Protocol: *DS6000-109 / REJOICE-Ovarian01*
IP: *Raludotatug Deruxtecan (R-DXd)*
Phase: *2/3*
Sponsor: *Daiichi Sankyo*

SCDU Ginecologia e Ostetricia, PI Annamaria Ferrero
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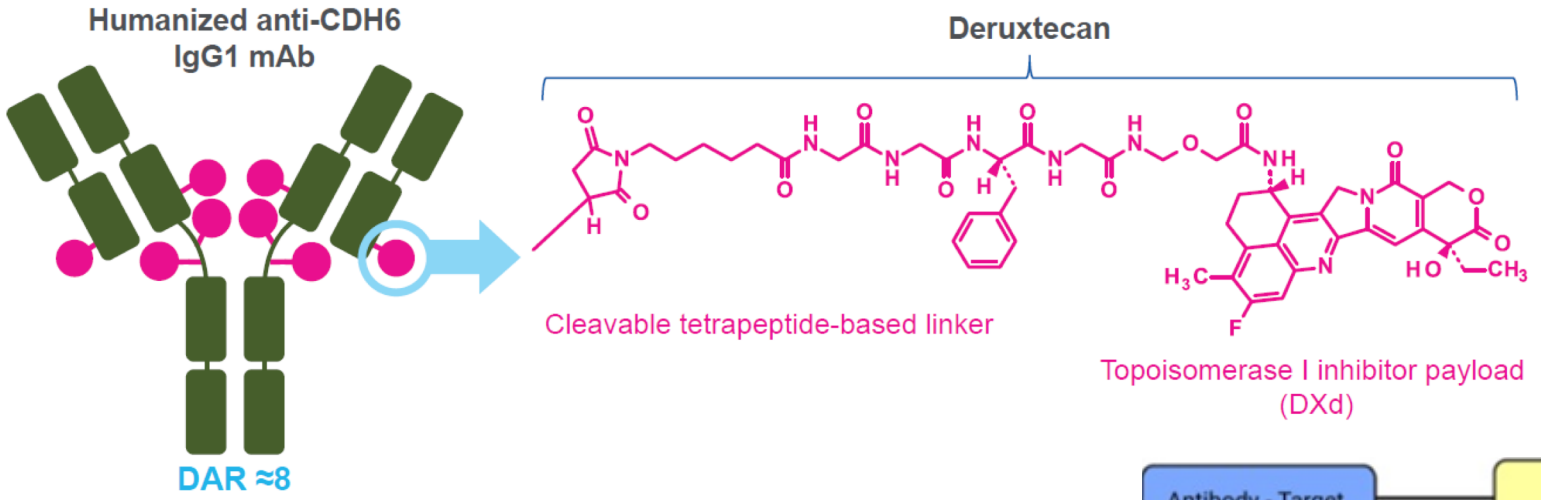
Project Overview

- **Study Title:** A Phase 2/3, Multicenter, Randomized Study of Raludotatug Deruxtecan (R-DXd), a CDH6-directed Antibody-drug Conjugate, in Subjects with Platinum-resistant, High-grade Ovarian, Primary Peritoneal, or Fallopian Tube Cancer **(REJOICE-Ovarian01).**

- **Protocol Number:** DS6000-109
  - › **ENGOT NUMBER:** ENGOT-ov77
  - › **GOG NUMBER:** GOG-3096

