REJOICE-Ovarian02: A Phase 1b/2 Study of Raludotatug Deruxtecan (R-DXd) With Other Anticancer Agents in Participants With Relapsed Ovarian Cancer After Platinum-Based Chemotherapy

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A. Oaknin[1]; J. Call[2]; R. Shapira Frommer[3]; O. Rosengarten[4]; R. Perets[5]; A. González Martín[6]; M. Gil-Martin[7]; L. Manso Sánchez[8]; L. Gilbert[9]; R. Redman[10]; P. Johannet[11]; R. Kristeleit[12]; R. Miller[13]; S. Banerjee[14]; S. Lheureux[15]; T. Zaid[16]; Q. Zhao[17]; S. Re[18]; C. Gonzalez[19]; D.L. Richardson[20]

[1]Medical Oncology Service, Vall d'Hebron Institute of Oncology, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [2]START Mountain Region, West Valley City, UT, USA; [3]Sheba Medical Center, Ramat Gan, Tel Aviv District, Israel; [4]Shaare Zedek Medical Center, Jerusalem, Israel; [5]Rambam Health Care Campus, Haifa, Israel; [6]Cancer Center Clínica Universidad de Navarra, Madrid, Spain; [7]Institut Català d'Oncologia L'Hospitalet, Barcelona, Spain; [8]Hospital Universitario 12 de Octubre, Madrid, Spain; [9]Research Institute, McGill University Health Centre, McGill University, Montreal, QC, Canada; [10]The University of Louisville, Brown Cancer Center, Louisville, KY, USA; [11]Memorial Sloan Kettering Cancer Center, New York City, NY, USA; [12]Guy's & St Thomas' NHS Foundation Trust and King's College London, London, UK; [13]Barts Health NHS Trust, London, UK; [14]Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; [15]Princess Margaret Cancer Centre, Toronto, ON, Canada; [16]Houston Methodist Hospital and Weill Cornell Medical College, Houston, TX, USA; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [19]MSD, Madrid, Spain; [20]Stephenson Cancer Center, University of Oklahoma Health Science Center/SCRI, Oklahoma City, OK, USA

OBJECTIVES

Primary

- Safety and tolerability including dose-limiting toxicities (DLTs), adverse events (AEs), and discontinuations of study treatment due to AEs

Secondary

- ORR (confirmed complete response or partial response) per RECIST version 1.1 as assessed by blinded independent central review (BICR)

INTRODUCTION

- The standard of care for primary systemic therapy for patients with high-grade serous ovarian cancer (HGSOC) includes platinum-based chemotherapy[1]; however, many patients experience disease recurrence. Recurrent HGSOC is invariably fatal, and there is a high unmet need for new therapies[2]
- Recurrent HGSOC is considered platinum sensitive if recurrence occurs ≥6 months after completing the last dose of platinum-based therapy and platinum resistant if recurrence occurs <6 months after completing platinum-based therapy[1]
  - Recommended treatment includes combination platinum-based chemotherapy for platinum-sensitive recurrent ovarian cancer (PSOC) and non-platinum cytotoxic agents with or without bevacizumab or targeted therapy (eg, bevacizumab or mirvetuximab soravtansine-gynx [for folate receptor α-expressing tumors]) for platinum-resistant recurrent ovarian cancer (PROC)[1]
- Cadherin-6 (CDH6) is overexpressed in several tumor types, including HGSOC.[3] In patients with cancer, overexpression of CDH6 has a role in lymph node metastases and is associated with poor prognosis; thus, it is a promising therapeutic target[3,4]
- R-DXd is an antibody-drug conjugate (ADC) consisting of a humanized anti-CDH6 monoclonal IgG1 antibody, an enzymatically cleavable peptide linker, and a cytotoxic topoisomerase I inhibitor (MAAA-1181a), with a target drug-to-antibody ratio of 8
- In a phase 1, first-in-human study (NCT04707248), R-DXd monotherapy showed preliminary antitumor activity and manageable safety in participants with advanced HGSOC[5]
  - Confirmed objective responses were observed in 18 of 37 efficacy-evaluable participants (ORR, 49% [95% CI, 32%–66%])[5]
  - Most AEs resolved with standard of care treatment and protocol-defined dose modification
- REJOICE-Ovarian02 (ClinicalTrials.gov, NCT06843447) is a phase 1b/2, open-label, multicenter, dose-escalation study evaluating the safety, tolerability, and preliminary antitumor activity of R-DXd combined with carboplatin or paclitaxel in participants with PSOC or combined with bevacizumab in participants with PROC
  - We describe the phase 1b, dose-escalation portion of this study

