

An open-label, randomized, multicenter, phase 3 study of trastuzumab deruxtecan versus standard of care chemotherapy with or without radiotherapy as adjuvant treatment for patients with HER2-expressing (IHC 3+/2+) endometrial cancer: DESTINY-Endometrial02 (DE-02; GOG-3122/ENGOT-en30)

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Plain Language Summary

- ### Why are we performing this research?
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, which is made up of a monoclonal antibody similar to trastuzumab connected to a medicine intended to kill cancer cells. The monoclonal antibody binds to a protein called human epidermal growth factor receptor 2 (HER2) on the surface of cancer cells. Upon entering the cell, the medicine becomes active and kills the cancer cells.^{1,2} T-DXd is approved in multiple countries for the treatment of HER2-positive and HER2-low and -ultralow breast cancer, HER2-positive gastric or gastroesophageal junction carcinoma, and *HER2*-mutant non-small cell lung cancer.^{3,4} It has also received accelerated approval in the United States for the treatment of HER2-positive (immunohistochemistry [IHC 3+]) solid tumors that cannot be taken out by surgery and have spread to other parts of the body (metastatic) that have progressed after prior systemic treatment and have no satisfactory alternative therapies,⁵ an approval based on a study that evaluated T-DXd in a wide range of solid tumor types, including endometrial cancer.⁶ The rate of HER2 overexpression in patients with endometrial cancer ranges from around 11-39% for IHC 2+ status and 4-17% for IHC 3+ status.⁶⁻¹⁰ Following current standard therapy after surgery, about 39-56% of patients with high-risk endometrial cancer will experience disease recurrence or death within 18 months of diagnosis, highlighting a significant unmet clinical need, particularly after surgery.¹¹ In DESTINY-PanTumor02, T-DXd demonstrated efficacy as second-line treatment for HER2-expressing (IHC 3+/2+) solid tumors, including endometrial cancer.¹² The purpose of DESTINY-Endometrial02 is to evaluate the efficacy and safety of T-DXd versus standard-of-care (SoC) chemotherapy, with or without radiotherapy (RT), as adjuvant treatment after surgery specifically in patients with HER2-expressing (IHC 3+/2+) endometrial cancer.
- ### How are we performing this research?
- DESTINY-Endometrial02 is an ongoing clinical study that is taking place at multiple locations to assess the effectiveness and safety of T-DXd treatment for HER2-expressing (IHC 3+/2+) endometrial cancer in the adjuvant setting. The primary outcome of interest is the length of time after primary treatment ends that the patient survives without any signs or symptoms of that cancer, according to established criteria.
- ### Who will participate in this study?
- To participate, people must be 18 years or older and have HER2-expressing (HER2 IHC 3+/2+) endometrial cancer. Some of the main reasons why people might not be able to participate in the study are if they have sarcomas, have measurable residual disease after surgery, have a history of myocardial infarction (heart attack) within 6 months of taking part in the study, or have a history of noninfectious interstitial lung disease (scarring of the lungs)/pneumonitis (inflammation of lung tissue without infection) that required steroid treatment.
- ### Where can I access more information?
- For more information about the DESTINY-Endometrial02 trial, please visit <https://clinicaltrials.gov/study/NCT07022483>. You can also speak to your doctor about this and other clinical studies.

- ### References
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Study Design

- DESTINY-Endometrial02/GOG-3122/ENGOT-en30/GINECO (NCT07022483; recruitment ongoing), a randomized, open-label phase 3 study, aims to further evaluate the efficacy and safety of T-DXd versus standard-of-care (SoC) chemotherapy, with or without radiotherapy (RT), as adjuvant treatment after surgery for patients with HER2-expressing (IHC 3+/2+) endometrial cancer with no evidence of disease
- DESTINY-Endometrial02 plans to enroll approximately 710 patients with HER2 IHC 3+/2+ status (with a maximum of 532 patients [75%] with IHC 2+ status) endometrial cancer
- Patients will be randomly assigned 1:1 to receive either T-DXd (5.4 mg/kg intravenously [IV] every 3 weeks [Q3W] with or without RT) for up to 17 cycles or SoC chemotherapy (carboplatin AUC 5 or 6 and paclitaxel 175 mg/m² Q3W, with or without RT or chemoradiotherapy [external beam RT plus cisplatin 50 mg/m²]) for up to 4 or 6 cycles
- Stratification factors include mismatch repair (MMR) status (deficient [dMMR] vs proficient [pMMR]), with pMMR further stratified by HER2 expression, FIGO 2023 stage (IIc vs III), and geographic region
- Treatment will commence within 8 weeks of surgery, and continue until completion of study intervention, radiographic disease recurrence, unacceptable toxicity, death, or discontinuation from treatment for any reason

DESTINY-Endometrial02 Study Design (GOG-3122/ENGOT-en30/GINECO [NCT07022483])

Patient population

- FIGO 2023 stage IIC or stage III, histologically confirmed endometrial cancer
- All histologies allowed except sarcomas (carcinosarcomas are eligible)
- HER2 IHC 3+ or 2+ per 2016 ASCO-CAP gastric cancer IHC scoring guidelines as confirmed by central laboratory testing

R
1:1
N ≈ 710

T-DXd 5.4 mg/kg
Q3W 17 cycles ±
optional RT^a

Carboplatin AUC 5 or 6 +
paclitaxel 175 mg/m² Q3W
4 or 6 cycles ± optional RT^a

Endpoints
Primary
• DFS (BICR)^b
Secondary
• OS

Estimated trial completion: March 2032.

For more information about the DESTINY-Endometrial02 trial, please visit <https://clinicaltrials.gov/study/NCT07022483>.

