Randomized, open-label, multicenter, Phase 3 study of trastuzumab deruxtecan (T-DXd) with rilvegostomig vs standard of care (SOC) in first-line, human epidermal growth factor receptor 2 (HER2)-expressing, locally advanced or metastatic (LA/m) biliary tract cancer (BTC): DESTINY-BTC01

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Plain language summary

Why are we performing this research?

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, which is a chemotherapy with a linker (together called deruxtecan) joined to an antibody (trastuzumab). Trastuzumab binds to a protein found on some cancer cells called human epidermal growth factor receptor 2 (HER2), where it releases the chemotherapy to kill these cells.[1,2] Rilvegostomig is an antibody that blocks the activity of two proteins called programmed cell death protein 1 (PD-1) and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT), making cancer cells more susceptible to being killed by the immune system.[3] In previous studies, T-DXd showed beneficial antitumor activity in people with biliary tract cancer who have higher-than-normal levels of HER2 (HER2-overexpressing, also known as immunohistochemistry 3+/2+).[4,5] The DESTINY-BiliaryTractCancer01 (DESTINY-BTC01) study is evaluating the effects of T-DXd in combination with rilvegostomig or T-DXd alone compared with the current standard treatment in people with previously untreated HER2-expressing biliary tract cancer.

How are we performing this research?

DESTINY-BTC01 is an ongoing study taking place at multiple locations worldwide to assess the benefit and possible side effects of T-DXd with rilvegostomig treatment in people with HER2-expressing biliary tract cancer. Side effects and how well people cope when taking T-DXd with rilvegostomig will be initially evaluated in 20 participants. If there are no safety concerns, approximately 600 participants will then receive either T-DXd with rilvegostomig, T-DXd alone, or the currently recommended treatment (chemotherapy [gemcitabine and cisplatin] with immunotherapy [durvalumab]).
The antitumor activity and the occurrence of side effects will be assessed and compared between each treatment group.

Who will participate in this study?

To participate, people must be age 18 years or above and have HER2-expressing biliary tract cancer that has spread to nearby tissue or other locations in the body, or that cannot be surgically removed. Participants must have not previously received treatment for locally advanced or metastatic biliary tract cancer. People cannot participate if they have a history of a heart attack (within 6 months of taking part) or non-infectious interstitial lung disease (scarring of the lungs) / pneumonitis (inflammation of lung tissue without infection).

Where can I access more information?

For more information about DESTINY-BTC01, please visit https://clinicaltrials.gov/study/NCT06467357. You can also speak to your doctor about this and other clinical studies.

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Study design and population

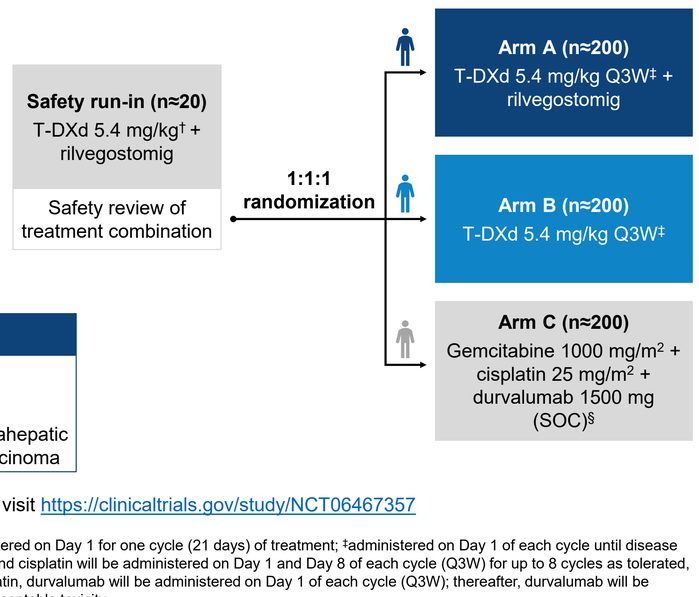
- DESTINY-BTC01 is an open-label, multicenter, randomized, Phase 3 study of first-line T-DXd with rilvegostomig or T-DXd monotherapy vs SOC in patients with HER2-expressing, unresectable, locally advanced, or metastatic BTC
- An initial safety run-in will enroll approximately 20 patients to evaluate the safety and tolerability of T-DXd in combination with rilvegostomig
  - In the absence of pre-determined safety signals and per independent data monitoring committee review, patients will be randomized 1:1:1 to three treatment arms (A, B, and C)

