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Real-world Effectiveness and Safety of Trastuzumab Deruxtecan (T-DXd) in Patients with HER2 Positive Advanced Gastric and Gastroesophageal Junction Adenocarcinoma (GC/GEJA): A Multicenter Prospective Study in China (RECOVER Study)

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Plain language summary

Why are we performing this research?

- Human epidermal growth factor receptor 2 (HER2)-positive gastric and gastroesophageal junction (GEJ) cancer is an aggressive disease with limited treatment options after progression on trastuzumab-based therapy[1-4].
- Trastuzumab deruxtecan (T-DXd) has shown meaningful clinical benefit in clinical trials[5,6], but real-world evidence in China is lacking.
- This study aims to understand how T-DXd works in routine clinical practice, including its effectiveness, safety, and impact on patients' quality of life.

How are we performing this research?

- This is a multicenter, prospective, non-interventional study conducted at 36 hospitals across China.
- Physicians treat patients with T-DXd according to routine clinical practice.
- Researchers will collect information from medical records, electronic questionnaires, and symptom diaries to evaluate treatment outcomes, safety, and patient-reported outcomes.
- Patients will be followed from the start of T-DXd treatment until death, withdrawal, loss to follow-up, or study completion.

Who will participate in this study?

- Adults (≥18 years) with locally advanced, unresectable, or metastatic HER2-positive gastric or GEJ adenocarcinoma.
- Participants must have received prior systemic therapy and be starting T-DXd as part of routine care.

Where can I access more information?

This study is expected to end in 2028. For more information about the RECOVER Study, please visit Study Details | NCT06846996 | Real-world Effectiveness and Safety of Trastuzumab Deruxtecan in Patients With Locally Advanced or Metastatic HER2-positive Gastric or Gastroesophageal Junction Adenocarcinoma in China | ClinicalTrials.gov. You may also speak to your doctor about clinical studies

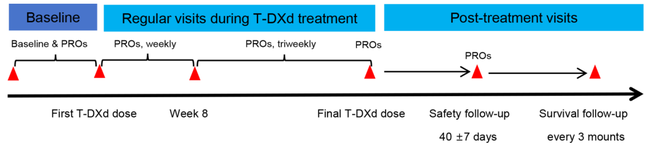
Background

- Gastric cancer ranks 5th in cancer incidence and cancer-related death globally, with ~40% of gastric cancer deaths occurring in China[1,7].
- HER2-positive gastric/GEJ adenocarcinoma represents a distinct molecular subtype, occurring in ~12% of Chinese cases.
- Trastuzumab plus chemotherapy improves first-line outcomes (ToGA trial), but 52.9% of patients do not respond, and effective post-trastuzumab options remain an unmet medical need.
- Based on KEYNOTE-811, pembrolizumab added to trastuzumab-chemotherapy was approved in China (June 2024) for first-line HER2-positive advanced gastric/GEJ adenocarcinoma with PD-L1 CPS≥1, significantly improving ORR, PFS, and OS[8].
- T-DXd, a HER2-directed antibody-drug conjugate with a high drug-to-antibody ratio and bystander effect, has demonstrated consistent efficacy across DESTINY-Gastric trials, winning approval in Japan and China for patients who failed prior trastuzumab-containing regimens.
- Retrospective data, mainly from Japan, suggest that broader real-world use may yield different outcomes than clinical trials[9,10].
- Real-world data from prospective cohorts about safety and efficacy of T-DXd in routine clinical practice are lacking.
- RECOVER is designed to generate prospective, real-world evidence on the effectiveness, safety, treatment patterns, and patient-reported outcomes of T-DXd in Chinese patients with HER2-positive advanced gastric/GEJ adenocarcinoma.
- The study will also explore biomarker correlations (HER2 immunohistochemistry [IHC], *in-situ* hybridization [ISH] and ctDNA) and factors associated with treatment duration and dose modification.

Study design

RECOVER is a multicenter, prospective, non-interventional observational study (NCT06846996)

- Participants receive T-DXd (starting dose 6.4 mg/kg IV Q3W) as part of clinical routine or per physician discretion.
- No drug will be provided or administered as part of the study protocol.



