REJOICE-PanTumor01: A Phase 2 signal-seeking study of raludotatug deruxtecan (R-DXd) in patients with advanced or metastatic gynecologic or genitourinary tumors

P040-4

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OBJECTIVES

- REJOICE-PanTumor01 is a global, open-label, Phase 2 signal-seeking study to evaluate the efficacy and safety of R-DXd monotherapy in previously treated patients with locally advanced or metastatic solid tumors. The study will include five tumor-specific cohorts:
  - Gynecologic cancers: endometrial cancer, cervical cancer, non-HGSOC
  - Genitourinary cancers: urothelial cancer, ccRCC
- Each cancer has a high unmet need in advanced and/or refractory disease

INTRODUCTION

- CDH6 is a cell–cell adhesion protein that is minimally expressed in healthy tissues[1,2] and is aberrantly expressed in many solid tumors, making it an attractive therapeutic target[2]
- Increased CDH6 expression in solid tumors has been reported to correlate with poor prognosis[3–5]
- R-DXd is a novel CDH6-directed ADC composed of a humanized CDH6 IgG1 monoclonal antibody covalently linked to a topoisomerase I inhibitor payload (DXd) via a cleavable linker (**Figure 1**)[6,7]
- In the ongoing Phase 1 study of R-DXd in patients with heavily pretreated OC (NCT04707248), R-DXd at doses of 4.8–6.4 mg/kg showed promising efficacy with a manageable safety profile, irrespective of CDH6 expression levels (based on available Phase 1 data; data cutoff: July 14, 2023)[8]
  - ORR was 48.6% (95% CI, 31.9–65.6), median DOR was 11.2 months (95% CI, 3.1–NE), DCR was 97.4% (95% CI, 86.2–99.9), and PFS was 8.1 months (95% CI, 5.3–NE)[8]
  - Grade ≥3 TEAEs were reported in 44.4% of patients[8]
  - Further investigation of R-DXd monotherapy is ongoing in the Phase 2/3 REJOICE-Ovarian01 study (NCT06161025), which is evaluating R-DXd efficacy and safety in patients with platinum-resistant OC[9]
- Herein we present REJOICE-PanTumor01, a Phase 2 signal-seeking study (NCT06660654) in patients with locally advanced or metastatic solid tumors selected irrespective of CDH6 expression level[10]

Figure 1: R-DXd was designed with 7 key attributes

The **mAb** directs the DXd ADC to the tumor cell

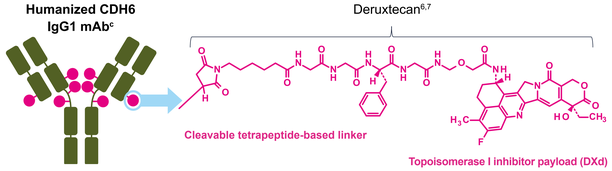
1. High drug-to-antibody ratio ~8[6,a]

The **linker** binds the mAb to the payload

2. Plasma-stable linker–payload[6,7,a]
3. Tumor-selective cleavable linker[6,a]

The **payload** induces cell death when delivered to the tumor

4. Topoisomerase I inhibitor[6,a]
5. High potency[6,7,a]
6. Short systemic half-life[7,a,b]
7. Bystander antitumor effect[6,a]

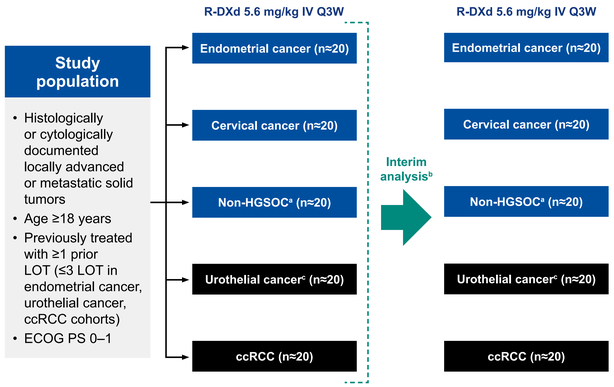


[a]The clinical relevance of these features is under investigation. [b]Based on animal data. [c]Image is for illustrative purposes only; actual drug positions may vary.

METHODS

- REJOICE-PanTumor01 (NCT06660654) is a global, open-label, Phase 2 signal-seeking study to evaluate the efficacy and safety of R-DXd monotherapy in patients with locally advanced or metastatic solid tumors who have received ≥1 prior line of standard treatment (≤3 prior lines in endometrial cancer, urothelial cancer, and ccRCC cohorts), irrespective of tumor CDH6 expression
- Cohorts are tumor-type specific and include:
  - Gynecologic cancers: endometrial cancer, cervical cancer, non-HGSOC
  - Genitourinary cancers: urothelial cancer, ccRCC
- Approximately 40 patients will be enrolled into each cohort (**Figure 2**). Key eligibility criteria are summarized in **Table 1**
  - Enrolled patients will receive R-DXd 5.6 mg/kg IV Q3W until disease progression (assessed by investigator per RECIST 1.1), unacceptable toxicity, death, or another reason per protocol
  - Tumor assessments will occur every 6 weeks (±7 days) from C1D1 for the first 48 weeks and then every 12 weeks thereafter
- The primary endpoints are ORR (investigator assessed) for the gynecologic and urothelial cohorts, DCR (investigator assessed) for the ccRCC cohort, and safety and tolerability (all cohorts) (**Table 2**)
- No formal hypothesis testing will be performed; ORR and DCR will be analyzed using the Clopper–Pearson method to determine 95% CI. PFS and DOR will be analyzed using the Kaplan–Meier method

