A randomized Phase 3 study of first-line trastuzumab deruxtecan with rilvegostomig or pembrolizumab in patients with HER2-expressing, mismatch repair-proficient, primary advanced or recurrent endometrial cancer: DESTINY-Endometrial01/GOG-3098/ENGOT-EN24

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Poster P16-03

Plain language summary

Why are we performing this research?

Some people with endometrial cancer have tumors with high levels of a protein called human epidermal growth factor receptor 2 (HER2), known as HER2-expressing (immunohistochemistry [IHC] 3+/2+) endometrial cancer; ~4–17% of endometrial cancers are HER2 IHC 3+ and ~11–39% are HER2 IHC 2+.[1–5] These cancers are often mismatch repair-proficient (which means one of the cellular systems that repairs mistakes when DNA is copied is working properly, known as pMMR) and are associated with features that suggest the disease could be more aggressive.[6,7] Currently, there are no approved first-line HER2-directed therapies for people with HER2-expressing, pMMR endometrial cancer. Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, which is a chemotherapy with a linker (together called deruxtecan) joined to an antibody (trastuzumab). T-DXd binds to HER2 on the surface of cancer cells. Once inside the cell, it releases the chemotherapy to kill these cells.[8,9] Rilvegostomig blocks both programmed cell death protein 1 (PD-1) and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) proteins;[10] pembrolizumab blocks PD-1.[11] Both drugs help the immune system kill cancer cells.[10,11] DESTINY-Endometrial01/GOG-3098/ENGOT-EN24 aims to investigate the effects of T-DXd in combination with rilvegostomig or pembrolizumab in people with HER2-expressing endometrial cancer.

How are we performing this research?

DESTINY-Endometrial01/GOG-3098/ENGOT-EN24 is an ongoing clinical study that is taking place at multiple locations worldwide to assess the benefit and possible side effects of T-DXd in combination with rilvegostomig or pembrolizumab versus chemotherapy (carboplatin/paclitaxel) with pembrolizumab in people with HER2-expressing, pMMR endometrial cancer. The primary outcome of interest is the length of time after participants are randomly assigned to treatment until the cancer grows, spreads or gets worse, or the participant dies from any cause.

Who will participate in this study?

People must be aged 18 years or older and have HER2-expressing (IHC 3+/2+), pMMR endometrial cancer that has spread from the original site to other parts of the body (advanced) or returned after a period of time during which the cancer was not detectable (recurrent). People cannot participate if they have had previous anticancer therapy, with the exception of one prior chemotherapy treatment given before or after surgery to try and cure their cancer, a history of organ transplant, a heart attack (within 6 months of taking part), or non-infectious interstitial lung disease (scarring of the lungs) / pneumonitis (inflammation of the lungs without infection) that required treatment with steroids.

Where can I access more information?

For more information about DESTINY-Endometrial01/GOG-3098/ENGOT-EN24, please visit https://clinicaltrials.gov/study/NCT06989112. You may also speak to your doctor about clinical studies.

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Background

- Human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) 3+ and IHC 2+ expression are observed in approximately 4–17% and 11–39% of endometrial cancer cases, respectively,[1–5] predominantly in mismatch repair-proficient (pMMR) tumors, and are associated with markers of aggressive disease[6–8]
- The addition of immune checkpoint inhibitors, including pembrolizumab (anti-programmed cell death protein 1 [PD-1] monoclonal antibody), to first-line chemotherapy has demonstrated improved clinical outcomes in patients with advanced or recurrent endometrial cancer.[9–11] However, in the absence of HER2-directed therapies in the first-line setting, there remains a continued need to further improve outcomes for patients with HER2-expressing, pMMR endometrial cancer
  - Given the established benefit of first-line immunotherapy plus chemotherapy in endometrial cancer,[9–11] replacing chemotherapy with a HER2-directed therapy offers the potential to enhance antitumor activity in HER2-expressing tumors
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate that is composed of an anti-HER2 monoclonal antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitory payload[12,13]
  - T-DXd is approved in multiple countries worldwide, including the US, for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors that have progressed after prior systemic treatment and/or have no satisfactory alternatives[14–16]
  - This approval was based, in part, on results from DESTINY-PanTumor02 Part 1, in which T-DXd demonstrated clinically meaningful activity in pretreated patients with HER2-expressing (IHC 3+/2+) solid tumors[17]
  - Particular benefit was observed in patients with gynecologic cancers, including those with endometrial tumors; investigator-assessed objective response rate (ORR) and median progression-free survival (PFS) were 57.5% (95% confidence interval [CI] 40.9, 73.0) and 11.1 months (95% CI 7.1, not evaluable [NE]), respectively, and median overall survival (OS) was 26.0 months (95% CI 12.8, NE), for patients with pretreated HER2-expressing endometrial tumors[17]
- Rilvegostomig is a monovalent, fragment crystallizable (Fc)-reduced, bispecific, humanized immunoglobulin G1 monoclonal antibody that binds with high affinity to PD-1 and human T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) receptors[18]
  - Rilvegostomig has shown encouraging preliminary efficacy and tolerability across tumor types,[19,20] including in combination with chemotherapy as a first-line treatment for gastric and gastroesophageal junction cancers[20]
  - In a preclinical study, T-DXd with a bispecific TIGIT/PD-1 antibody (a murine surrogate of rilvegostomig) enhanced tumor growth inhibition compared with T-DXd monotherapy[21]

