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A Phase 1/2 study of Rinatabart Sesutecan (Rina-S) in Patients With Advanced Ovarian or Endometrial Cancer

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Declaration of Interests

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Advisory board participation: Aadi Biosciences, OnCusp Therapeutics

Background

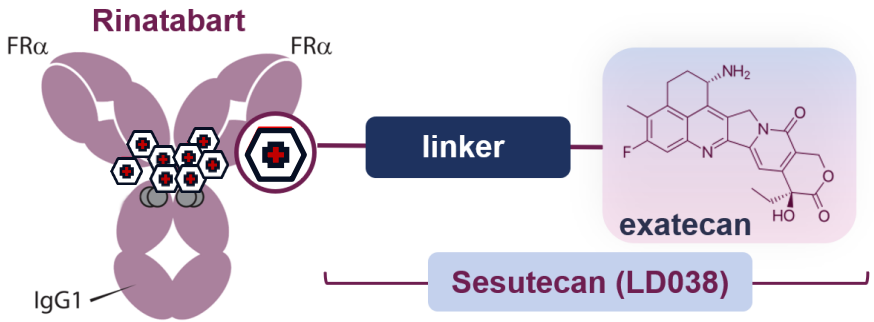
- OC and EC continue to have high unmet needs[1]
- Patients with PROC have a poor prognosis, and treatment options remain limited[2,3]
- Novel, efficacious therapies are needed for patients with EC who have received prior platinum-based chemotherapy and anti-PD-(L)1[4-9]

FRα is overexpressed on multiple solid tumors, including OC and EC[10]

Rinatabart sesutecan (Rina-S) is an investigational, novel ADC composed of[11]:

- A human monoclonal antibody directed at FRα
- A novel hydrophilic protease-cleavable linker
- Exatecan, a topoisomerase I inhibitor

Rina-S features a high, homogenous drug-to-antibody ratio of 8[10]



ADC, antibody-drug conjugate; CT, chemotherapy; EC, endometrial cancer; FRα, folate receptor α; OC, ovarian cancer; PD-(L)1; programmed cell death protein-1/ programmed death-ligand 1; PROC, platinum-resistant ovarian cancer.

1. International Agency for Research on Cancer. 2024. https://gco.iarc.fr/tomorrow/. Accessed: August 9, 2024. 2. Havasi A, et al. *Medicina* 2023;59:544. 3. Atallah GA, et al. *Int J Mol Sci* 2023;24:1-20. 4. Mirza MR, et al. *N Engl J Med* 2023;8;388:2145-2158. 5. Eskander RN, et al. *N Engl J Med* 2023;388:2159-2170. 6. Westin SN, et al. *J Clin Oncol* 2024;42:283-299. 7. Colombo N, et al. *Lancet Oncol* 2024. doi: 10.1016/S1470-2045(24)00334-6. 8. Oaknin A, et al. *Clin Cancer Res* 2023;29:4564-4574. 9. O'Malley DM, et al. *J Clin Oncol* 2022;40:752-761. 10. Ledermann JA, et al. *Ann Oncol* 2015;26(10):2034-2043. 11. Call J, et al. *J Immunother Cancer* 2023;11(Suppl 1):803.

Study Design and Patient Demographics

Objective: Report safety and efficacy of single-agent Rina-S Q3W from dose escalation (OC and EC) and dose expansion (OC) of an open-label, multicenter phase 1/2 study (NCT05579366)[1]

Study Design

Part A – Dose Escalation

- Solid tumors[a] dose escalation (n = 53) included patients regardless of FRα expression with previously treated OC (n = 32; 23 received Rina-S 100-120 mg/m^2 Q3W) and EC (n = 11; 5 received Rina-S 100-120 mg/m^2 Q3W)

