Background Rinatabart sesutecan (Rina-S) is an antibody-drug conjugate (ADC) consisting of a human monoclonal antibody that selectively binds FRα, a novel cleavable hydrophilic linker, and a topoisomerase 1 inhibitor payload, exatecan. The hydrophilic linker confers superior physicochemical properties and pharmacokinetics compared to conventional linkers in preclinical models. Rina-S exerts robust antitumor activity in mouse xenograft models of multiple tumor types with high, moderate, and low FRα expression, consistent with the broad potency and bystander activity of the exatecan payload. Here we present emerging data from the first-in-human trial (NCT05579366).

Methods PRO1184–001 is an ongoing, phase 1/2, open-label, dose escalation and expansion study. Eligible patients have locally advanced and/or metastatic/unresectable solid tumors, including epithelial ovarian cancer (EOC), endometrial cancer, non-small cell lung cancer (NSCLC), breast cancer, or mesothelioma. Patients must have measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or mRECIST 1.1 for pleural mesothelioma. FRα tumor expression levels were retrospectively tested using the Ventana immunohistochemistry FOLR1 assay. Primary objectives are to identify the maximum tolerated dose, recommended phase 2 dose, and evaluate safety and tolerability.

Results As of 09 June 2023, 10 patients have been treated with Rina-S at 60 (n=3) and 120 (n=7) mg/m². Tumor types included platinum-resistant/refractory EOC (n=5), endometrial cancer (n=2), NSCLC (n=2), and mesothelioma (n=1). Patients received a median of 4 (range, 1 to 9) prior treatments. Eight patients completed the DLT period and had post-baseline tumor assessments per RECIST. The other 2 patients, who had FRα-negative tumors, discontinued due to early clinical progression. Patients have received between 1 and 8 cycles and 5 remain on treatment.

The most common treatment-related adverse events (AEs) were nausea (n=5), decreased white blood cell counts (n=3), and fatigue, decreased lymphocyte counts, and decreased neutrophil counts (n=2 each); most events were Grade 1 or 2. Treatment-related ≥ Grade 3 hematologic AEs were reported for 2 patients treated at 120 mg/m². No ocular toxicity or interstitial lung disease was observed. No DLTs were observed.

Antitumor activity was observed at both dose levels and in patients with high, medium, and low FRα expression, including an ongoing confirmed partial response in a patient with endometrial cancer and decreased tumor measurements in additional patients.

Conclusions Emerging data suggest a promising safety profile for Rina-S, with most AEs being mild or moderate and consistent with findings in preclinical studies. Antitumor activity has been observed at well tolerated dose levels. Dose escalation continues.

Trial Registration Clinicaltrials.gov NCT05579366

Ethics Approval The study obtained ethics approval (WCG Institutional Review Board; ID 20223552) and participants gave informed consent prior to taking part.

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