An open-label, randomized, multicenter, phase 3 study of trastuzumab deruxtecan (T-DXd) with bevacizumab (BEV) vs BEV monotherapy as first-line maintenance therapy in HER2-expressing ovarian cancer: DESTINY-Ovarian01 (DO-01, ENGOT-ov89/GEICO144-O/GOG-3112/APGOT-OV13)

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Plain Language Summary

Why are we performing this research?

- Many patients with ovarian cancer have tumors that express the human epidermal growth factor receptor 2 (HER2) protein[1-5]
- These patients with HER2 expression are more likely to have more advanced disease stages, higher recurrence rates, and shorter survival times[5-7]
- Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody bound to a cytotoxic chemotherapy agent (antibody-drug conjugate) that is designed to target and kill tumor cells expressing HER2[8-10]
- In the DESTINY-PanTumor02 study, T-DXd monotherapy demonstrated antitumor activity in patients with heavily pretreated ovarian cancer[11]
- Based on these results, T-DXd has been approved in several countries for use in patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] 3+) solid tumors, including ovarian cancer, who have received prior systemic treatment and have no satisfactory alternative treatment options[12,13]
- Bevacizumab (BEV) is a vascular endothelial growth factor–directed antibody that has been approved in combination with chemotherapy for first-line treatment for adults with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer[14]
- Additional preclinical data have shown that the combination of T-DXd and BEV is more effective than either T-DXd or BEV alone[15]

How are we performing this research?

- DESTINY-Ovarian01 will have 2 parts: a safety run-in phase and a randomization phase
- The safety run-in phase will enroll around 20 participants who will receive T-DXd (5.4 mg/kg intravenously every 3 weeks) in combination with BEV (15.0 mg/kg intravenously every 3 weeks) and be followed for at least 2 cycles
- Safety is the primary endpoint for the safety run-in phase
- If there are no new safety concerns, the randomization phase will begin where 562 participants will be randomly assigned 1:1 to receive either T-DXd in combination with BEV or BEV alone
- Progression-free survival and overall survival are the primary and key secondary endpoints for the randomization phase, respectively
- In all cases, participants will receive up to 34 cycles of T-DXd and 16 cycles of BEV (or up to 22 cycles, including doses given with first-line therapy) or until discontinuation criteria are met (eg, discontinuation due to unacceptable side effects)
- After treatment has ended, a follow-up period will continue to further assess the safety and effectiveness of the treatment

Who will participate in this study?

- Adults with histologically confirmed epithelial high-grade ovarian, fallopian tube, or primary peritoneal tumors, who have centrally confirmed HER2 expression (IHC 3+/2+/1+), newly diagnosed with International Federation of Gynecology and Obstetrics stage III or IV and show no clinical evidence (physical examination, imaging, or presence of CA-125) of disease progression following first-line therapy, and who are ineligible for poly (ADP-ribose) polymerase inhibitors are eligible to participate in the trial

Where can I access more information?

- To learn more about this study, you can visit: https://clinicaltrials.gov/study/NCT06819007

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Background

- Many patients with ovarian cancer (OC) have tumors expressing human epidermal growth factor receptor 2 (HER2), with HER2 immunohistochemistry (IHC) scores reported as follows[1-5]:
  - IHC 3+: 4%-6%
  - IHC 2+: 0%-28%
  - IHC 1+: 2%-21%
- Reported HER2 IHC scores vary significantly across studies and can be attributed to several factors, including intra- and intertumoral heterogeneity, variations in sample derivation from tumor blocks or tissue microarrays, and differences in detection methods and assay techniques used to determine and assess IHC status[2,6]
- HER2 overexpression (IHC 3+/2+) in OC is associated with a poor prognosis characterized by more advanced disease stages, higher recurrence rates, and shorter survival times[5,7,8]
- In the single-arm, phase 2 DESTINY-PanTumor02 study (NCT04482309), T-DXd monotherapy demonstrated antitumor activity in patients with heavily pretreated OC[9,10]
  - In patients with locally or centrally confirmed HER2 expression (IHC 3+/2+; n = 40), T-DXd produced an objective response rate (ORR) of 45%, a median duration of response (DoR) of 11.3 months, a median progression-free survival (PFS) of 5.9 months, and a median overall survival (OS) of 13.2 months[9]
  - In patients with centrally confirmed HER2 IHC expression, clinical activity was also seen in patients with IHC 1+ (ORR of 20%; n = 5) and IHC 0 (ORR of 60%; n = 5), although the sample size was small[10]
- Based on the results of DESTINY-PanTumor02, T-DXd has been approved in several countries for use in patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors, including OC, who have received prior systemic treatment and have no satisfactory alternative treatment options[11,12]
- Vascular endothelial growth factor (VEGF) overexpression in OC is linked to malignant progression, ascites development, and worse overall prognosis[13,14]
- Bevacizumab (BEV), an anti-VEGF antibody, has demonstrated efficacy in combination with chemotherapy and as maintenance therapy for patients with OC and is approved for use in combination with carboplatin and paclitaxel, followed by BEV as a single agent, for stage III or IV epithelial OC following initial surgical resection[15]
- Nonclinical data in OC models have also shown that combining T-DXd with BEV significantly enhances antitumor activity compared with either therapy alone[10]

