Trastuzumab Deruxtecan in Human Epidermal Growth Factor Receptor 2–Expressing Biliary Tract Cancer (HERB; NCCH1805): A Multicenter, Single-Arm, Phase II Trial

Akihiro Ohba, MD[1]; Chigusa Morizane, MD, PhD[1]; Yasuyuki Kawamoto, MD, PhD[2]; Yoshito Komatsu, MD, PhD[2]; Makoto Ueno, MD, PhD[3]; Satoshi Kobayashi, MD[3]; Masafumi Ikeda, MD, PhD[4]; Mitsuhito Sasaki, MD[4]; Junji Furuse, MD, PhD[3,5]; Naohiro Okano, MD, PhD[5]; Nobuyoshi Hiraoka, MD, PhD[6]; Hiroshi Yoshida, MD, PhD[6]; Aya Kuchiba, PhD[7]; Ryo Sadachi, PhD[7]; Kenichi Nakamura, MD, PhD, MBA[8]; Naoko Matsui, BS[8]; Yoshiaki Nakamura, MD, PhD[9]; Wataru Okamoto, MD, PhD[10]; Takayuki Yoshino, MD, PhD[9]; and Takuji Okusaka, MD, PhD[1]

DOI https://doi.org/10.1200/JCO.23.02010

ABSTRACT

PURPOSE Treatment options for patients with unresectable or recurrent biliary tract cancer (BTC) who progress on a gemcitabine-containing regimen are limited. In addition, the significance of anti–human epidermal growth factor receptor 2 (HER2) therapy in HER2-expressing BTC has not been sufficiently investigated.

METHODS In this phase II trial, participants from five institutions in Japan were enrolled. Eligible patients had pathologically confirmed unresectable or recurrent BTC with centrally confirmed HER2-positive (immunohistochemistry [IHC]3+ or IHC2+ and in situ hybridization [ISH]+) or HER2-low (IHC2+ and ISH−, IHC1+, and IHC0 and ISH+) and were refractory or intolerant to a gemcitabine-containing regimen. The patients received 5.4 mg/kg trastuzumab deruxtecan (T-DXd) once every 3 weeks until disease progression or unacceptable toxicity. The primary end point was the confirmed objective response rate (ORR) in HER2-positive BTC by an independent central review (threshold ORR, 15%; expected ORR, 40%).

RESULTS A total of 32 patients were enrolled and treated. Among these patients, 22 with HER2-positive disease comprised the primary efficacy population and had a confirmed ORR of 36.4% (90% CI, 19.6 to 56.1; $P = .01$), meeting the primary end point. Eight with HER2-low disease comprised the exploratory population and had a confirmed ORR of 12.5%. The most common ≥grade 3 treatment-related adverse events were anemia (53.1%) and neutropenia (31.3%). Eight patients (25.0%) had interstitial lung disease (ILD), including two grade 5 events.

CONCLUSION T-DXd showed promising activity in patients with HER2-positive BTC and a signal of efficacy in patients with HER2-low BTC. Although the safety profile was generally manageable, ILD requires careful monitoring and early intervention.

ACCOMPANYING CONTENT

Oncology Grand Rounds, p. 3170

Appendix

Data Sharing Statement

Protocol

Accepted April 17, 2024
Published August 5, 2024

J Clin Oncol 42:3207-3217

View Online Article

INTRODUCTION

Biliary tract cancer (BTC) include intrahepatic and extrahepatic cholangiocarcinomas, gallbladder cancer, and cancer of the ampulla of Vater.[1] Only 10%-40% of patients with BTC have resectable disease, and most patients are typically diagnosed at an advanced stage.[2] Combination chemotherapy has been the standard first-line treatment for patients with advanced BTC after a phase III trial established the effectiveness of cisplatin plus gemcitabine.[3] A recent phase III trial reported that additional durvalumab or pembrolizumab in combination with chemotherapy improved overall survival (OS).[4,5] However, the efficacy of second-line chemotherapy after disease progression with these first-line therapies is limited. Fluorouracil, leucovorin, and oxaliplatin (FOLFOX) demonstrated a survival advantage compared with the best supportive care; however, despite toxic combination therapy, the progression-free survival (PFS) and objective response rate (ORR) were approximately 4 months and 5%, respectively.[6] In addition, this combination chemotherapy regimen is not always indicated and fluoropyrimidine alone is still occasionally used in clinical practice. S-1 (an oral fluoropyrimidine) is used as an alternative in Asian countries in second-line setting; however, the reported ORR ranged from 7.5% to 22.7%.[7-9] Thus, further investigations are needed to develop more effective second- or later-line treatment options for patients with progressive BTC.

