR:

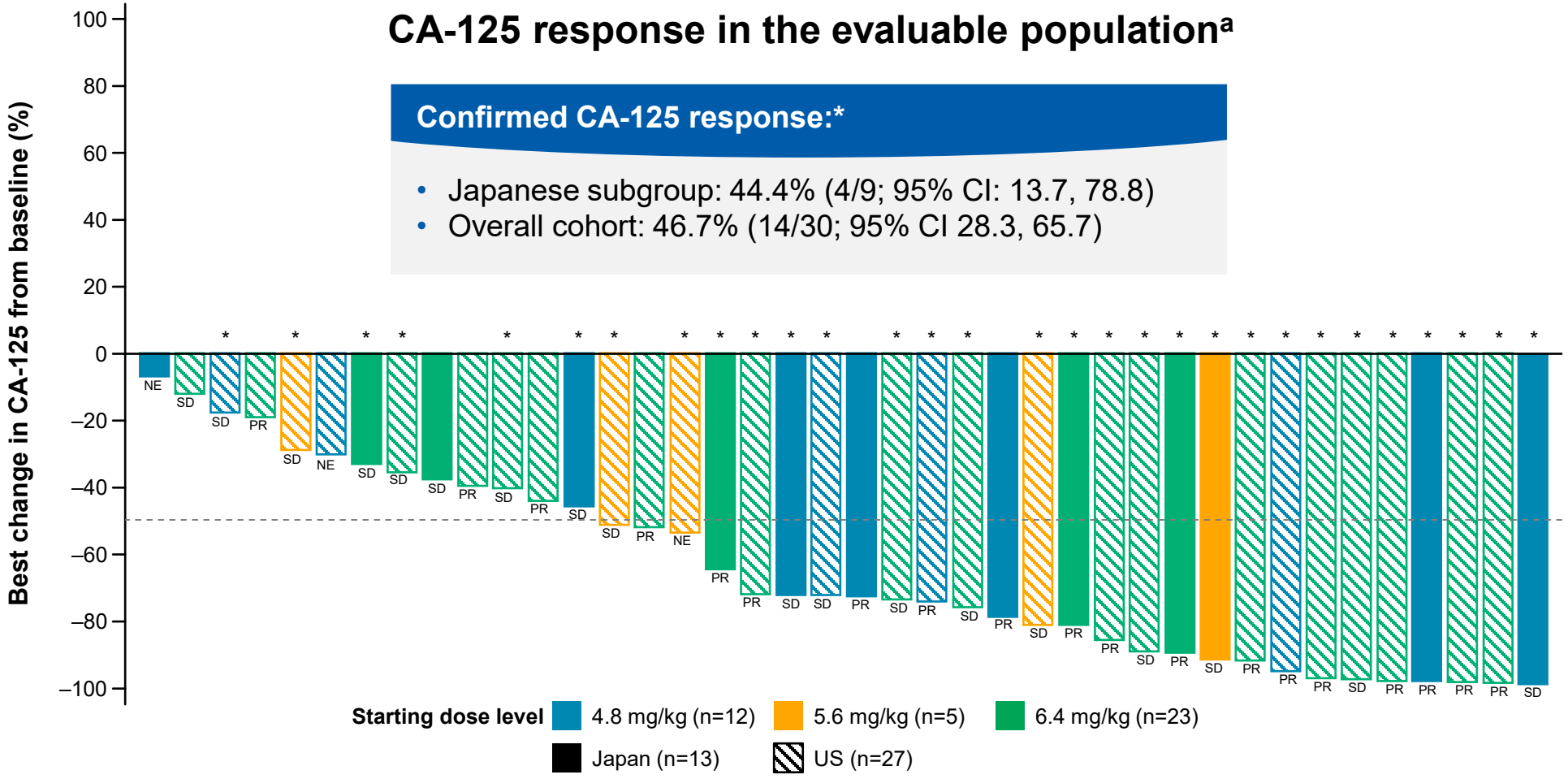
- Japanese subgroup: 5.9 weeks (95% CI: 5.1, NE)
- Overall cohort: 5.7 weeks (95% CI 5.3, 11.4)

Data cutoff: July 14, 2023.