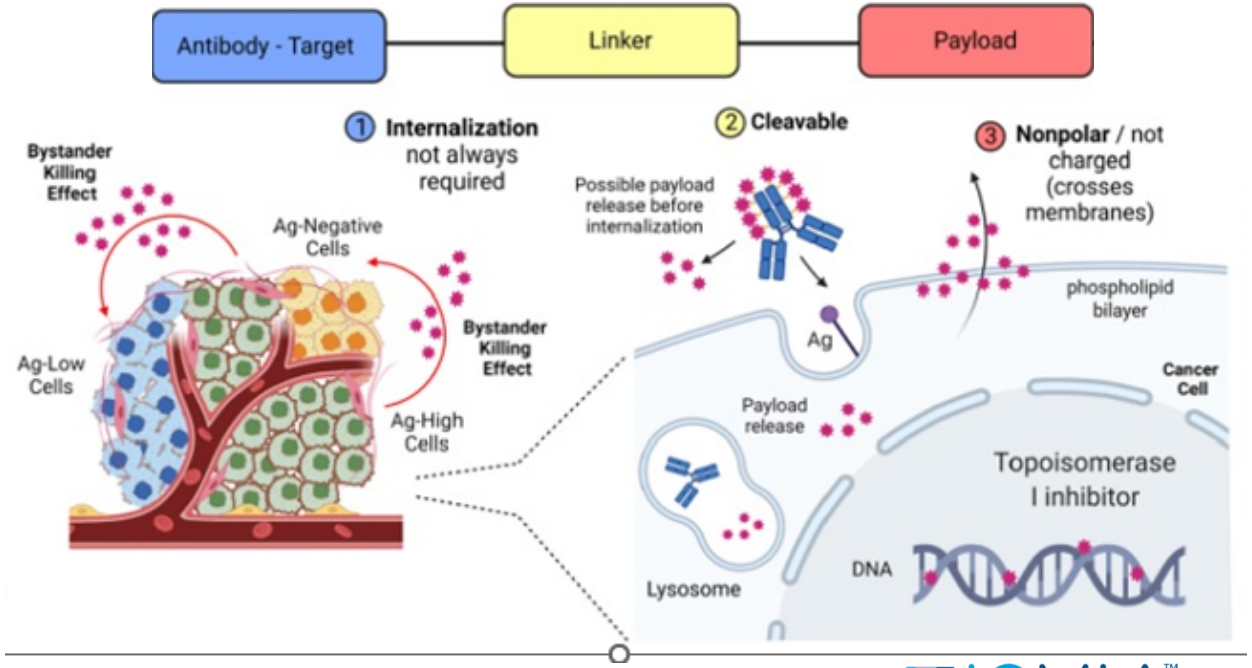
- **Study Population:**
  - Platinum-resistant ovarian, Primary Peritoneal, or Fallopian Tube Cancer
  - 1 to 3 prior systemic lines of anticancer therapy
  - Prior bevacizumab (unless ineligible)
  - Any CDH6 expression level (i.e. no patient selection based on target expression)

IP: Raludotatug Deruxtecan (R-DXd, DS-6000)



High drug to antibody ratio (DAR) ≈ 8

- A humanized anti-CDH6 IgG1 monoclonal antibody[4] attached to
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



Study Objectives

DS6000-109 Is Phase 2/3 Study Which Consists Of A Combination Of 2 Parts

Phase 2:

Primary Endpoint:

- To evaluate BICR assessed Overall Response Rate (ORR) at each dose level of R-DXd

Key Secondary Endpoints:

- To evaluate investigator assessed ORR at each dose level of R-DXd
- To evaluate the duration of response (DoR) at each dose level of R-DXd

Phase 3:

Dual Primary Endpoints:

- To evaluate BICR assessed progression free survival (PFS) and Overall Response Rate (ORR) with R-DXd treatment compared with Investigator's choice

Key Secondary Endpoint:

- To evaluate OS with R-DXd treatment compared with Investigator's choice
- To assess quality of life (QoL), symptoms, and physical functioning from patient-reported outcome (PRO) – to be confirmed after exploring Phase 2 QoL results.

Eligibility

Inclusion Criteria (1/3)

- Age ≥18 years or the minimum legal adult age (whichever is greater) at the time the ICF is signed
- Subjects with histologically or cytologically documented high-grade serious ovarian cancer (OVC), high-grade endometrioid OVC, primary peritoneal cancer, or fallopian tube cancer
- At least one lesion, not previously irradiated, amenable to biopsy, and must consent to provide a pretreatment biopsy and on-treatment biopsy tissue sample (on-treatment biopsy sample not required for the Phase 3 part of study).*
- **Fresh pretreatment biopsy may be waived for subjects who consent to provide an archival tumor tissue sample from a lesion not previously irradiated, performed within 6 months of consent and AFTER treatment with their most recent cancer therapy regimen.*
- Has received at least 1 but no more than 3 prior systemic lines of anticancer therapy:
  - Neoadjuvant ± adjuvant considered 1 line of therapy
  - Maintenance therapy (eg, bevacizumab, poly-ADP ribose polymerase (PARP) inhibitors) will be considered part of the preceding line of therapy
  - Therapy changed due to toxicity in the absence of progression will be considered part of the same line
  - Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance.
  - *At least 1 line of therapy containing bevacizumab*, unless subject is not eligible for treatment with bevacizumab due to precautions/intolerance.
  - Note: Subjects must have radiologically progressed on or after their most recent line of systemic therapy. Biochemical progression will not be considered progression for this study.