Patient population (N≈620)

- Unresectable, locally advanced, or metastatic BTC
- Histologically confirmed HER2 IHC 3+/2+ tumors (proportion of patients enrolled with IHC 2+ tumors will be capped at 40% of the total randomized population)
- No prior treatment in the advanced/metastatic disease setting
- WHO/ECOG performance status of 0 or 1
- Measurable disease per RECIST 1.1*

Stratification factors

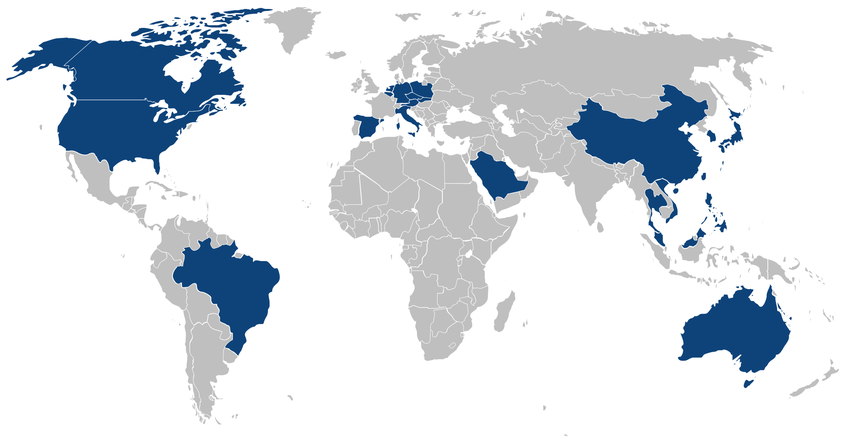
- HER2 expression status: IHC 3+ vs IHC 2+
- PD-L1 status: tumor area positivity ≥1% vs <1%
- Primary tumor location: gallbladder cancer vs intrahepatic cholangiocarcinoma vs extrahepatic cholangiocarcinoma



For more information about DESTINY-BTC01, please visit https://clinicaltrials.gov/study/NCT06467357

*Not a requirement for patients enrolled in the safety run-in; †administered on Day 1 for one cycle (21 days) of treatment; ‡administered on Day 1 of each cycle until disease progression per RECIST 1.1 or unacceptable toxicity; §gemcitabine and cisplatin will be administered on Day 1 and Day 8 of each cycle (Q3W) for up to 8 cycles as tolerated, per local guidelines; when in combination with gemcitabine and cisplatin, durvalumab will be administered on Day 1 of each cycle (Q3W); thereafter, durvalumab will be administered Q4W until disease progression per RECIST 1.1 or unacceptable toxicity
BTC, biliary tract cancer; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed cell death ligand 1; Q3W, once every 3 weeks; Q4W, once every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SOC, standard of care; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization

First patient enrolled: August 12, 2024 | Currently recruiting patients



Countries with participating study sites*

Australia, Austria, Belgium, Brazil, Canada, China, Czechia, Germany, Italy, Japan, Malaysia, Netherlands, Philippines, Poland, Republic of Korea, Saudi Arabia, Slovakia, Spain, Taiwan, Thailand, United States of America, Vietnam