Part B – Dose Expansion

- Planned tumor-specific dose expansion includes OC, EC, and *EGFR*-mutant NSCLC regardless of FRα expression[b]
- **Cohort B1 - OC Dose Expansion**
  - Inclusion criteria
    - Histologically or cytologically confirmed OC (must have epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer)
    - Prior treatment (1-3 prior lines for PROC or 4 prior lines regardless of platinum-sensitivity status)
    - ECOG PS 0-1
    - Measurable disease per RECIST v1.1
    - Adequate hematologic, hepatic, renal, and cardiac function
  - Randomized 1:1 to receive Rina-S 100 mg/m^2 or Rina-S 120 mg/m^2 Q3W

Patient Demographics and Disease Characteristics in OC Dose Expansion

OC Dose Expansion	Rina-S 100 mg/m^2 n = 22	Rina-S 120 mg/m^2 n = 20
Age, median (range), years	62.5 (42-82)	64.5 (37-83)
Prior lines of therapy, median (range)	3 (1-5)	3 (1-4)
Bevacizumab, n (%)	20 (90.9)	18 (90.0)
PARPi, n (%)	15 (68.2)	13 (65.0)
Mirvetuximab soravtansine, n (%)	4 (18.2)	4 (20.0)
Platinum sensitivity status, n (%)		
Resistant	20 (90.9)	19 (95.0)
Sensitive	2 (9.1)	1 (5.0)

DCO: July 28, 2024

[a]Patient populations included patients with epithelial OC, EC, HER2- BC, NSCLC, and mesothelioma. [b]FRα levels retrospectively assessed.
BC, breast cancer; DCO, data cutoff; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FRα, folate receptor α; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PARPi, poly-ADP ribose polymerase inhibitor; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; Rina-S, rinatabart sesutecan.

1. National Library of Medicine. https://www.clinicaltrials.gov/study/NCT05579366. Accessed: August 7, 2024.

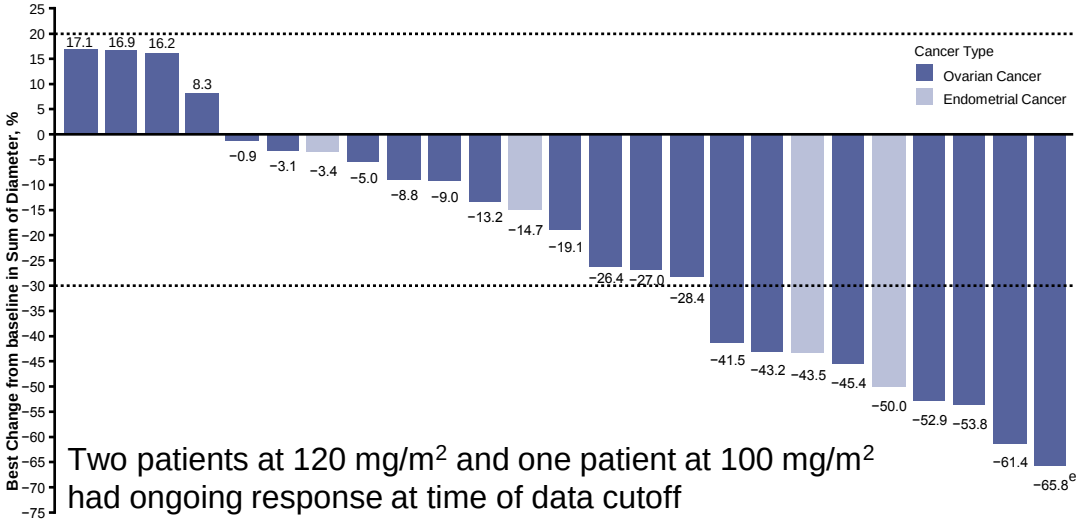
Antitumor Activity | OC, EC – Dose Escalation

Rina-S Q3W showed encouraging antitumor activity in patients with heavily pretreated OC and EC