CONTEXT

Key Objective

About 5%-30% of patients with biliary tract cancer (BTC) have human epidermal growth factor receptor 2 (HER2)–positive disease, and several HER2-targeted therapies have been reported to be effective for those patients. The HERB trial investigated the efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients with HER2-expressing BTC.

Knowledge Generated

Of 22 patients with HER2-positive disease, the confirmed objective response rate (ORR) was 36.4%, meeting the primary end point. Of eight patients with HER2-low disease in the exploratory population, ORR was 12.5%. T-DXd showed promising activity in patients with HER2-positive BTC and a signal of efficacy in patients with HER2-low BTC.

Relevance *(E.M. O'Reilly)*

Antibody drug conjugates are proving to be a highly important therapeutic class of drugs. T-DXd is the first of its kind to demonstrate activity in biliary cancers and provides ongoing pathway validation for the importance of HER2 in these diseases.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD.

Several targeted therapies have been developed for patients with progressive BTC. A phase III trial reported that the PFS associated with ivosidenib, an isocitrate dehydrogenase-1 (*IDH1*) inhibitor, was improved compared with a placebo in patients with *IDH1*-mutant BTC.[10] With respect to fibroblast growth factor receptor-2 (*FGFR2*) inhibitors, infigratinib, pemigatinib, and futibatinib achieved an ORR of 18.8%, 35.5%, and 41.7%, respectively, in patients with BTC harboring *FGFR2* fusions or rearrangements in phase II trials.[11-13] A combination of dabrafenib and trametinib showed an ORR of 51% in patients with the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E mutation in a phase II trial.[14] In summary, these molecularly targeted agents have been developed for patients with BTC after second-line therapy and have generally demonstrated an ORR of 20%-50%.

Human epidermal growth factor receptor 2 (HER2) overexpression, gene amplification, or both have been reported in 15%-30% of gallbladder cancers, 10%-20% of extrahepatic cholangiocarcinomas and cancer of the ampulla of Vater, and 3%-5% of intrahepatic cholangiocarcinomas.[15,16] HER2-targeted therapies have been effective in many cancer types, including breast and gastric cancers.[17,18] Regarding HER2-positive BTC, the antitumor activity of several agents has been reported in case reports or case series, and pertuzumab plus trastuzumab showed an ORR of 23% in the HER2-positive BTC cohort of 39 patients in a phase II basket study.[19]

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of a humanized monoclonal anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor (payload).[20] The bystander effect of the payload, which readily crosses cell membranes, contributes to a cytotoxic effect on HER2-low tumors and heterogeneous HER2-expressing tumors, such as gastric cancer and BTC.[21] In the early stages of its development, T-DXd was shown to be effective in patients with HER2-positive metastatic breast cancer who had previously been treated with trastuzumab emtansine and in patients with advanced HER2-positive gastric cancer who had previously been treated with trastuzumab.[22] Recently, the survival benefits of T-DXd for HER2-positive metastatic breast cancer after trastuzumab and a taxane compared with trastuzumab emtansine[23] and HER2-low metastatic breast cancer in the second- or later-line compared to the physician's choice of chemotherapy have also been established.[24] T-DXd is one of the most effective HER2 inhibitors and is expected to be potent against HER2-low cancers. We chose the dose of 5.4 mg/m^2 because the fact that efficacy was comparable and safety was better in breast cancer was shown at the time of designing this trial. Recently, a similar trend has been reported in colorectal cancer,[25] which may support our choice of dose. Since the pharmacokinetic (PK) profiles of T-DXd in BTC were unclear, and human antihuman antibody (HAHA) was important for the resistance mechanism, we included them in the exploratory analysis.

Therefore, we aimed to investigate the efficacy and safety of T-DXd in patients with HER2-positive BTC refractory or intolerant to treatment including gemcitabine. In addition, we performed an exploratory evaluation of the HER2-low BTC cohort.

METHODS

Patients

Adult patients (age 20 years and older) with unresectable or recurrent BTC (intrahepatic and extrahepatic

cholangiocarcinomas, gallbladder cancer, and cancer of the ampulla of Vater) who met the following criteria were eligible to participate in the trial: a histologic diagnosis of adenocarcinoma or adenosquamous carcinoma, confirmed HER2 expression by central pathologic examination, refractory or intolerant to treatment including gemcitabine, an Eastern Cooperative Oncology Group performance status of 0 or 1, ≥1 measurable lesion, adequate organ function, and a left ventricular ejection fraction >50%. Patients were excluded if they had interstitial lung disease (ILD) requiring steroid therapy, or lung disease that could not be ruled out by imaging at screening. Patients who received previous anti-HER2 therapy were not excluded. More details are provided in the protocol.

