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Efficacy of Trastuzumab Deruxtecan and Biomarker Changes in HER2-Positive Gastric Cancer: EN-MARK Study Protocol

Akira Ooki[1], Hiroki Osumi[1], Ken Shimada[2], Nozomu Machida[3], Hiroki Hara[4], Manabu Takamatsu[5], Naoki Ishizuka[6], Aya Katayama[7], Wataru Hashimoto[8], Kensei Yamaguchi[1]

[1]Department of Gastroenterological Chemotherapy, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [2]Department of Medical Oncology, Showa University Koto Toyosu Hospital, Tokyo, Japan; [3]Department of Gastroenterology, Kanagawa Cancer Center, Kanagawa, Japan; [4]Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan; [5]Department of Pathology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [6]Center for Digital Transformation of Healthcare, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [7]Oncology Medical Science Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan; [8]Data Intelligence Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan

Plain language summary

Why are we performing this research?

- The potential loss of HER2 positivity after 1L T-mab–based treatment in patients with HER2-positive gastric cancer has been reported. However, there have not been detailed reports on biomarker changes including HER2 status during 2L therapy (the next therapy after the first treatment was not successful)
- Based on this background, we designed this study to evaluate how well T-DXd works (also known as efficacy) in 3L treatment and to explore the relationship between biomarker changes after 1L treatment and the efficacy of T-DXd
- The EN-MARK study evaluates the efficacy of T-DXd as a 3L treatment for HER2-positive, unresectable, advanced or recurrent GEA
  - It serves as the first prospective study to sequentially assess both tumor tissue and blood samples for HER2 status in the same patient after T-mab–based 1L treatment
  - The results will provide additional insights into the optimal use of T-DXd in clinical practice

How are we performing this research?

- Patients with HER2-positive (known as IHC 3+ or IHC 2+/ISH+) gastric or GEJ adenocarcinoma are recruited from 30 Japanese institutions from April 26, 2024, to February 28, 2026
- Patients are treated with 2L SoC and 3L T-DXd
- Blood and tumor tissue (optional) samples are collected from patients for biomarker analyses

Who will participate in this study?

- Patients with HER2-positive gastric or GEJ adenocarcinoma (aged ≥18 years, prior T-mab treatment, failure of 1L therapy, ECOG PS 0-2)

Where can I access more information?

- This study is expected to end on February 29, 2028. For more information about EN-MARK, please visit https://jrct.niph.go.jp/en-latest-detail/jRCTs031240055. You may also speak to your doctor about clinical studies

Background

- T-mab–containing regimens serve as the standard 1L treatment in patients with HER2-positive, advanced GEA[1]
- T-DXd has demonstrated improved survival outcomes in the ≥3L setting in patients with HER2-positive, advanced GEA in Japan[2]
- However, approximately 30%-70% of patients with HER2-positive, advanced GEA develop a potential loss of HER2 positivity after 1L T-mab–based treatment[3-5]
- Currently, there is a lack of understanding regarding the profile of the sequential HER2 status after 1L treatment with T-mab and the potential impact on the efficacy of 3L T-DXd in patients who may have lost HER2 expression

The EN-MARK study aims to evaluate the efficacy of T-DXd as a 3L treatment for HER2-positive, unresectable, advanced or recurrent GEA

Study rationale

- The antitumor activity of T-DXd in GEA may depend on the level of HER2 expression[6]
- Considering the potential loss of HER2 positivity after 1L treatment,[3-5] reassessment of HER2 status using tumor biopsies prior to 3L T-DXd treatment may be necessary to identify patients suitable for the therapy
- However, obtaining repeat tumor biopsy samples may pose medical risks due to invasive procedures, especially for those with recurrent GEA after gastrectomy
- Analyses of ctDNA and HER2 ECD levels using blood samples may be an alternative to predict the efficacy of 3L T-DXd and guide therapeutic decisions in patients with GEA[6]
- The EN-MARK study (trial ID: jRCTs031240055) was designed based on the findings and hypothesis derived from the Phase 2 WJOG7112G (T-ACT) study, which showed that patients with a longer T-mab–free interval tended to achieve improved survival outcomes when treated with T-mab beyond progression[3] (**Fig. 1**, **Fig. 2**)

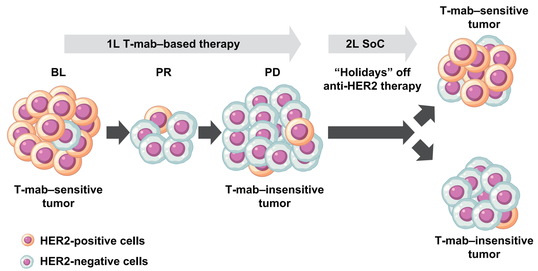
Fig. 1 Study rationale

Patients with a longer T-mab–free interval showed a trend toward improved survival when treated with T-mab beyond progression[3]

The mean *ERBB2* (HER2) gene copy number was also higher in patients with longer T-mab–free intervals than in those with shorter intervals[3]

Hypothesis:
Patients whose disease progresses on HER2-targeted therapy owing to drug-selected clonal expansion may regain HER2 expression and sensitivity to HER2-targeted therapy after a defined break from HER2-signaling blockade through 2L chemotherapy without a HER2-targeted agent