Study Design

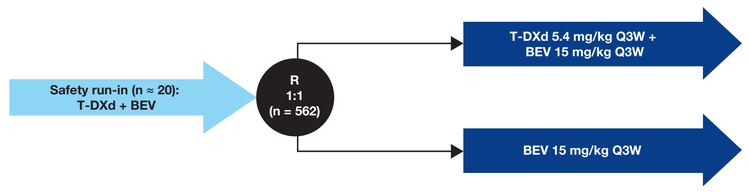
Trial Design

- DESTINY-Ovarian01 (DO-01; ENGOT-ov89/GEICO144-O/GOG-3112/APGOT-OV13 [NCT06819007]) is a global, multicenter, open-label, randomized, phase 3 trial designed to evaluate the efficacy and safety of T-DXd with BEV compared with BEV monotherapy as first-line maintenance therapy in HER2-expressing (IHC 3+/2+/1+) advanced high-grade epithelial OC, not eligible for poly (ADP-ribose) polymerase (PARP) inhibitors, and no evidence of disease progression after first-line therapy

DESTINY-Ovarian01 Study Design (ENGOT-ov89/GEICO144-O/GOG-3112/APGOT-OV13 [NCT06819007])

Patient population

- Adult (≥18 years)
- Histologically confirmed diagnosis of epithelial high-grade ovarian, fallopian tube, or primary peritoneal carcinoma
- Centrally confirmed HER2 expression (IHC 3+/2+/1+)[a]
- International Federation of Gynecology and Obstetrics (FIGO) stage III or IV
- No disease progression after first-line therapy[b]
- ECOG PS of 0 or 1
- Received SoC BEV with platinum-based chemotherapy



Participants will receive T-DXd for a maximum of 34 cycles and BEV for up to 16 cycles (a maximum of 22 cycles, including the doses given in combination with first-line chemotherapy) or until disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

[a]With a minimum of 168 participants (30%) for HER2 IHC 3+ and a maximum of 82 participants (15%) for HER2 IHC 1+.

[b]No disease progression is defined as no residual disease after primary debulking surgery (PDS) or complete response (CR)/partial response (PR)/stable disease (SD) as per response evaluation criteria in solid tumors version 1.1 (RECIST v1.1) assessed by the investigator at the end of front-line chemotherapy (after completion of ≥6 and ≤8 cycles of front-line carboplatin-paclitaxel ± BEV); there should be no clinical evidence of disease progression as per physical examination, imaging, or presence of cancer antigen 125 (CA-125) throughout the patient's front-line treatment and prior to trial randomization.

Safety Run-In Phase

- The nonrandomized safety run-in phase of the study will assess the safety of T-DXd (5.4 mg/kg intravenously [IV] every 3 weeks [Q3W]) in combination with BEV (15.0 mg/kg IV Q3W) in 20 participants
- If no safety signal is identified after the 20 participants have been followed for at least 2 cycles, the randomization phase will begin

Randomization Phase

- Approximately 562 participants will be assigned 1:1 to receive T-DXd (5.4 mg/kg IV Q3W) in combination with BEV (15.0 mg/kg IV Q3W) or BEV monotherapy (15.0 mg/kg IV Q3W)
  - Of the 562 participants, approximately 480 participants with IHC 3+/2+ status constitute the basis for the analysis of the primary and key secondary endpoints
- Participants will be stratified by HER2 expression, outcome of surgery, and histology
  - HER2 IHC score: IHC 3+ versus 2+ versus 1+
  - Outcome of surgery: No residual disease after PDS versus residual disease after PDS or interval debulking surgery or no surgery
  - Histology: High-grade serous versus nonserous

Countries with participating study sites

Australia, Austria, Belgium, Brazil, Bulgaria, **China (Mainland)**, Czech Republic, Denmark, France, Germany, Greece, Hungary, India, Israel, Italy, **Japan**, Malaysia, Poland, Romania, Singapore, South Korea, Spain, Sweden, Taiwan, United Kingdom, **United States**

Study start: March 19, 2025 | Recruiting

The study will be conducted at ~253 study sites in 26 countries across 4 regions (North America, South America, Europe, Asia/Pacific).
Countries shown in bold will participate in the safety run-in phase.