Here, we describe the Phase 3 DESTINY-Endometrial01/GOG-3098/ENGOT-EN24 study (NCT06989112), evaluating the efficacy and safety of first-line T-DXd with rilvegostomig or pembrolizumab versus chemotherapy with pembrolizumab in patients with HER2-expressing (IHC 3+/2+), pMMR primary advanced or first recurrent endometrial cancer

Key inclusion criteria

- Age ≥18 years
- Histologically confirmed epithelial endometrial carcinoma; all histologies are permitted with the exception of sarcomas (carcinosarcomas are allowed)
- Primary advanced (International Federation of Gynecology and Obstetrics [FIGO] Stage III/IV) or first recurrent endometrial carcinoma:
  - Primary Stage III with measurable target disease at baseline per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 based on investigator assessment
  - Primary Stage IV or first recurrent disease regardless of measurable disease at baseline
- HER2 expression (IHC 3+/2+) and pMMR by prospective central IHC testing
- Adequate formalin-fixed paraffin-embedded tumor tissue sample for central IHC testing
- Naïve to first-line systemic anticancer therapy:
  - One prior line of (neo)adjuvant chemotherapy, including trastuzumab, with curative intent is permitted in patients with recurrent disease if recurrence or progression occurred ≥6 months after the last dose of chemotherapy
  - No prior exposure to antibody-drug conjugates or immune checkpoint inhibitors, including anti-PD-1 / programmed cell death ligand 1 / programmed cell death ligand 2 and anti-cytotoxic T lymphocyte-associated protein 4 antibodies, and therapeutic anticancer vaccines
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Left ventricular ejection fraction ≥50% within 28 days of randomization
- Protocol-defined adequate organ and bone marrow function within 14 days of randomization

Key exclusion criteria

- History of organ transplant
- Uncontrolled intercurrent illness
- Spinal cord compression or clinically active central nervous system metastases
- History of myocardial infarction (within 6 months prior to randomization), symptomatic congestive heart failure, clinically significant arrhythmia, or cardiomyopathy of any etiology
- History of non-infectious interstitial lung disease (ILD) / pneumonitis that required treatment with steroids, or current/suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Lung-specific intercurrent clinically significant illnesses
- Autoimmune, connective tissue, or inflammatory disorders where there is documented or suspected pulmonary involvement at screening
- Active or prior documented autoimmune or inflammatory disorders requiring chronic treatment with steroids or other immunosuppressive treatment
- Active primary immunodeficiency or active infectious diseases including human immunodeficiency virus, tuberculosis, and hepatitis A, B, or C
- Uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals
- Multiple primary malignancies within 3 years prior to screening, except for adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors that have been curatively treated
- Any concurrent anticancer treatment without an adequate washout period prior to the first dose of study intervention (excluding hormonal therapy for non-cancer–related conditions)

Study design

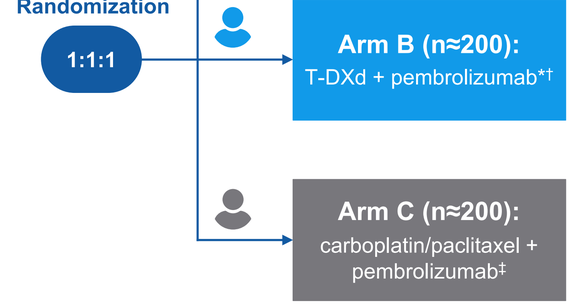
- DESTINY-Endometrial01/GOG-3098/ENGOT-EN24 is an open-label, sponsor-blinded, randomized, controlled, multicenter, Phase 3 study of first-line T-DXd with rilvegostomig or pembrolizumab versus chemotherapy with pembrolizumab in patients with HER2-expressing (IHC 3+/2+), pMMR, primary advanced or first recurrent endometrial cancer
  - Patients will be randomized 1:1:1 to three treatment arms (A, B, and C)

Patient population (N≈600)

- Primary advanced or first recurrent histologically confirmed endometrial cancer
- HER2 expression (IHC 3+/2+) and pMMR by central IHC testing
- Naïve to first-line systemic anticancer therapy
- One prior line of (neo)adjuvant chemotherapy if recurrence / disease progression occurred ≥6 months after prior chemotherapy
- No prior exposure to ADCs or ICIs
- ECOG performance status 0 or 1