[a]Median follow-up for DOR: 8.1 months (range, 2.4–11.2). The efficacy 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. Change from baseline in target tumor size was assessed per RECIST v1.1. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan were included in the spider plot. In the Japanese subgroup, 3 patients were recently enrolled and had no post-baseline scans.

CI, confidence interval; DOR, duration of response; NE, not estimable; OVC, ovarian cancer; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TTR time to response.

R-DXd treatment resulted in marked CA-125 reduction in both Japanese and US patients with OVC

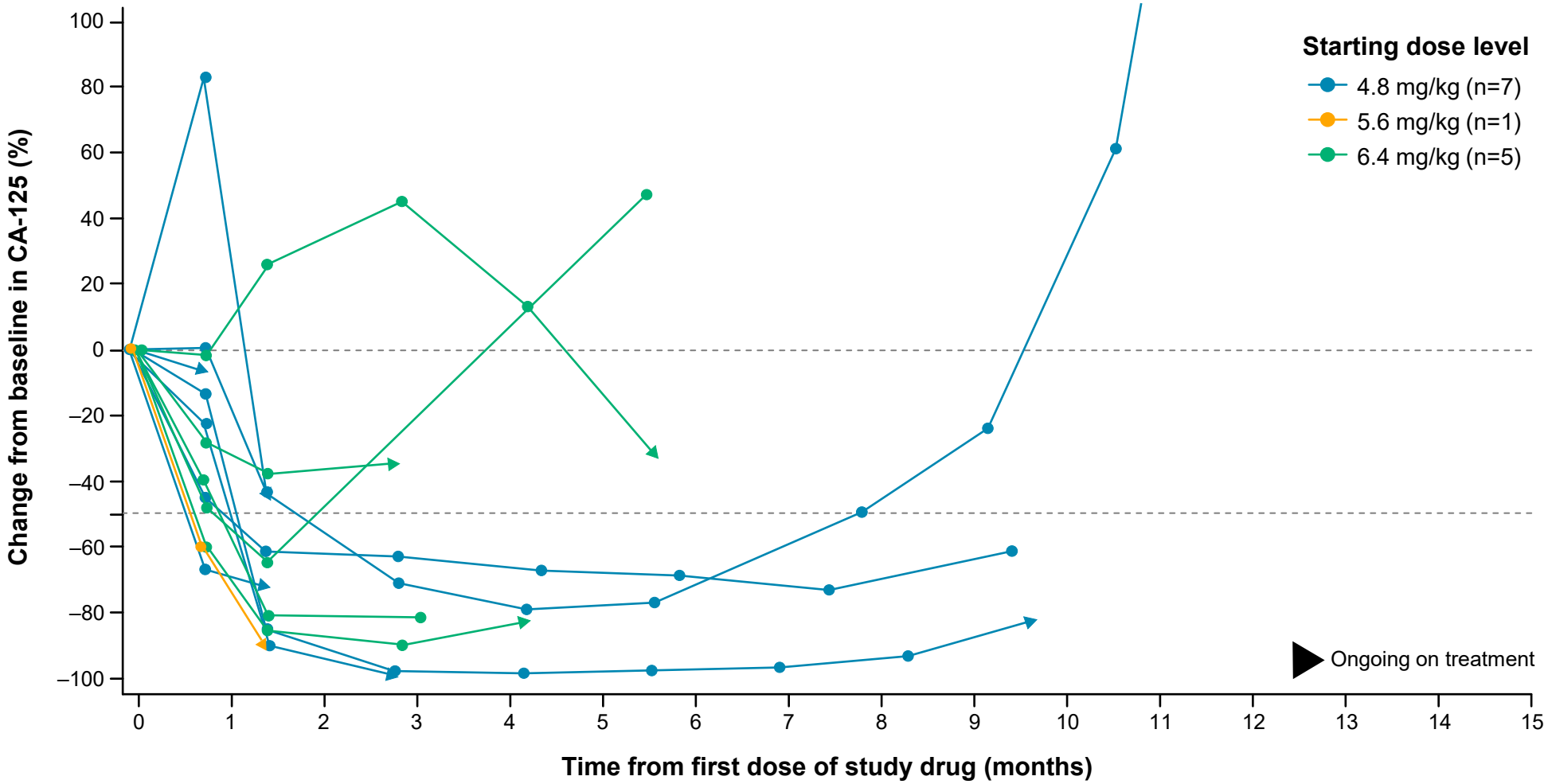


Data cutoff: July 14, 2023.

[a]The CA-125 evaluable population included patients with a baseline CA-125 value and ≥1 post-baseline CA-125 value. *Patients were evaluable for a confirmed CA-125 response if they had a baseline CA-125 sample ≥2x ULN obtained ≤2 weeks prior to treatment initiation according to the GCIG criteria; CA-125 response was defined as a ≥50% reduction in CA-125 levels (confirmed and maintained for ≥28 days) from a pre-treatment sample.

CA-125, cancer antigen 125; CI, confidence interval; GCIG, Gynaecologic Cancer Intergroup; NE, not evaluable; OVC, ovarian cancer; PFS, progression-free survival; PR, progressive response; SD, stable disease; ULN, upper limit of normal.

R-DXd treatment resulted in a CA-125 reduction in heavily pretreated Japanese patients with OVC



Data cutoff: July 14, 2023.

The CA-125 evaluable population included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason. Change from baseline in target tumor size was assessed per RECIST v1.1. Only subjects with measurable disease at baseline and ≥1 post-baseline tumor scan were included in the spider plot. In the Japanese subgroup, 3 patients were recently enrolled and had no post-baseline scans.

CA-125, cancer antigen 125; OVC, ovarian cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