Key Inclusion Criteria

- Age ≥18 years
- Histologically confirmed diagnosis of epithelial high-grade ovarian, fallopian tube, or primary peritoneal carcinoma (including but not limited to serous, endometrioid, clear cell, carcinosarcoma, mucinous)
- Newly diagnosed FIGO stage III or IV
- HER2 expression (IHC 3+/2+/1+), based on 2016 American Society of Clinical Oncology–College of American Pathologists gastric cancer IHC scoring guidelines, by prospective central testing. For patients in the safety run-in phase, HER2 expression assessed by either local (if available) or central assessment is acceptable. Submission of the pathology report is required for patients enrolled based on local HER2 IHC results
- No clinical evidence (physical examination, imaging, or CA-125) of disease progression, defined as no residual disease after PDS or CR/PR/SD as per RECIST v1.1 assessed by the investigator, after completion of at least 6 cycles and maximum of 8 cycles of front-line carboplatin-paclitaxel ± BEV (intravenous or intraperitoneal or neoadjuvant/adjuvant chemotherapy or hyperthermic intraperitoneal chemotherapy is allowed)
- Adequate tumor tissue sample available for HER2 assessment by a central laboratory
  - Tumor tissue block or sufficient tissue slides are required for HER2 testing and retrospective homologous recombination deficiency (HRD) status determination
  - Participants in the safety run-in phase who are enrolled based on local HER2 IHC results are recommended to provide tumor tissue sample from the same specimen for central assessment
- Local HRD or breast cancer gene *(BRCA)* test result available. Participants with wild-type *BRCA* will have a local HRD test result, as applicable
- Received standard-of-care (SoC) BEV with first-line carboplatin and paclitaxel per approved indication and clinical guidelines and is eligible to continue single-agent BEV maintenance per SoC and investigator discretion

Key Exclusion Criteria

- Ovarian, fallopian tube, or peritoneal cancer of nonepithelial origin
- Pathological *BRCA* mutation per local test
- Receipt of PARP inhibitor as maintenance per SoC and investigator discretion. Reason the participant is not eligible for PARP inhibitor will be recorded in the electronic case report form as follows:
  - HRD negative
  - HRD positive with SD as best response after platinum
  - HRD positive nonserous histology
  - HRD positive, but safety concern (safety concern to be specified)
  - HRD tested, but inconclusive
- Previous cerebrovascular accident, transient ischemic attack, or subarachnoid hemorrhage within 6 months before randomization
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of anticoagulation therapy)
- History of hemorrhagic disorders, abdominal fistula, gastrointestinal perforation, or active gastrointestinal bleeding within 6 months before randomization
- Evidence of active or ongoing bowel obstruction
- Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder such as pulmonary emboli (within 3 months of trial randomization), severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion, and pneumonectomy
- History of (noninfectious) interstitial lung disease (ILD)/pneumonitis that required steroids, current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening

Key Study Endpoints

Safety run-in phase

1° Primary
- Safety

Randomization phase

1° Primary
- PFS by blinded independent central review (BICR) in the HER2 IHC 3+/2+ population

2° Key secondary
- OS in the HER2 IHC 3+/2+ population

2° Other secondary
- PFS by BICR in the HER2 IHC 3+/2+/1+ population
- OS in the HER2 IHC 3+/2+/1+ population
- PFS and PFS from time of randomization to second progression by investigator in the HER2 IHC 3+/2+ and 3+/2+/1+ populations
- Confirmed ORR and DoR by BICR in the HER2 IHC 3+/2+ and 3+/2+/1+ populations
- Time to first and second subsequent therapy in the HER2 IHC 3+/2+ and 3+/2+/1+ populations
- Safety endpoints
- Patient-reported outcomes

Exploratory
- Clinical benefit rate (CBR) by BICR in the HER2 IHC 3+/2+ and IHC 3+/2+/1+ populations
- PFS assessed by CA-125 in HER2 in the IHC 3+/2+ and IHC 3+/2+/1+ populations
- Health-related quality-of-life assessments

Poster

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Abbreviations

BRCA, breast cancer gene; BEV, bevacizumab; CA-125, cancer antigen 125; CR, complete response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; IHC, immunohistochemistry; ILD, interstitial lung disease; IV, intravenously; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PDS, primary debulking surgery; PR, partial response; PFS, progression-free survival; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; SoC, standard of care; T-DXd, trastuzumab deruxtecan; VEGF, vascular endothelial growth factor.

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