Study Design and Treatment

This was an open-label, single-arm, multicenter, phase II trial conducted in Japan. Patients were screened at 30 sites belonging to SCRUM-Japan, a nationwide genome screening project, and eligible patients were enrolled in the trial at five trial sites. A screening study on HER2 expression for BTC (UMIN000036697) was conducted to identify patients with HER2-expressing BTC. A central pathologic examination consisting of immunohistochemistry (IHC) and in situ hybridization (ISH) of archival tissue confirmed the HER2-expressing status. For IHC, an anti-HER2 antibody (I-VIEW PATHWAY [4B5]; Ventana Medical Systems, West Sussex, United Kingdom) and the PathVysion HER2 DNA Probe Kit (Abbott Laboratories, Abbott Park, IL) were used. HER2 testing and scoring algorithms complied with the ASCO and College of American Pathologists guidelines for gastroesophageal adenocarcinoma.[26] HER2-positive was defined as IHC3+ or 2+/ISH +, and HER2-low was defined as IHC/ISH 2+/−, 1+/+, 1+/−, or 0/+. T-DXd was administered every 3 weeks at a dose of 5.4 mg/kg until radiologic or clinical disease progression or unacceptable toxicity, including grade ≥2 ILD.

Study End Points

For tumor assessment, computed tomography or magnetic resonance imaging was performed every 6 weeks until 24 weeks and every 12 weeks thereafter. The measurements were based on the RECIST version 1.1, by blinded independent central review (BICR) or local investigator review (LIR). All efficacy analyses were performed for the full analysis set (FAS), defined as the population of all applicable enrolled patients with a measurable lesion, excluding those who did not receive the study treatment and those who were later confirmed to be ineligible. Safety was assessed for the safety analysis set (SAS), defined as the population of all enrolled patients, excluding those who did not receive the study treatment. The primary end point was confirmed ORR in the HER2-positive BTC by BICR. It was defined as the proportion of complete and partial responses confirmed after at least 4 weeks among HER2-positive FAS. Secondary end points were confirmed ORR in patients in the HER2-low BTC and all enrolled BTC by BICR, confirmed ORR by LIR in each cohort, disease control rate (DCR) by BICR and LIR in each cohort, PFS by LIR and BICR, OS in each cohort, and incidence of adverse events. The duration of response (DoR) was assessed by LIR as post hoc analysis. Exploratory analyses included investigating the PK profiles of T-DXd, total antibody, and MAAA-1181a (topoisomerase I inhibitor payload) in serum concentrations and estimating the incidence of HAHA. More details are provided in the protocol.

Safety

All adverse events during the study period were recorded and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. Cases of ILD were assessed by symptoms, laboratory data, and imaging.

Statistical Analysis

The planned number of HER2-positive BTC for the primary analysis was 24. We assumed a threshold ORR of 15% and an expected ORR of 40% for HER2-positive patients to achieve a one-sided alpha error of .05 and 80% power. Seven confirmed objective responses were needed to declare the study positive. To investigate the signs of efficacy in HER2-low disease, an exploratory cohort with up to eight patients was set up.

The binomial test was performed for the null hypothesis of true ORR is less than or equal to the threshold ORR of 15%. The 90% and 95% CIs for the ORR by BICR, the 95% CI for the ORR by LIR, and the DCR were estimated with the Clopper and Pearson methods. The median PFS and OS were estimated using the Kaplan-Meier method, and the Brookmeyer and Crowley method was used to calculate the 95% CI. The probabilities of PFS and OS were estimated using the Kaplan-Meier method, and Greenwood's formula was used to calculate the 95% CI. DoR was also analyzed with the same methods for the PFS and OS. All analyses were performed using SAS software (version 9.4).

Trial Oversight

This study was registered at jRCT (jRCT2091220423) and JMACCT-CTR (JMA-IIA00423) and conducted after protocol approval by the institutional review boards of the participating institutions and in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice in Japan, and applicable regulatory requirements. All the participants provided written informed consent.

RESULTS

Study Participants

A total of 300 patients were screened and 296 patients had both results of IHC and ISH. Among 296 patients, 61 (17 IHC3+, 44 IHC2+/ISH+; 20.6%) were HER2-positive, 120

(40.5%) were HER2-low, and 115 (38.9%) were HER2-negative. The disposition of the enrolled patients is shown in the flowchart (Fig 1). A total of 32 patients (24 HER2-positive and eight HER2-low) were enrolled between June 21, 2019, and July 9, 2020, and all patients had adenocarcinoma. As two HER2-positive patients were eventually found to be ineligible, the number of patients in the FAS was 30. At the time of data cutoff on July 9, 2021, the median duration of follow-up for survival of the HER2-positive BTC was 7.1 months (IQR, 4.7-14.6), all patients discontinued the study treatment, and four patients were still alive (Appendix Tables A1-A3, online only). The patient characteristics are displayed in Table 1. In the HER2-positive BTC (n = 22), 50.0% of patients had gallbladder cancer, 90.9% had metastatic disease, 72.7% were administered study treatment as third- or later-line therapy, and 45.5% had an IHC3+ HER2 status. All specimens were obtained from the initial diagnostic biopsy or surgical specimen before systemic therapy for advanced disease.

