Raludotatug Deruxtecan in Participants With Gastrointestinal Cancers: Phase 2 REJOICE-GI01 Trial

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OBJECTIVES

- To evaluate the efficacy and safety of R-DXd for locally advanced, unresectable or metastatic PDAC, BTC, CRC, and GEAC

Primary

- Objective response rate (ORR) per RECIST v1.1 by blinded independent central review (BICR)

Secondary

- Safety and tolerability (AEs, discontinuation due to AEs)
- Duration of response (DOR) per RECIST v1.1 by BICR
- Progression-free survival (PFS) per RECIST v1.1 by BICR
- Overall survival (OS)

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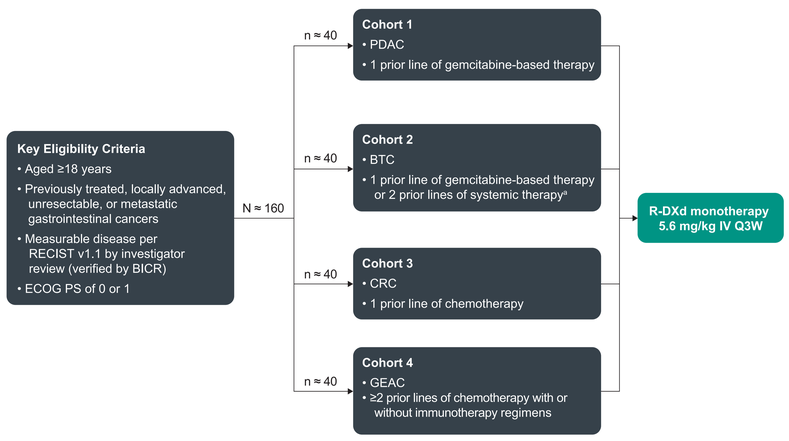
BACKGROUND

- Gastrointestinal cancers such as pancreatic ductal adenocarcinoma (PDAC), biliary tract cancer (BTC), colorectal cancer (CRC), and gastroesophageal adenocarcinoma (GEAC) are associated with poor prognoses, in advanced stages with 5-year survival rates ranging from 3%-15%[1,2]
- There is a strong clinical need for alternative therapies that improve survival and reduce adverse events (AEs) beyond the current standard of care
- Cadherin-6 (CDH6) is a transmembrane protein that is overexpressed in several cancers, including gastrointestinal cancers, and is associated with a poor prognosis[3-5]
- Raludotatug deruxtecan (R-DXd) is a first-in-class CDH6-targeting antibody-drug conjugate (ADC) comprising a humanized anti-CDH6 immunoglobulin G1 monoclonal antibody (mAb), cleavable linker, and topoisomerase I inhibitor payload (MAAA-1181a)[5]
  - In the ongoing phase 1 DS600-A-U101 study, R-DXd monotherapy showed promising antitumor activity in participants with heavily pretreated ovarian cancer who had a wide range of CDH6 expression, including little to no expression[6]
- The nonrandomized, open-label, phase 2 REJOICE-GI01 trial (NCT06864169) is designed to evaluate R-DXd for locally advanced, unresectable, or metastatic PDAC, BTC, CRC, and GEAC

METHODS

Study design



[a]First-line gemcitabine-based therapy and second-line noncytotoxic therapy for actionable molecular alterations.

Participant eligibility

Key inclusion criteria

- All cohorts
  - Aged ≥18 years
  - Histologically confirmed locally advanced, unresectable or metastatic gastrointestinal cancer
  - Measurable disease per RECIST v1.1 by investigator review and verified by BICR
  - ECOG PS of 0 or 1
  - Life expectancy of ≥3 months
  - Adequate organ function
- Cohort 1
  - PDAC
  - 1 prior line of gemcitabine-based therapy
- Cohort 2
  - BTC (intra- or extrahepatic cholangiocarcinoma or gallbladder cancer)
  - 1 prior line of gemcitabine-based therapy or 2 prior lines of systemic therapy (first-line gemcitabine-based therapy and second-line noncytotoxic therapy for actionable molecular alterations)
- Cohort 3
  - CRC
  - Locally determined pMMR or not MSI-H tumor status
  - 1 prior line of chemotherapy including a fluoropyrimidine plus oxaliplatin regimen
  - Treated with anti-VEGF treatment, anti-EGFR mAb, or encorafenib plus anti-EGFR mAb, if indicated and available
- Cohort 4
  - GEAC
  - ≥2 prior lines of chemotherapy, including a fluoropyrimidine and platinum doublet, with or without immunotherapy regimens
  - Eligible regardless of HER2 status and those who are HER2 positive must have received anti-HER2 therapy