OC and EC Dose Escalation	Rina-S 100 and 120 mg/m^2 n = 26[a]
Confirmed ORR,[b] % (95% CI)	30.8 (14.3-51.8)
Best overall response,[b] n (%)	
PR	8 (30.8)
SD	15 (57.7)
PD	3 (11.5)
DCR, % (95% CI)	88.5 (69.8-97.6)
Median DOR, weeks (95% CI)	35.3 (20.14-NE)

Median prior lines treatment, n (range): 4 (1-13)[c]
Treatment duration, range: 0.6-57.7+ weeks[c]
Median on-study follow-up, n: 34.6 weeks[d]

Best Change in Target Lesion in OC and EC Dose Escalation



Two patients at 120 mg/m^2 and one patient at 100 mg/m^2 had ongoing response at time of data cutoff

Median no. of cycles: 5.0+

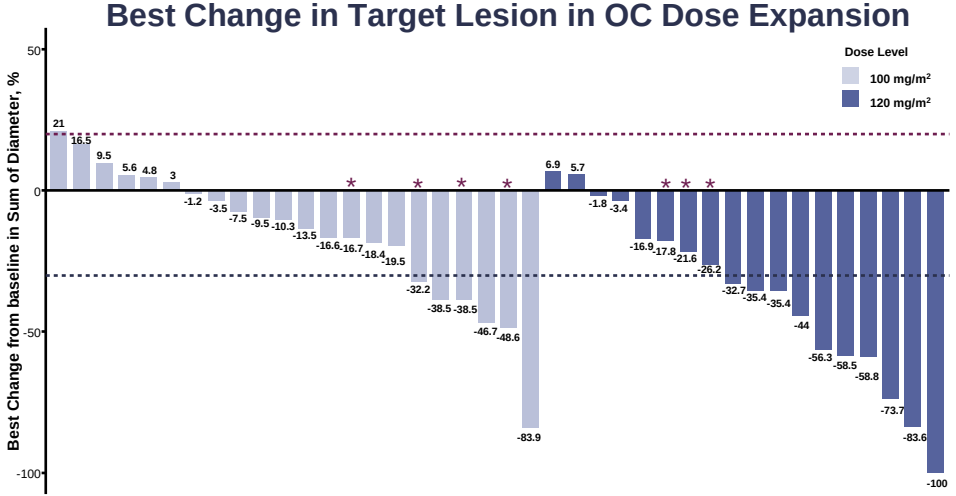
[a]Response-evaluable population; includes all treated patients who had a baseline and at least 1 evaluable postbaseline tumor assessment, or who had documented PD any time after their first dose of Rina-S. Response assessment per RECIST v1.1. [b]Based on investigator assessment. [c]For all patients who received Rina-S 100 mg/m^2 or 120 mg/m^2. [d]For patients with OC and EC who received Rina-S 100 mg/m^2 or 120 mg/m^2. [e]Per RECIST v1.1 patient had a best response of SD; patient had PR at week 6 followed by PD at week 12.
CI confidence interval; DCR, disease control rate; DOR, duration of response; EC, endometrial cancer; OC, ovarian cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; Rina-S, rinatabart sesutecan; SD, stable disease.

Antitumor Activity | OC – Dose Expansion

Rina-S showed encouraging antitumor activity at 120 mg/m^2 Q3W, including a complete response, in patients with heavily pretreated OC

OC Dose Expansion	Rina-S 100 mg/m^2 n = 22[b]	Rina-S 120 mg/m^2 n = 18[b]
Confirmed ORR,[a,b] % (95% CI)	18.2 (5.2-40.3)	50.0 (26.0-74.0)
Best overall response,[b] n (%)		
CR	0	1 (5.6)
PR	4 (18.2)	8 (44.4)
SD	15 (68.2)	7 (38.9)
PD	3 (13.6)	1 (5.6)
Not evaluable	0	1 (5.6)
DCR, % (95% CI)	86.4 (65.1-97.1)	88.9 (65.3-98.6)
Median DOR (95% CI)	NR (NR-NR)	