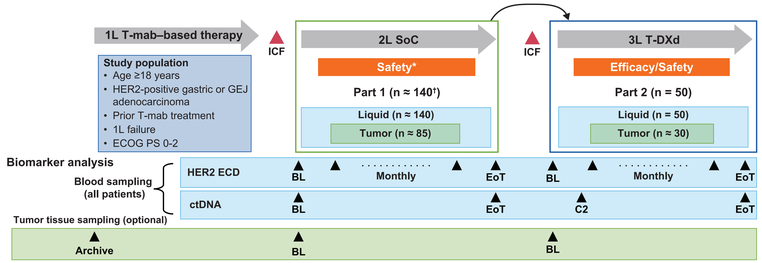
Fig. 2 Biological rationale for 3L HER2-targeted therapy after 1L anti-HER2 T-mab therapy



Study design

- **Study design:** Prospective, single-arm, multicenter, two-part study (**Fig. 3**)
  - Part 1 (n≈140*1): To assess dynamic biomarker changes and collect clinical information during standard 2L treatment
  - Part 2 (n=50*2 as RES): To investigate the efficacy and safety of T-DXd alongside biomarker changes
- **Study period:** April 26, 2024, to February 29, 2028
- **Follow-up period for each patient:** Acquisition of informed consent in Part 1 to 6 months after the registration date of the last study patient in Part 2

Fig. 3 Study scheme



*AEs with a causal relationship to study-specific procedures (e.g., bleeding or shock from tumor biopsy). †Predicted number of patients to reach 50 patients in Part 2.

Treatment and clinical assessments

- **T-DXd treatment**
  - Administered intravenously (6.4 mg/kg) every 3 weeks
  - Continued until documented disease progression, withdrawal of consent, or discontinuation
- **Clinical assessment**
  - Treatment response: Assessed using CT or MRI at baseline and every 8 weeks (±2 weeks) while on treatment; local assessment based on RECIST version 1.1
  - AEs: Coded using MedDRA and graded by the investigator based on CTCAE version 5.0
    - Part 1: AEs with a causal relationship with study-specific procedures (e.g., bleeding or shock from tumor biopsy)
    - Part 2: Grade ≥3 AEs, ILD of all grades, and AEs with a causal relationship with study-specific procedures

Blood and tumor tissue sample analysis

- **Blood samples**
  - Centrally analyzed using Guardant360® (Guardant Health, Redwood City, CA, USA) for ctDNA
  - Analyzed at participating institutions or testing laboratories for HER2 ECD
- **Tumor tissue samples for HER2 status (optional)**
  - Centrally analyzed using HercepTest™ mAb pharmDx (Agilent Dako, Santa Clara, CA, USA) for IHC
  - Centrally analyzed using PathVysion HER-2 DNA Probe Kit (Abbott, Abbott Park, IL, USA) for ISH

Key inclusion criteria

Part 1

- Age ≥18 years
- HER2-positive (IHC3+ or IHC2+/ISH+) gastric or GEJ adenocarcinoma
- ECOG PS 0-2
- Disease progression on and after treatment with T-mab–containing regimens in the 1L setting

Part 2

- ECOG PS 0-2
- Participation in Part 1 of this study and refractory or intolerant to 2L treatment
- Measurable target lesions based on RECIST version 1.1 as confirmed by the investigator

Key exclusion criteria

Part 1

- Previous complications or medical history of ILD
- Advanced multiple primary malignancies
- T-DXd treatment history
- Anticancer therapy after 1L treatment with a T-mab–containing regimen
- Scheduled to receive T-mab as 2L treatment

Part 2

- Previous complications or medical history of ILD
- Advanced multiple primary malignancies
- Anticancer therapy after treatment in Part 1 of the study

Key study endpoints

1° Primary endpoint

- Investigator-assessed ORR of 3L T-DXd in Part 2 (defined as the proportion of patients with CR or PR according to RECIST version 1.1)

2° Secondary endpoints

- PFS, TTF, and OS in Part 2
- Treatment toxicity of T-DXd (according to CTCAE version 5.0) in Part 2

Poster

Supplementary material

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This study is sponsored by Daiichi Sankyo Co., Ltd. Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize T-DXd in March 2019, except in Japan, where Daiichi Sankyo maintains exclusive rights for T-DXd. Daiichi Sankyo is responsible for the manufacturing and supply of T-DXd

Abbreviations

1L, first-line; 2L, second-line; 3L, third-line; AE, adverse event; BL, baseline; CR, complete response; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumor DNA; ECD, extracellular domain; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICF, informed consent; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; jRCT, Japan Registry of Clinical Trials; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RES, response evaluable set; SoC, standard of care; T-DXd, trastuzumab deruxtecan; T-mab, trastuzumab; TTF, time to treatment failure

*1: Assuming that 65% of Part 1 patients are transferred to Part 2 and 60% of patients who have transferred to Part 2 meet the RES criteria, 140 patients are required in Part 1 to secure 50 patients in Part 2 with a probability of ≥80%

*2: This study is designed for exploratory purposes, and therefore, the target number of patients for Part 2 has been established based on its feasibility. A lower threshold of ORR for T-DXd (15%) was set in reference to other 3L gastric cancer data for nivolumab (ORR=14.0% [ATTRACTION-2 Japan subgroup†], 14.5% [DELIVER†]). The expected ORR of T-DXd was set at 33% based on the result of DESTINY-Gastric01 (43%)† and an opinion of the principal investigator. Collection of 50 patients at a one-sided significance level of 5% satisfies the power of approximately 90%

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