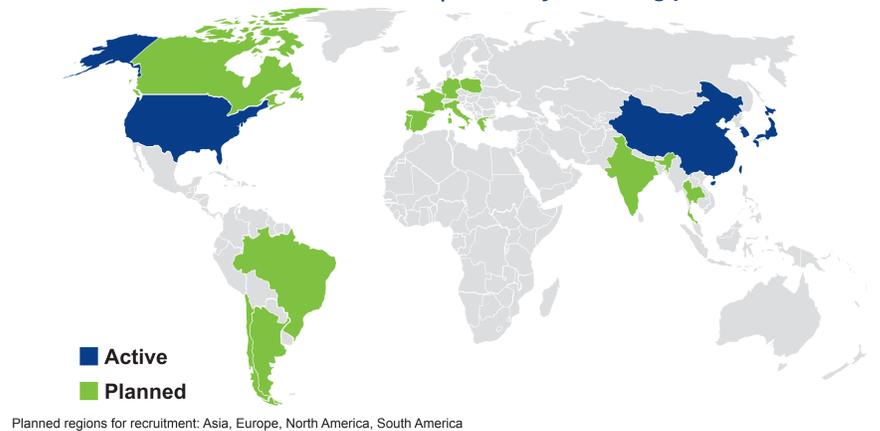
^aRT administered at the investigators' discretion and must be decided (yes or no) prior to randomization.

^bAssessed by BICR or by histopathologic confirmation of recurrence by local assessment.

Countries with participating study sites

China, Japan, South Korea, Taiwan, and the United States

Start date: October 2025 | Currently recruiting patients



Background

- Human epidermal growth factor receptor 2 (HER2) expression occurs in a wide range of solid tumors and is associated with biologically aggressive tumor types, poor clinical outcomes, and reduced response to chemotherapy¹⁻³
- The prevalence of HER2 overexpression in patients with endometrial cancer ranges from approximately 11-39% for IHC 2+ status and 4-17% for IHC 3+⁴⁻⁸
- There are currently no HER2-directed therapies approved for HER2-expressing endometrial cancer in the adjuvant setting
- Following current standard of care adjuvant treatment, approximately 39-56% of patients with high-risk endometrial cancer will experience disease recurrence or death within 18 months of diagnosis, highlighting a significant unmet clinical need, particularly in the adjuvant setting⁹
- 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 inhibitor payload^{10,11}
- T-DXd has been approved in many countries worldwide for the treatment of HER2-positive and HER2-low and -ultralow breast cancer, HER2-positive gastric or gastroesophageal junction carcinoma, and *HER2*-mutant non-small cell lung cancer^{12,13}
- In April 2024, the US Food and Drug Administration granted accelerated approval for the use of T-DXd in adult patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] 3+) solid tumors that have progressed after prior systemic treatment and have no satisfactory alternative therapies^{12,14}; this approval was based, in part, on results from the multicenter, non-randomized, open-label phase 2 DESTINY-PanTumor02 study, in which T-DXd was shown to have antitumor activity in a cohort of patients with heavily pretreated metastatic endometrial cancer¹⁵

Key Inclusion Criteria

- Adults ≥18 years
- Histologically confirmed diagnosis of epithelial endometrial cancer, all histologies except for sarcomas (carcinosarcomas are allowed)
- Newly diagnosed FIGO 2023 stage IIC (including stage IICmp53abn) or stage III; stage IIC includes disease with aggressive histological types with any myometrial involvement; stage III includes disease with local and/or regional spread of the tumor of any histological subtype
- HER2 expression (IHC 3+/2+) according to 2016 ASCO-CAP gastric cancer IHC scoring guidelines as confirmed by central laboratory testing
- Adequate archived tumor tissue sample available for assessment of HER2 status by central laboratory

Key Exclusion Criteria

- Uterine mesenchymal tumor such as an endometrial stromal sarcoma, leiomyosarcoma, or other types of pure sarcomas; adenocarcinomas are also not allowed
- Recurrent or FIGO 2023 stage IV endometrial cancer
- Measurable residual tumor after surgery assessed by blinded independent central review (BICR)
- Known presence of a *POLE* mutation based on an approved and/or validated local test, according to local regulations, if available
- History of myocardial infarction (<6 months prior to randomization/enrollment) or symptomatic congestive heart failure
- History of noninfectious interstitial lung disease (ILD)/pneumonitis requiring steroids, or current/suspected ILD/pneumonitis that cannot be ruled out by imaging at screening

Key Study Endpoints

- Primary endpoint**
 - DFS^a
- Key secondary endpoint**
 - OS
- Other secondary endpoints**
 - DFS^b
 - Distant metastatic, local, or regional recurrence^a
 - Patient-reported outcomes
 - Safety

^aAssessed by BICR or by histopathologic confirmation of recurrence by local assessment.

^bAssessed by investigator or by histopathologic confirmation of recurrence by local assessment.



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Abbreviations
IHC: immunohistochemistry; FIGO: International Federation of Gynecology and Obstetrics; AUC: area under the curve; BICR: blinded independent central review; CAP: College of American Pathologists; DFS: disease-free survival; MMR: mismatch repair deficiency; pMMR: proficient mismatch repair; dMMR: deficient mismatch repair; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; IV: intravenous; MMR: mismatch repair; pMMR: proficient mismatch repair; dMMR: deficient mismatch repair; FIGO: International Federation of Gynecology and Obstetrics; Q3W: every 3 weeks; R: randomization; RECIST v1.1: Response Evaluation Criteria in Solid Tumors, version 1.1; RT: radiotherapy; T-DXd: trastuzumab deruxtecan.

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