Stratification factors

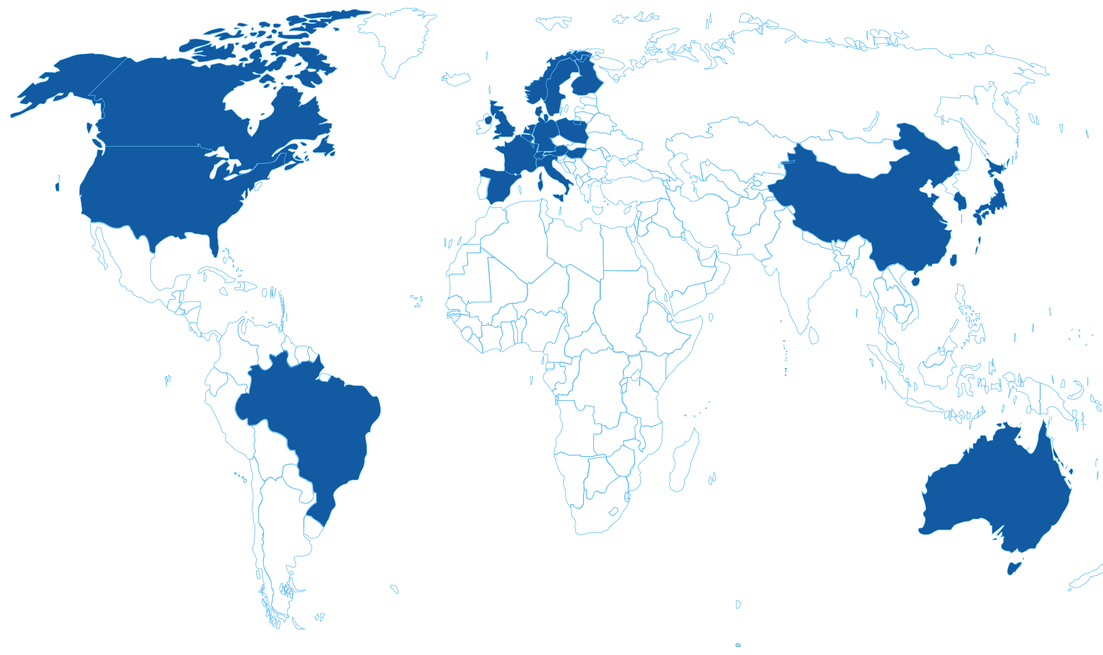
- HER2 expression: IHC 3+ versus 2+
- PD-L1 status: tumor area positivity ≥1% versus <1%
- Geographical region: Asia versus non-Asia



For more information about the DESTINY-Endometrial01/GOG-3098/ENGOT-EN24 study, please visit https://clinicaltrials.gov/study/NCT06989112

*Treatment will continue until objective disease progression per RECIST 1.1 as assessed by the investigator and confirmed by BICR, or other discontinuation criteria are met, whichever occurs first; †IV Q3W; ‡Q3W for six cycles followed by maintenance pembrolizumab IV Q6W for up to a total of 20 cycles (~24 months accounting for combination and maintenance phases) or until other discontinuation criteria are met, whichever occurs first
ADC, antibody-drug conjugate; BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; IV, intravenous; PD-L1, programmed cell death ligand 1; pMMR, mismatch repair-proficient; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Enrollment start: March 2025 | Currently recruiting patients



Countries with participating study sites

Australia, Austria, Belgium, Brazil, Canada, China, Denmark, Finland, France, Germany, Hungary, Italy, Japan, Netherlands, Norway, Poland, Republic of Korea, Spain, Sweden, Switzerland, Taiwan, UK, US

Key study endpoints

Primary endpoints

- PFS per RECIST 1.1 as assessed by blinded independent central review (BICR) in Arm A versus Arm C and Arm B versus Arm C

Secondary endpoints

- OS (key endpoint)
- Investigator-assessed PFS*
- Time to second progression or death
- Investigator- and BICR-assessed:
  - ORR*
  - Duration of response*
- BICR-assessed PFS in Arm A versus Arm B
- Frequency of adverse events (AEs), serious AEs, AEs of special interest,† and changes from baseline in clinical laboratory assessments and vital signs‡
- Patient-reported tolerability
- Serum concentrations of T-DXd, total anti-HER2 antibody, deruxtecan, and rilvegostomig
- Presence of anti-drug antibodies for T-DXd and rilvegostomig

*Per RECIST 1.1; †AEs and serious AEs graded according to the Medical Dictionary for Regulatory Activities and National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; ‡plus electrocardiogram, echocardiogram / multiple gated acquisition results

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This study is sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

Acknowledgments

We thank the patients who are participating in this study, as well as their families and caregivers. The anti-TIGIT component of rilvegostomig is derived from COM902 developed by Compugen Ltd.

Under the guidance of the authors and in accordance with Good Publication Practice (GPP) guidelines, medical writing and editorial support was provided by Abbie Dodd, BSc, of Helios Medical Communications, part of the Helios Global Group, and was funded by AstraZeneca.

Disclosures

Dr. Trinke Jakobi Nøttrup reports honoraria or consultation fees from AbbVie, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eisai, MSD, and GlaxoSmithKline.

Previously presented at ESMO 2025, Final Publication Number: 1223TiP, Brian Slomovitz et al. Reused with permission.

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