Sample size rationale

The study uses descriptive statistical methods and has no formal hypothesis testing. The target enrollment was determined to be approximately 260 by estimating the precision required for

- Primary endpoint: rwTTF
  - Assumed median rwTTF at 5.5 months
  - Study period 18 months
    - ✓ Enrollment period: 12 months
    - ✓ Follow-up duration of 6 months based on DESTINY-Gastric06
  - Assumed dropout rate: 15%
  - Required precision: ±1.5 months around the median estimate
  - 150 participants to achieve the required precision
- Key secondary endpoint: incidence of grade ≥3 TRAEs
  - Assumed incidence: 65%
  - Desired precision: ±6.0%
  - 260 participants to achieve the required precision

Statistical analysis plan

- Interim analysis
  - 6 months after enrollment of 150 patients or occurrences of approximately 35% of rwTTF events, whichever earlier.
- Final analysis
  - 6 months after the last patient initiates T-DXd treatment.

Key inclusion criteria

- Patients with histologically confirmed diagnosis of locally advanced, unresectable, or metastatic gastric or GEJ adenocarcinoma.
- Patients aged ≥18 years at the time of first T-DXd administration and being able to provide written informed consent.
- HER2-positive status, defined as IHC 3+ or IHC 2+ with ISH positivity.
- Patients who have received prior systemic therapy, meet NMPA–approved indication for T-DXd or deemed clinically appropriate by the treating physician.
- Decision to initiate first T-DXd treatment is made prior to signing the informed consent form. Participants who have already initiated T-DXd within 21 days before enrolment are eligible if a signed and dated informed consent is available.

Key exclusion criteria

- Pregnant or breastfeeding at the time of enrolment.
- Currently participating in a blinded interventional clinical trial or scheduled to participate in such a trial at the time of enrollment.
- Known hypersensitivity to the active drug substance or any excipients contained in the T-DXd formulation.
- Any condition or circumstance that, in the investigator's judgement, would render the participant unsuitable for study participation.

Key study endpoints

1° Primary endpoints

- rwTTF
  - Calculated as the interval from the first dose of T-DXd to the earliest date of treatment discontinuation due to disease progression, physician decision, adverse event, or death.

2° Secondary endpoints

- All-grade TRAEs and physician-reported AESIs (incl. ILD/pneumonitis and LVEF decrease)
- rwTTNT
  - Calculated as the interval from the first dose of T-DXd to the start of next line treatment or death, whichever occurs earlier.

Exploratory endpoints

- rwPFS
  - Calculated as the interval from the first dose of T-DXd to clinical or radiological progression or death
- OS
  - Calculated as the interval from the first dose of T-DXd to death from any cause.
- T-DXd treatment patterns
- PROs
  - Assessed using FACT-Ga and QLQ-C30
- Correlation between plasma ctDNA HER2 copy number and HER2 status in matched tumor samples.

Disclosures

†Tong Xie and Zhi Peng contributed equally to this work and are considered as co-first authors.

Author Qingsong Jiao is employee of Department of Medical Affairs, Daiichi Sankyo (China) Holdings Co., Ltd. All other authors declare no competing interests.

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Abbreviations

AESI, Adverse event of special interest, HER2, Human epidermal growth factor receptor 2; GEJ, gastroesophageal junction; IHC, immunohistochemistry; ISH, *in-situ* hybridization; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; Q3W, every 3 weeks; rwTTF, real-world time to treatment failure; rwPFS, real-world progression-free survival; rwTTNT, real-world time to next treatment; PROs, patients-reported outcomes; T-DXd, Trastuzumab deruxtecan; TRAEs, treatment-related adverse events; NMPA, National medical products administration; OS, overall survival; FACT-Ga, Functional assessment of cancer therapy-gastric; QLQ-C30, Quality of life questionnaire core 30

References

1. Bray F, et al. *CA Cancer J Clin* 2024; **74**(3): 229-63.
2. Cao W, et al. *Chin J Cancer Res* 2025; **37**(6): 912-28.
3. Bang YJ, et al. *Lancet* 2010; **376**(9742): 687-97.
4. Thuss-Patience PC, et al. *Lancet Oncol* 2017; **18**(5): 640-53.
5. Shitara K, et al. *N Engl J Med* 2020; 382(25): 2419-30.
6. Shitara K, et al. *N Engl J Med* 2025; 393(4):336-348.
7. Qi J, et al. *Lancet Public Health* 2023;8(12):e943-e955.
8. Liang Y, et al. *Cancer Med* 2025;14(22):e71379.
9. Kawakami H, et al. *Gastric Cancer* 2025;28(1):51-61.
10. Matsumoto T, et al. *J Clin Med* 2022;11(8):2247.

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