Key exclusion criteria

- Prior exposure to other CDH6-targeted agents
- Prior exposure to irinotecan or another topoisomerase I inhibitor, including the payload of ADC
- Received prior systemic anticancer therapy within 4 weeks or 5 half-lives (whichever is shorter) and has not recovered to grade ≤1 or baseline from any associated AEs before allocation
- Received an investigational agent or has used an investigational device with 4 weeks before study treatment
- History of noninfectious interstitial lung disease (ILD)/pneumonitis that required steroids or has current ILD/pneumonitis, and/or suspected ILD/pneumonitis
- Has clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses
- Has uncontrolled or significant cardiovascular disease
- Has a known additional malignancy that is progressing or has required active treatment within the past 3 years
- Has known active central nervous system metastases and/or carcinomatous meningitis
- Active autoimmune disease that has required systemic treatment in the past 2 years
- Has not adequately recovered from major surgery or has ongoing surgical complications
- HIV-infected participants with a history of Kaposi sarcoma and/or multicentric Castleman disease
- Received a live or live-attenuated vaccine within 30 days before the first dose of study treatment

Assessment and follow-up

	Detail
Tumor response	• Response assessments (including CT or MRI) will be performed at 6 weeks from the date of allocation, then every 6 weeks, or more frequently if clinically indicated • After 48 weeks, assessments will be performed every 12 weeks until any criteria for discontinuation are met
AEs	• AEs will be monitored and assessed by investigators throughout the study and for 40 days after cessation of study treatment • Serious AEs will be monitored and assessed by investigators throughout the study and for 90 days after cessation of study treatment (40 days, if new anticancer therapy is initiated) • Severity will be graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0

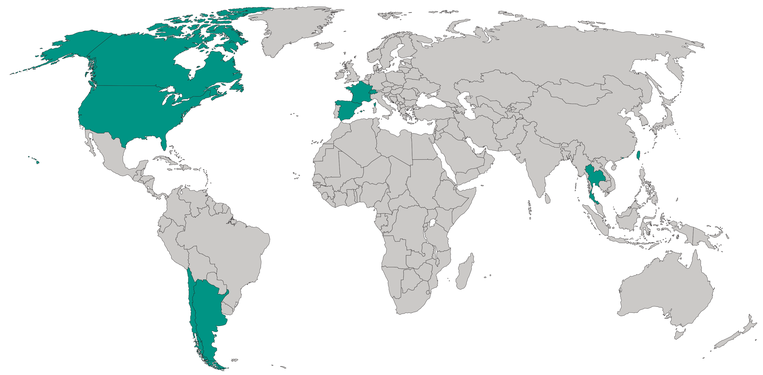
Analyses

	Detail
Efficacy	• Efficacy analyses will be conducted in the all-participants-as-treated population, comprising all allocated participants who received ≥1 dose of study treatment • ORR (95% CI) will be evaluated using the Clopper and Pearson exact binomial method • DOR, PFS, and OS will be estimated using the Kaplan-Meier method
Safety	• Safety analyses will be conducted in the all-participants-as-treated population, comprising all allocated participants who received ≥1 dose of study treatment • AEs will be summarized descriptively

CURRENT STATUS

Sites of enrollment for the REJOICE-GI01 study (green)

- Argentina, Canada, Chile, France, Hong Kong, Spain, Switzerland, Taiwan, Thailand, and the United States



ABBREVIATIONS

CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; IV, intravenously; MRI, magnetic resonance imaging; MSI-H, microsatellite instability high; pMMR, proficient mismatch repair; Q3W, every 3 weeks; VEGF, vascular endothelial growth factor.

REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2025. Atlanta: American Cancer Society; 2025.
2. Siegel RL et al. *CA Cancer J Clin.* 2024;74:12-49.
3. Hartana CA et al. *Br J Cancer.* 2016;115:957-966.
4. Ma C et al. *Oncol Lett.* 2018;15:9498-9506.
5. Suzuki H et al. *Mol Cancer Ther.* 2024;23:257-271.
6. Moore KN et al. *Gynecol Oncol.* 2024;190:S6-S7.

ACKNOWLEDGEMENTS

The authors thank the participants and their families for their involvement in the study, all investigators, and site personnel. Medical writing and/or editorial assistance was provided by Bresler Swanepoel, PhD, and Cindi A. Hoover, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Daiichi Sankyo Company, Limited, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

DISCLOSURES

Makoto Ueno declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Aska, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Incyte, J-Pharma, MSD, Nihon Servier, Nippon Boehringer Ingelheim, Novartis, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, Viatris, and Yakult Honsha; and grants or contracts from Amgen, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Chiome Bioscience, Chugai Pharmaceutical, DFP, Eisai, Incyte, J-Pharma, Jazz Pharmaceuticals, MSD, Nihon Servier, Novartis, Novocure, Ono Pharmaceutical, Revolution Medicine, and Taiho Pharmaceutical.

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Presented at the ESMO Congress 2025; Berlin, Germany, and online; October 17-21, 2025

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