*Additional countries to be considered for participation

Background

- Biliary tract cancer (BTC) is an aggressive disease with an estimated 5-year survival rate at diagnosis of 11% (across all stages of disease), which decreases to 2% in patients with metastatic disease[1,2]
- First-line treatment with gemcitabine, cisplatin, and immunotherapy has demonstrated clinical benefit in locally advanced or metastatic BTC and is standard of care (SOC) in this setting; however, outcomes need further improvement given the poor prognosis that remains for these patients[3–6]
- Human epidermal growth factor receptor 2 (HER2) expression (immunohistochemistry [IHC] 3+/2+) is seen in a wide range of solid tumors, including in 16–33% of BTCs, and is associated with poor prognosis[7–10]
- Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate approved in multiple countries worldwide for the treatment of HER2-positive and HER2-low breast cancer, HER2-positive gastric or gastroesophageal junction adenocarcinoma, and HER2-mutant non-small cell lung cancer[11,12]
- T-DXd has demonstrated clinically meaningful benefit in pretreated patients with HER2-expressing, locally advanced or metastatic BTC and in patients with HER2-positive, unresectable or recurrent BTC, as shown in the BTC cohort of the Phase 2 DESTINY-PanTumor02 and the Phase 2 HERB study[13,14]
  - In April 2024, based in part on the results of DESTINY-PanTumor02, T-DXd received accelerated approval in the US for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors that have progressed after prior systemic treatment and who have no satisfactory alternatives[11]
- Rilvegostomig is a bispecific, humanized immunoglobulin G1 antibody targeting programmed cell death protein 1 (PD-1) and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT), which is under clinical investigation in patients with BTC after curative intent resection[15]

Considering the clinically meaningful antitumor activity of T-DXd demonstrated in BTC, the DESTINY-BTC01 study (NCT06467357) is evaluating the efficacy and safety of T-DXd with rilvegostomig or T-DXd monotherapy vs SOC in HER2-expressing, locally advanced, or metastatic BTC in the first-line setting

Key inclusion criteria

- Age ≥18 years
- Body mass ≥30 kg
- Unresectable, previously untreated, locally advanced, or metastatic BTC
- Prior perioperative and/or adjuvant treatment is permitted if >6 months between end of adjuvant treatment and diagnosis of locally advanced or metastatic disease
- At least 1 measurable target lesion as assessed by the investigator based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1*
- Histologically confirmed HER2-expressing (IHC 3+/2+) tumors, scored using current American Society of Clinical Oncology / College of American Pathologists guidelines for scoring HER2 in gastric cancer[16]†
- World Health Organization / Eastern Cooperative Oncology Group performance status of 0 or 1
- Left ventricular ejection fraction ≥50% within 28 days of receiving study treatment
- Protocol-defined adequate organ and bone marrow function within 14 days of randomization

*Required only for the randomized portion of the study; †locally confirmed HER2 IHC test results will be used to determine eligibility for the safety run-in; for the randomized portion of the study, HER2 status will be determined by prospective central testing or IHC 3+ local test result

Key exclusion criteria

- Any concurrent anticancer treatment
- Histologically confirmed ampullary carcinoma
- Prior treatment with HER2-targeting therapies, antibody-drug conjugates, immune checkpoint inhibitors, or therapeutic anticancer vaccines
- Current or prior immunosuppressive treatment within 14 days of receiving first dose of study treatment*
- Spinal cord compression or clinically active central nervous system metastases†
- Active autoimmune, connective tissue, or inflammatory disorders requiring systemic treatment within 2 years of enrollment, or where there is documented or suspected pulmonary involvement
- Pleural effusion, ascites, or pericardial effusion that requires drainage, peritoneal shunt, or cell-free and concentrated ascites reinfusion therapy
- History of non-infectious interstitial lung disease (ILD) / pneumonitis, current or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Unresolved toxicities (other than alopecia) from previous anticancer therapies that have not been resolved to Grade ≤1 or baseline‡
- History of myocardial infarction within 6 months of randomization/enrollment