Treatment duration, range: 3.0-42.0+ weeks
Median on-study follow-up: 24 weeks



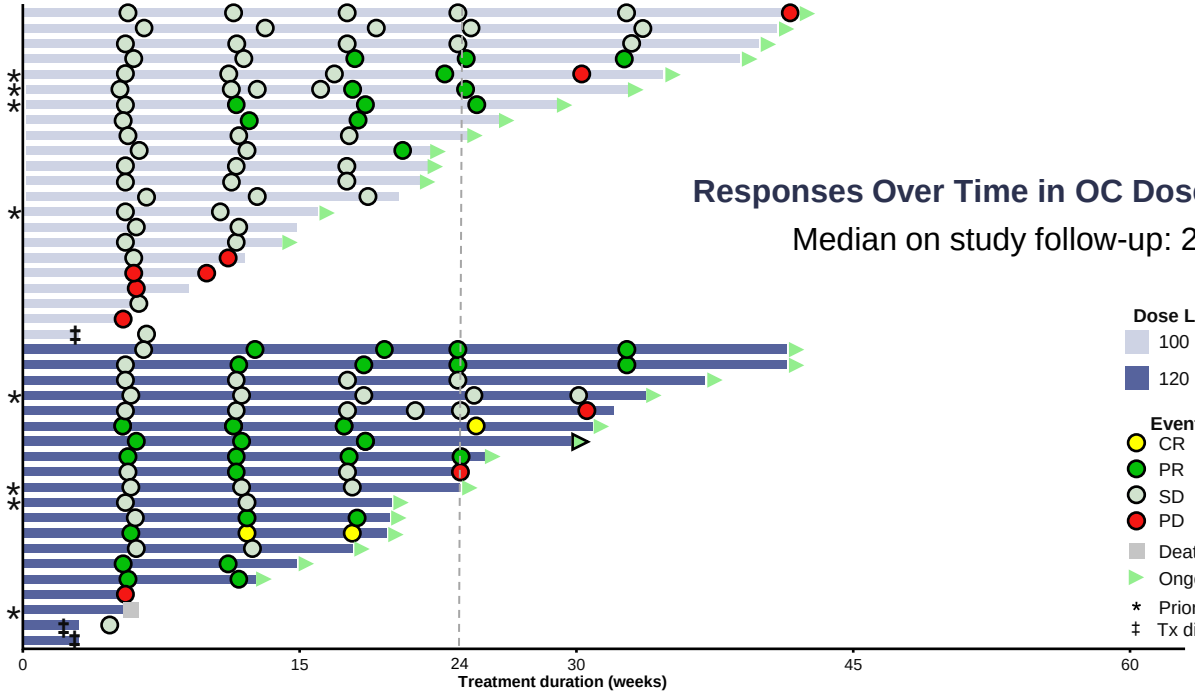
***Prior mirvetuximab soravtansine treatment[c]**

Median no. of cycles: 6.5 (100 mg/m^2) and 7.0+ (120 mg/m^2)

[a]Based on investigator assessment. [b]Response-evaluable population. [c]One patient in the 120 mg/m^2 cohort with prior mirvetuximab soravtansine was not response-evaluable.
CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; OC, ovarian cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; Rina-S, rinatabart sesutecan; SD stable disease.

Antitumor Activity | OC – Dose Expansion

Most responses with Rina-S 120 mg/m^2 Q3W were observed early (at week 6) and all confirmed responses with 120 mg/m^2 were ongoing at the time of data cutoff in patients with heavily pretreated OC