Eligibility

Inclusion Criteria (2/3)

- Has platinum-resistant disease:
  - If a subject had only 1 line of platinum therapy, must have received at least 4 cycles of platinum, must have had a best response of not PD, and then progressed between >90 and ≤180 days after the date of the last dose of platinum
  - If a subject had 2 or 3 lines of platinum therapy, must have received at least 2 cycles of platinum and have progressed on or within 180 days after the date of the last dose of platinum
- Has had prior PARP inhibitors for subjects with documented breast cancer gene (BRCA) mutation (germline and/or somatic), unless the subject is not eligible for treatment with a PARP inhibitor.
- Has had prior treatment with mirvetuximab soravtansine for subjects with documented high folate receptor alpha expression, unless the subject is not eligible for treatment with mirvetuximab soravtansine due to precautions/ intolerance, or if the treatment is not approved or available locally.
- Has at least 1 measurable lesion evaluated by CT or MRI according to RECIST v1.1
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Required baseline local laboratory data (within 7 days before start of study drug administration):
  - ❑ Alanine aminotransferase (ALT) and aspartate aminotransferase (AST):
    - ❑ ≤3 × upper limit of normal (ULN) in subjects with no liver metastasis and ≤5.0 × ULN in subjects with liver metastasis
    - ❑ Total bilirubin ≤1.5 × ULN (≤3 × ULN total and ≤1.5 × ULN direct bilirubin are acceptable for subjects with Gilbert's syndrome)
  - ❑ Absolute neutrophil count (ANC) ≥1.5 × 10^9/L (growth factor support allowed up to 14 days before laboratory assessment for eligibility)
  - ❑ Platelet count ≥100 × 10^9/L (transfusion allowed up to 14 days before laboratory assessment for eligibility)
  - ❑ Hemoglobin ≥9.0 g/dL (transfusion and/or growth factor support allowed up to 14 days before laboratory assessment for eligibility)
  - ❑ Serum creatinine ≤1.5 × ULN or creatinine clearance ≥40 mL/min as calculated using the Cockcroft-Gault equation.
  - ❑ Serum albumin ≥2.5 g/dL
  - ❑ Adequate blood clotting function: International normalized ratio and either activated partial thromboplastin time or partial thromboplastin time ≤1.5 × ULN, unless the subject is receiving anticoagulant therapy as long as activated partial thromboplastin time or partial thromboplastin time is within the therapeutic range of intended use of anticoagulants

Eligibility

Inclusion Criteria (3/3)

- For female of childbearing potential: :
  - Negative serum pregnancy test at 72 hours before the first dose of study drug and must be willing to use highly effective birth control upon enrollment, during the Treatment Period, and for 7 months following the last dose of study drug.
  - Female subjects must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.
- Is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
- For Phase 3 (Part B) only: Subjects must be eligible for one of the treatments included in the Investigator's choice of chemotherapy arm and must not have received it previously for OVC.

Eligibility

Exclusion Criteria (1/5)

- Has clear cell, mucinous, or sarcomatous histology, mixed tumors containing any histology, or low-grade/borderline OVC
- Inadequate washout period before Cycle 1 Day 1, defined as follows:
  - Major surgery <28 days
  - Radiation therapy <28 days (if palliative stereotactic radiation therapy without abdominal radiation, ≤14 days)
  - Systemic anticancer therapy (including antibody-drug therapy, retinoid therapy, hormonal therapy) <28 days or 5 half-lives, whichever is shorter, before starting study drug
  - Chloroquine/hydroxychloroquine <14 days
  - Exposure to another investigational drug within 28 days prior to start of study treatment or current participation in other therapeutic investigational procedures
- Clinically active brain metastases, spinal cord compression, or leptomeningeal carcinomatosis, defined as untreated or symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with untreated and asymptomatic brain metastases or subjects with treated brain metastases who are no longer symptomatic and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy, at the investigator's discretion.
  - *Note: If there is a history or suspicion of central nervous system metastasis, a computed tomography (CT) scan of the head or magnetic resonance imaging (MRI) of the brain must be performed at baseline.*

Eligibility

Exclusion Criteria (2/5)

- Any of the following within the past 6 months prior to randomization:
  - cerebrovascular accident
  - transient ischemic attack or
  - other arterial thromboembolic event
- Has a history of (noninfectious) ILD/pneumonitis that required corticosteroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
- Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within three months of the study enrollment, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion, etc.) and any autoimmune, connective tissue, or inflammatory disorders with potential pulmonary involvement (ie, rheumatoid arthritis, Sjogren's syndrome, sarcoidosis, etc.), or prior pneumonectomy
- Uncontrolled or significant cardiovascular disease, including the following:
  - QTcF interval >470 ms (average of triplicate determinations)
  - Diagnosed or suspected long QT syndrome, or known family history of long QT syndrome
  - History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or Torsade de Pointes
  - Subject has bradycardia of less than 50 bpm (as determined by central reading) unless the subject has a pacemaker
  - History of second- or third-degree heart block. Candidates with a history of heart block may be eligible if they currently have pacemakers and have no history of fainting or clinically relevant arrhythmia with pacemakers
  - Myocardial infarction within 6 months prior to screening
  - Uncontrolled angina pectoris within 6 months prior to screening
  - New York heart association (NYHA) Class 3 or 4 congestive heart failure
  - Left ventricular ejection fraction (LVEF) <50% or institutional lower limit of normal as measured by echocardiography or multi-gated acquisition scan
  - Coronary/peripheral artery bypass graft within 6 months prior to screening
  - Uncontrolled hypertension (resting systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)
  - Complete left or right bundle branch block