*Excluding intranasal, inhaled, or topical steroids; local steroid injections; systemic corticosteroids at physiological doses; and steroids given as premedication for hypersensitivity reactions or as an antiemetic; †defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms; patients with clinically inactive brain metastases that are no longer symptomatic and who do not require treatment with corticosteroids or anticonvulsants may be included in the study, if they have recovered from the acute toxic effect of radiotherapy (whole brain radiotherapy must have ended ≥2 weeks before randomization); ‡patients may be enrolled with chronic, stable Grade 2 toxicities (defined as no worsening to >Grade 2 for at least 3 months prior to the first dose of study treatment and managed with standard-of-care treatment) that the investigator considers related to previous anticancer therapy

Key study endpoints

1° Primary endpoints

- **Safety run-in:** safety and tolerability of T-DXd with rilvegostomig according to frequency of adverse events (AEs), serious AEs, and AEs of special interest,* and changes from baseline in laboratory parameters
- **Randomized portion of the trial:** overall survival (OS) in the subgroup of patients with HER2 IHC 3+ BTC receiving T-DXd with rilvegostomig (**Arm A**) vs SOC (**Arm C**)

2° Secondary endpoints (randomized portion of the trial)

T-DXd with rilvegostomig (Arm A) vs SOC (Arm C):

- OS in the HER2 IHC 3+/2+ population

T-DXd monotherapy (Arm B) vs SOC (Arm C):

- OS in the HER2 IHC 3+/2+ and IHC 3+ populations

2° Other secondary endpoints (randomized portion of the trial)†

- Investigator assessed (per RECIST 1.1):
  - Progression-free survival
  - Objective response rate
  - Duration of response
- OS (T-DXd with rilvegostomig [**Arm A**] vs T-DXd monotherapy [**Arm B**])
- Frequency of AEs, serious AEs, and AEs of special interest*
- Patient-reported tolerability, described according to symptomatic AEs and overall side-effect bother
- Immunogenicity, assessed by presence of anti-drug antibodies for T-DXd and rilvegostomig
- Serum concentrations of T-DXd, total anti-HER2 antibody, DXd, and rilvegostomig

*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; †evaluating T-DXd with rilvegostomig and T-DXd monotherapy vs SOC, and T-DXd with rilvegostomig vs T-DXd monotherapy, unless otherwise stated, in the HER2 IHC 3+/2+ and IHC 3+ populations

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please visit: https://bit.ly/4eXoi7H

Poster

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Acknowledgments

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Disclosures

Masafumi Ikeda reports personal financial interests with AbbVie, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, EA Pharma, Eisai, Eli Lilly Japan, Fujifilm Toyama Chemical, GlaxoSmithKline, Guardant Health Japan, Incyte Biosciences Japan, MSD, NIHON SERVIER, Nippon Kayaku, Nobelpharma, Novartis, Ono, Rakuten Medical, Taiho, Taisho Pharmaceutical, Takeda, Teijin Pharma, and Yakult; reports institutional financial interests with AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiome Bioscience, Chugai Pharmaceutical, Delta-Fly Pharma, Eisai, Eli Lilly Japan, Invitae, J-Pharma, Merck Biopharma, Merus N.V., MSD, NIHON SERVIER, Nobelpharma, Novartis, Ono, and Syneos Health; has participated on an advisory board for Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai, GlaxoSmithKline, MSD, NIHON SERVIER, and Novartis; as a steering committee member for Chugai Pharmaceutical, Eisai, NIHON SERVIER, Novartis, Rakuten Medical, and Takeda; as a coordinating principal investigator for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiome Bioscience, Chugai Pharmaceutical, Delta-Fly Pharma, Eisai, Eli Lilly Japan, Invitae, J-Pharma, Merck Biopharma, Merus N.V., MSD, NIHON SERVIER, Nobelpharma, Novartis, Ono, and Syneos Health; and as an invited speaker for AbbVie, AstraZeneca, Chugai Pharmaceutical, EA Pharma, Eisai, Eli Lilly Japan, Fujifilm Toyama Chemical, Guardant Health Japan, Incyte Biosciences Japan, MSD, NIHON SERVIER, Nippon Kayaku, Nobelpharma, Novartis, Ono, Taiho, Taisho Pharmaceutical, Takeda, Teijin Pharma, and Yakult.

DESTINY BiliaryTractCancer01

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