Figure 2: Study design



Until PD,[d] unacceptable toxicity, death, study closure, or withdrawal of consent

Follow-up

Safety: 40 days[e]

Long-term survival: 90 days

[a]Including clear cell, low-grade endometrioid, low-grade serous, or mucinous OC. [b]Interim nonbinding futility analysis will be performed for each cohort when 20 patients have undergone 12 weeks of follow-up from study drug initiation or have discontinued per protocol. [c]A minimum of 20 patients in the 2L setting who have previously received enfortumab vedotin and pembrolizumab in combination will be enrolled. [d]Assessed by investigator per RECIST 1.1. [e]Forty days after the last study drug administration or 30 days after the last study drug administration if the patient starts a new anticancer treatment, whichever occurs first.

Table 1: Enrollment criteria

Key inclusion criteria
• Histologically or cytologically documented locally advanced or metastatic endometrial cancer, cervical cancer, non-HGSOC,[a] urothelial cancer, or ccRCC
• Age ≥18 years
• ECOG PS 0–1
• ≥1 prior lines of standard therapy (≤3 prior lines in endometrial cancer, urothelial cancer, and ccRCC cohorts)
• Progressive disease (radiologically documented) on or after most recent systemic therapy
• ≥1 lesion not previously irradiated and amenable to biopsy; patients must consent to provide a pretreatment biopsy or provide an archival tumor sample collected following completion of most recent systemic therapy
• ≥1 measurable lesion (per RECIST 1.1)
• Each cohort also contains cohort-specific inclusion criteria
Key exclusion criteria
• Clinically active brain metastasis, spinal cord compression, or leptomeningeal carcinomatosis, defined as untreated or symptomatic
• Prior exposure to other CDH6-targeting agents or ADCs with a related exatecan derivative
• History of ILD/pneumonitis that required corticosteroids; current or suspected ILD/pneumonitis
• Clinically severe pulmonary compromise
• Uncontrolled or significant cardiovascular disease
• Current or active infections: uncontrolled systemic bacterial, fungal, or viral infections requiring IV antibiotics; active HIV, HBV, or HCV

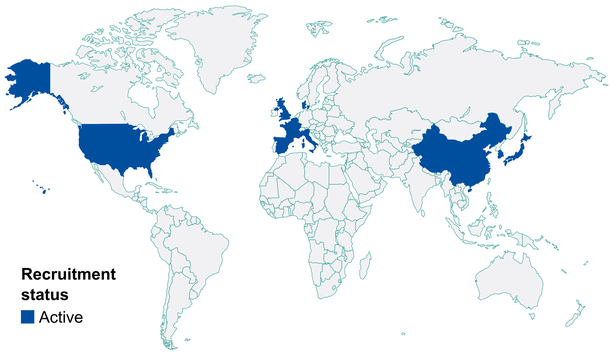
[a]Including clear cell, low-grade endometrioid, low-grade serous, or mucinous OC.

Table 2: Study endpoints

Primary endpoints
• ORR[a] (all except ccRCC cohort)
• DCR[a] (ccRCC cohort only)
• TEAEs, SAEs, and AESIs
Secondary endpoints
• ORR[a] (ccRCC cohort only)
• DCR[a] (all except ccRCC cohort)
• PFS[a]
• DOR[a]
• TTR[a]
• Pharmacokinetics
• Immunogenicity

[a]Assessed by investigator per RECIST 1.1.

Figure 3: Enrollment status



Enrollment began in January 2025 and is ongoing in Belgium, China, Denmark, France, Italy, Japan, Republic of Korea, Spain, the United Kingdom, and the United States

Estimated study completion: September 30, 2027

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ABBREVIATIONS

2L, second-line; **ADC**, antibody–drug conjugate; **AESI**, adverse event of special interest; **C1D1**, Cycle 1 Day 1; **ccRCC**, clear cell renal cell carcinoma; **CDH6**, cadherin 6; **CI**, confidence interval; **DCR**, disease control rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HBV**, hepatitis B virus; **HCV**, hepatitis C virus; **HIV**, human immunodeficiency virus; **IgG1**, immunoglobulin G1; **ILD**, interstitial lung disease; **IV**, intravenous; **LOT**, line of therapy; **mAb**, monoclonal antibody; **NE**, not estimable; **non-HGSOC**, non–high-grade serous ovarian cancer; **OC**, ovarian cancer; **ORR**, objective response rate; **PD**, progressive disease; **PFS**, progression-free survival; **Q3W**, every 3 weeks; **R-DXd**, raludotatug deruxtecan; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event; **TTR**, time to response.

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DISCLOSURES

Kenichi Harano was a speaker for AstraZeneca, Chugai, Eizai, MSD, Taiho, and Takeda, has served in an advisory role for AstraZeneca, Chugai, Taiho, and Takeda, and received institution research funding from AstraZeneca, Chugai, Daiichi-Sankyo, MSD, and Takeda.

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