Eligibility

Exclusion Criteria (3/5)

- Chronic steroid treatment (>10 mg/day) with the exception of the following:
  - Inhaled steroids for asthma, chronic obstructive pulmonary disease,
  - Mineralocorticoids (eg, fludrocortisone) for subjects 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
  - Intra-articular steroid injections.
- History of malignancy other than epithelial OVC, primary peritoneal cancer, or fallopian tube cancer within 3 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (e.g., 5- year OS rate >90%) and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, ductal carcinoma in situ, or Stage 1 uterine cancer)
- Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE version 5.0, Grade ≤1 or baseline
  - Note: Subjects may be enrolled with chronic, stable Grade 2 toxicities (defined as no worsening to Grade >2 for 3 months prior to randomization and managed with SOC treatment) that the investigator deems related to previous anticancer therapy, following discussion with the Sponsor, such as the following:
    - Chemotherapy-induced neuropathy
    - Fatigue
    - Endocrinopathies, which may include hypothyroidism, hyperthyroidism, Type 1 diabetes, hyperglycemia, adrenal insufficiency
    - Skin pigmentation (vitiligo)
- Prior exposure to other CDH6-targeted agents or an ADC that consists of an exatecan derivative that is a topoisomerase I inhibitor (eg, trastuzumab deruxtecan, datopotamab deruxtecan)
- History of hypersensitivity to any excipients in the R-DXd or any known contraindication to treatment with, including hypersensitivity to, the study drug(s)

Eligibility

Exclusion Criteria (4/5)

- Has a known human immunodeficiency virus (HIV) infection that is not well controlled. Subjects must be tested for HIV viral load during the Screening Period if acceptable by local regulations or institutional review boards (IRBs)/ethics committees (ECs). All the following criteria are required to define an HIV infection that is well controlled: undetectable viral ribonucleic acid (RNA) load, CD4+ counts/levels of >350 cells/μL, no history of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the past 12 months, and stable for at least 3 weeks on the same anti-HIV retroviral medications.
    - If an HIV infection meets the above criteria, the subject's viral RNA load and CD4+ cell count should be monitored per local standard of care (eg, every 3 months)
- Has any evidence of severe or uncontrolled systemic diseases (including active bleeding diatheses or active infection, substance abuse) or other factors which in the investigator's opinion makes it undesirable for the subject to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required
- Has an active or uncontrolled hepatitis B and/or hepatitis C infection. Subjects must be tested for hepatitis B (hepatitis B virus surface antigen [HBsAg] and anti-hepatitis B core antigen [HBc]) and hepatitis C virus antibody (HCV Ab) during the Screening Period. Subjects are eligible if they meet the following conditions:
    - Have been curatively treated for hepatitis C virus (HCV) infection as demonstrated by undetectable HCV RNA
    - b. Have received hepatitis B virus (HBV) vaccination with only anti-hepatitis B surface antibody (HBs) positivity and no clinical signs of hepatitis
    - c. Are HBsAg- and anti-HBc+ (ie, those who have cleared HBV after infection) and meet conditions i to iii of criterion "d" below
    - D. Are HBsAg+ with chronic HBV infection (lasting 6 months or longer) and meet conditions i to iii below:
        - (i) HBV DNA viral load <2000 IU/mL
        - (ii) Have normal transaminase values, or, if liver metastases are present, abnormal transaminases with a result of AST/ALT <3 × ULN that are not attributable to HBV infection
        - (iii) Start or maintain antiviral treatment if clinically indicated as per the Investigator

Eligibility

Exclusion Criteria (5/5)

- Female who is pregnant or breastfeeding or intends to become pregnant during the study
- Psychological, social, familial, or geographical factors that would prevent regular follow-up
- Prior or ongoing clinically relevant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the investigator's opinion, could affect the safety of the subject; alter the absorption, distribution, metabolism, or excretion of the study drug; or confound the assessment of study results
- Has a history of receiving live-attenuated vaccine (mRNA and replication-deficient adenoviral vaccines are not considered attenuated live vaccines) within 30 days prior to the first exposure to study intervention
- For Phase 3 (Part B) only: Subjects are ineligible if they have a history of any contraindication included in the approved local label for the control group treatment.

Thank you for your time!