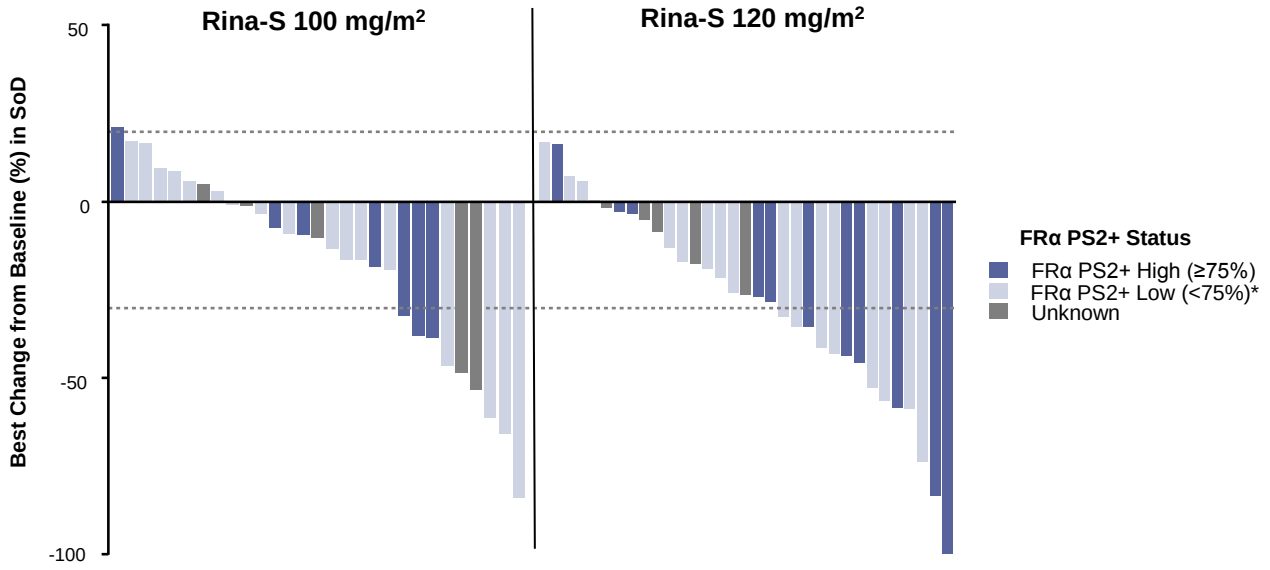


[a]One patient in 120 mg/m^2 cohort with prior mirvetuximab was not response-evaluable. [b]Reasons for discontinuation included alanine aminotransferase increased (n = 1; related to treatment), neutrophil count decreased (n = 1; related to treatment), and a small intestinal perforation and rectal hemorrhage (n = 1; not related to treatment; same patient).
CR, complete response; MIRV, mirvetuximab soravtansine; OC, ovarian cancer; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; Rina-S, rinatabart sesutecan; SD, stable disease; tx, treatment.

Response by FRα Expression | OC – Dose Escalation & Expansion

Responses in patients with OC were observed regardless of FRα expression levels

Best Change in Target Lesion SoD by FRα PS2+ Status in OC Dose Escalation and Expansion



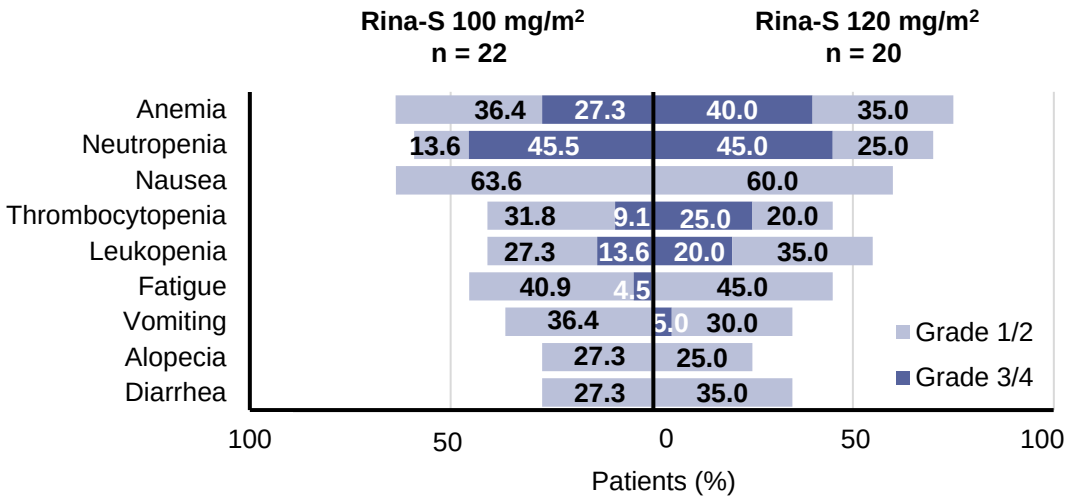
*Clinical activity was observed at lower cutoffs (FRα PS1+ <25%).
FRα, folate receptor α; OC, ovarian cancer; PS, positive staining; SoD, sum of diameter; Rina-S, rinatabart sesutecan.