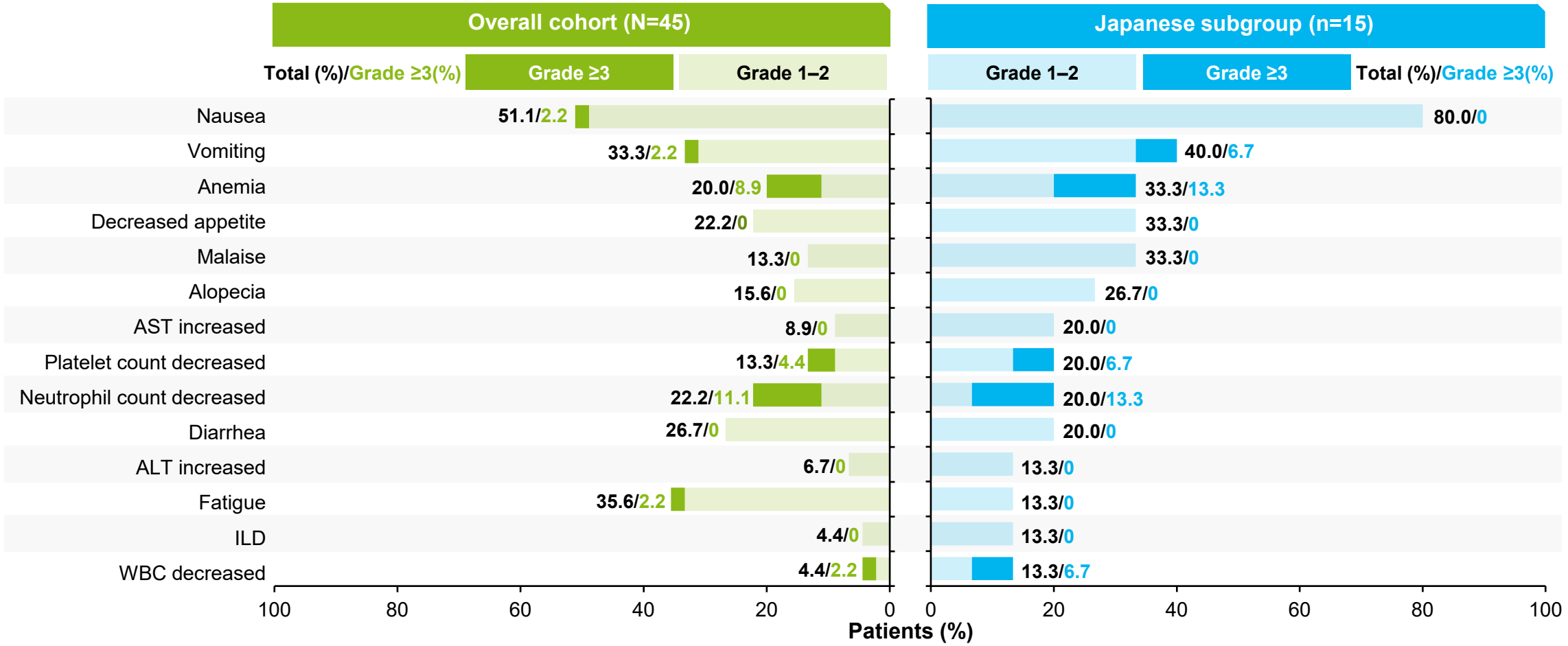
Overall safety summary

The safety profile in the Japanese subgroup was consistent with that of the overall cohort, which is deemed manageable

	Overall N=45	Japanese n=15
Any TEAE, n (%)	42 (93.3)	13 (86.7)
Grade ≥3	20 (44.4)	6 (40.0)
Treatment-related TEAE, n (%)	41 (91.1)	13 (86.7)
Grade ≥3	12 (26.7)	6 (40.0)
Grade 5	0	0
SAE, n (%)	11 (24.4)	3 (20.0)
Grade ≥3	10 (22.2)	2 (13.3)
Dose modifications,[a] n (%)		
Drug discontinuation	5 (11.1)	2 (13.3)
Dose interruption	14 (31.1)	5 (33.3)
Dose reduction	7 (15.6)	2 (13.3)

Data cutoff: July 14, 2023.
[a]Dose modifications associated with TEAE.
In the Japanese subgroup, patients received R-DXd at doses of 4.8 mg/kg (n=7), 5.4 mg/kg (n=3), and 6.4 mg/kg (n=5). In the overall cohort, 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).
SAE, serious adverse events; TEAE, treatment-emergent adverse event.

Safety: most common TEAEs (≥10%)[a] related to R-DXd



Drug-related ILD (Grade 2) was reported in 1 patient in the Japanese subgroup treated with R-DXd 6.4 mg/kg

Data cutoff: July 14, 2023.
[a]TEAEs related to treatment reported in ≥10% of Japanese subgroup.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; TEAE, treatment-emergent adverse event; WBC, white blood cells.

Conclusions

- R-DXd is the first CDH6-directed ADC to demonstrate promising efficacy in patients with heavily pretreated OVC who were not selected based on tumor CDH6 expression
- Efficacy of R-DXd treatment (4.8–6.4 mg/kg) was consistent between the Japanese subgroup and the overall cohort
  - 50% of patients in the Japanese OVC subgroup achieved an ORR: 1 CR and 5 PRs
  - Median DOR was 11.2 months[a]
  - Median PFS was 12.4 months[b]
- The safety profile of R-DXd in the Japanese subgroup was:
  - Manageable and consistent with the safety profile in the overall cohort
  - Consistent with the safety profile observed with 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, including in Japan

Data cutoff: July 14, 2023.
[a]Median follow-up for DOR: 8.1 months (range, 2.4–11.2). [b]Median follow-up for PFS: 2.8 months (range, 0–12.4).
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.

Acknowledgements

- We thank the patients, their families, and their caregivers for their 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 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)