Poster

https://bit.ly/3ZFAzZ7

Plain Language Summary

https://bit.ly/3HaxR7R

METHODS

Study design, participants, and treatment

Figure. REJOICE-Ovarian02 study design (phase 1b portion[a])

ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.
[a] REJOICE-Ovarian02 consists of 2 parts: a phase 1b, dose-escalation portion and a phase 2, dose-expansion portion.
[b] Approximately 78 participants will be enrolled in the phase 1b portion of the study. The actual number of doses to be assessed in each cohort depends on the determination of the MTD based on DLTs using the Bayesian optimal interval design. Once the MTD is determined for each arm, the totality of the data collected will be used to determine the preliminary RP2D for that cohort.
[c] Participants continue to receive R-DXd (cohort A-1 arms 1 and 2) or R-DXd plus bevacizumab (cohort B-1) until disease progression per RECIST version 1.1 and verified by BICR or until another criterion for discontinuation of study treatment is met.
[d] Participants receive up to 6 cycles of carboplatin or paclitaxel.

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Female	• Cerebrovascular accident, transient ischemic attack, or other arterial thromboembolic event <6 mo before allocation
• Aged ≥18 y	• Uncontrolled or significant cardiovascular disease
• Pathologically documented diagnosis of high-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer	• Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses
• Relapsed disease after 1–3 prior lines of therapy	• Grade ≥2 peripheral neuropathy
• Cohort A-1 arms 1 and 2 (PSOC): radiographic evidence of disease progression ≥6 mo (≥180 d) after the last dose of platinum-based therapy	• Prior anti-CDH6 therapy
• Cohort B-1 (PROC): radiographic evidence of disease progression <6 mo (<180 d) after the last dose of platinum-based therapy[a]	• Prior therapy with an ADC containing an exatecan derivative that is a topoisomerase I inhibitor
• Cohort B-1: participant is a candidate for bevacizumab treatment	• Prior systemic anticancer therapy within 4 wk or 5 half-lives (whichever is shorter) before allocation
• Provided tumor tissue from a core or excisional biopsy of a tumor lesion not previously irradiated	• Prior radiotherapy within 2 wk of first dose of study treatment, or has radiation-related toxicities requiring corticosteroids[b]
• Measurable disease per RECIST version 1.1	• Chronic steroid treatment (>10 mg prednisone or equivalent per day)[c]
• ECOG PS of 0 or 1	• Additional malignancy that is progressing or required active treatment within the past 3 y
• Adequate organ function as determined by protocol-specified laboratory values	• Active CNS metastases and/or carcinomatous meningitis[d]
	• History of (noninfectious) pneumonitis/ILD that required steroids or current pneumonitis/ILD

CNS, central nervous system; ILD, interstitial lung disease.
[a] Participants with primary platinum-refractory ovarian cancer (disease that has progressed on or within 12 weeks after the first platinum-based therapy) are not eligible.
[b] 2 weeks or fewer of palliative radiotherapy for non-CNS disease is permitted; the last palliative radiotherapy treatment must have been performed ≥7 days before the first dose of study treatment.
[c] With the exception of inhaled steroids for asthma or chronic obstructive pulmonary disease, mineralocorticoids for participants with orthostatic hypotension, topical steroids for mild skin conditions, low-dose supplemental corticosteroids for adrenocortical insufficiency, premedication for treatment groups and/or premedication in case of any hypersensitivity, and intra-articular steroid injections.
[d] Participants with previously treated brain metastases are eligible provided they are radiologically stable for ≥4 weeks as confirmed by repeat imaging performed during the study screening, are clinically stable, and have not required steroid treatment for ≥14 days before the first dose of study treatment.

Assessments

- AEs are monitored from the time of study treatment allocation until 40 days after the last dose (90 days for serious AEs in cohort B-1) and graded in severity according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
- DLTs are evaluated between day 1 and day 21 of cycle 1