Overall Safety

- In dose escalation at 100 - 120 mg/m^2 (n = 35), the most common any grade TEAEs were cytopenias[a] (34.3% - 60.0%)
- No signals of ocular toxicities, neuropathy, or ILD were observed

OC Dose Expansion	Rina-S 100 mg/m^2 n = 22	Rina-S 120 mg/m^2 n = 20
Any-grade TEAE, %	100.0	100.0
Grade 3/4	63.6	60.0[b]
TEAEs leading to dose reductions, %	18.2	20.0
TEAEs leading to treatment discontinuation[c], %	4.5	10.0
GCSF use[d], %	31.8	50.0

Common TEAEs (>25%) in OC Dose Expansion



[a]Events included neutropenias, anemia, leukopenias, and thrombocytopenias. [b]One Grade 5 acute respiratory failure was unrelated to the study treatment. [c]Reasons for discontinuation included alanine aminotransferase increased (n = 1; related to treatment), neutrophil count decreased (n = 1; related to treatment), and a small intestinal perforation and rectal hemorrhage (n = 1; not related to treatment; same patient). [d]GCSF-prophylaxis was not permitted in cycle 1.
GCSF, granulocyte colony-stimulating factor; ILD, interstitial lung disease; OC, ovarian cancer; Rina-S, rinatabart sesutecan; TEAE, treatment-emergent adverse event.

Conclusions

- Rina-S, an investigational, novel ADC directed at FRα, showed encouraging antitumor activity as a single agent given Q3W in patients with heavily pretreated OC and EC in dose escalation
- Treatment with Rina-S at 120 mg/m^2 Q3W resulted in a confirmed ORR of 50.0%, including one complete response, in patients with heavily-pretreated OC in dose expansion; all responses were ongoing at data cutoff
  - Based on these results 120 mg/m^2 has been selected for further evaluation
- Responses with Rina-S were observed regardless of FRα expression levels and in patients with prior MIRV exposure
- Treatment with Rina-S was well tolerated, with manageable TEAEs
  - Hematologic AEs were manageable without significant dose reductions and with low rates of treatment discontinuation
  - No signals of ocular toxicities, neuropathy, or ILD were observed
- Based on these findings, further evaluation of Rina-S is ongoing as a single-agent and in combination[a]
  - EC dose expansion (Cohort B2, fully-enrolled): single agent Rina-S in patients with EC after ≥1 prior lines of therapy including with prior platinum and ICI
  - PROC dose expansion (Part C, enrolling): single agent Rina-S in patients with PROC after 1-3 prior lines of therapy

[a]Part D is evaluating Rina-S in combination with carboplatin in patients with PSOC (cohort D1), in combination with bevacizumab in patients with PROC (cohort D2), and in combination with pembrolizumab in patients with EC (cohort D3).
ADC, antibody-drug conjugate; AE, adverse event; EC, endometrial cancer; FRα, folate receptor α; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; MIRV, mirvetuximab soravtansine; OC, ovarian cancer; PROC, platinum-resistant ovarian cancer. Rina-S, rinatabart sesutecan; TEAEs, treatment-emergent adverse events

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