Table 2. Definition of DLTs

• Grade 4 thrombocytopenia of any duration or grade 3 thrombocytopenia lasting ≥7 d
• Grade ≥3 thrombocytopenia associated with clinically significant bleeding
• Grade 4 lymphocytopenia lasting ≥14 d
• Grade 4 anemia of any duration
• Any other grade 4 hematologic toxicity lasting ≥7 d
• Grade 3 or 4 febrile neutropenia
• Grade 4 AST or ALT increases or any abnormality resulting in DILI/Hy's Law
• Grade ≥3 nonhematologic toxicities except - Grade 3 nausea/vomiting or diarrhea for <3 d with adequate antiemetic and other supportive care - Grade 3 fatigue for <7 d
• The following other nonhematologic toxicities: symptomatic CHF of any grade, LVEF abnormality (decline to <40%, absolute >20% decline from baseline, or any decline from baseline leading to discontinuation of study treatment), grade ≥2 ILD or pneumonitis, any grade 3 or 4 nonhematologic laboratory value if clinically significant medical intervention is required or if the abnormality leads to hospitalization or persists for >1 wk - Exceptions: clinically nonsignificant, treatable or reversible laboratory abnormalities including amylase or lipase without clinical evidence of pancreatitis, uric acid, etc
• Any delay in treatment with the planned dose of ≥21 d or discontinuation of study treatment due to a toxicity during the DLT evaluation period
• Grade 5 toxicity

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHF, congestive heart failure; DILI, drug-induced liver injury; LVEF, left ventricular ejection fraction.

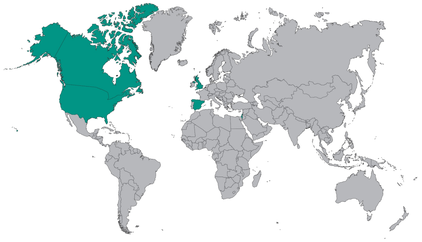
- Tumor imaging is performed at screening, 6 weeks from the date of study treatment allocation, every 6 weeks through week 48, and every 12 weeks thereafter until disease progression, pregnancy, withdrawal of consent, or death
  - Objective responses are confirmed by a repeat scan performed ≥4 weeks after the first indication of a response is observed

Analyses

- Safety and efficacy will be assessed in all allocated participants who receive ≥1 dose of study treatment (ie, all participants as treated)
- DLTs will be assessed in all participants as treated who meet the criteria for DLT evaluation (finished cycle 1 without a DLT or experienced a DLT in cycle 1)
- Dose escalation and determination of the MTD will be based on DLTs using the Bayesian optimal interval design
- The estimated DLT rates among participants treated at the preliminary RP2D will be provided with 90% Bayesian credible intervals
- Point estimates of confirmed ORRs will be provided with 95% CIs using the Clopper and Pearson exact binomial method

CURRENT STATUS

- Enrollment began in April 2025, and the study is planned across 5 countries and 21 sites



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ACKNOWLEDGMENTS

The authors thank the participants and their families and all investigators and site personnel who participated in this study. This study was sponsored by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) and Daiichi Sankyo, Inc., Basking Ridge, NJ, USA. Medical writing assistance was provided by Tina Nie, PhD, of ICON plc (Blue Bell, PA, USA). This assistance was funded by MSD.

CONTACT INFORMATION

Contact Dr. Ana Oaknin at aoaknin@vhio.net for questions or comments

DISCLOSURES

Ana Oaknin reports consulting fees from Agenus, AstraZeneca, Clovis Oncology, Corcept Therapeutics, Deciphera Pharmaceuticals, Daiichi Sankyo, Debiopharm International, Eisai, Exelisis, F. Hoffmann-La Roche, Genmab, GSK, ImmunoGen, Itheos, MSD, Mersana Therapeutics, Myriad Genetics, Novocure, OncoXerna Therapeutics, PharmaMar, Regeneron, Sattuclabs, Seagen–Pfizer, Sutro Biopharma, TORL Therapeutics, Zentalis, and Zymeworks; payment or honoraria for lectures, presentations, speakers bureaus, or manuscript writing from Peerview, Peervoice, Medscape, AstraZeneca, and GSK; support for attending meetings or travel from AstraZeneca, PharmaMar, and Roche; participation on a data safety monitoring board or advisory board from Agenus, AstraZeneca, Clovis Oncology, Corcept Therapeutics, Deciphera Pharmaceuticals, Daiichi Sankyo, Debiopharm International, Eisai, Exelisis, F Hoffmann-La Roche, Genmab, GSK, ImmunoGen, Itheos, MSD, Mersana Therapeutics, Myriad Genetics, Novocure, OncoXerna Therapeutics, PharmaMar, Regeneron, Sattuclabs, Seagen–Pfizer, Sutro Biopharma, TORL Therapeutics, Zentalis, and Zymeworks; leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid, for Gynecologic Cancer Intergroup and European Society for Medical Oncology; and other financial or non-financial interests in Gynecologic Cancer Intergroup, European Society for Medical Oncology, American Society of Clinical Oncology, Spanish Society of Medical Oncology, and GOG Foundation.

Presented at the European Society for Medical Oncology (ESMO) Gynaecological Cancers Annual Congress; Vienna, Austria; June 19–21, 2025.