Efficacy

The response data for each cohort are shown in Table 2. The primary end point of the confirmed ORR by BICR in the HER2-positive BTC was 36.4% (90% CI, 19.6 to 56.1; one-sided $P = .01$ for rejecting threshold response rate of 15%) with eight of 22 patients obtaining a confirmed objective response, including two complete responses. The median time to response was 1.6 months (95% CI, 1.3 to 2.8). In HER2-low BTC, one patient (IHC2+/ISH−) achieved a partial response by BICR, resulting in a confirmed ORR of 12.5% (95% CI, 0.3 to 52.7). The confirmed DCR by BICR was 81.8% (95% CI, 59.7 to 94.8) in the HER2-positive BTC and 75.0% (95% CI, 34.9 to 96.8) in the HER2-low BTC. The responses of the subgroups are summarized in Appendix Table A4. Figure 2A shows a waterfall plot of maximum tumor shrinkage from the baseline in target lesions by BICR in all eligible patients (waterfall plots by HER2 status are shown in Appendix Fig A1). The median DoR by LIR for the whole responder population in the HER2-positive BTC was estimated to be 7.4 months (95% CI, 2.8 to not applicable; Fig 2B). Figure 2C shows a spider plot of tumor volume changes by LIR in all eligible patients. The median PFS by LIR was 5.1 months (95% CI, 3.0 to 7.3) in the HER2-positive BTC and 3.5 months (95% CI, 1.2 to 5.5) in the HER2-low BTC (Figs 3A and 3B). The median OS was 7.1 months (95% CI, 4.7 to 14.6) in the HER2-positive BTC and 8.9 months (95% CI, 3.0 to 12.8) in the HER2-low BTC (Figs 3C and 3D).

Safety

SAS included all enrolled patients (n = 32). Treatment-related adverse events in SAS patients are shown in

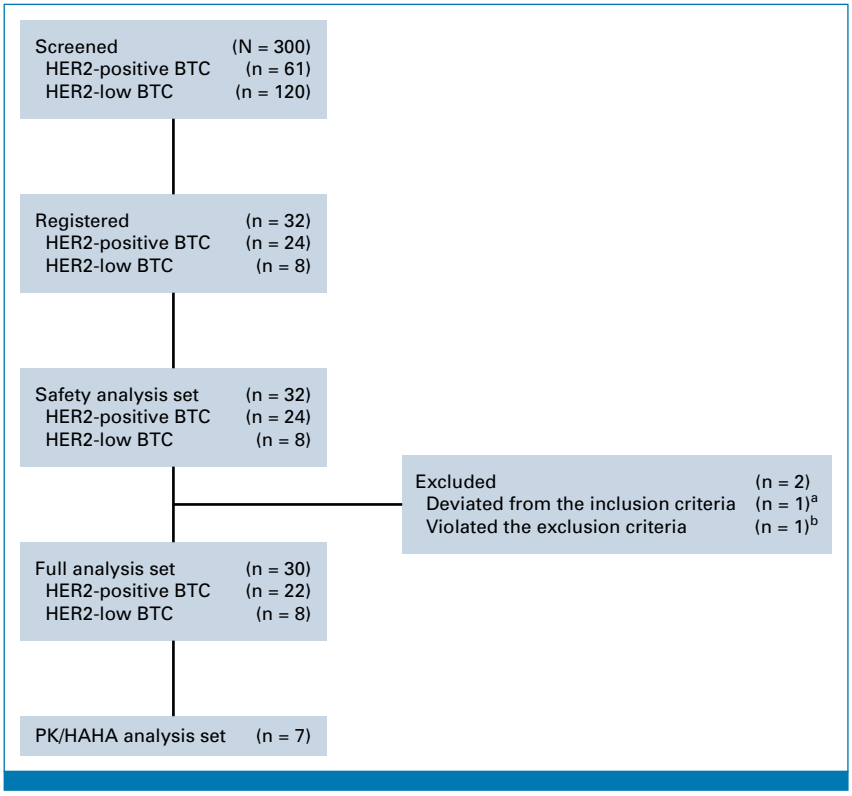

FIG 1. Study flow diagram. BTC, biliary tract cancer; HAHA, human antihuman antibody; HER2, human epidermal growth factor receptor 2; PK, pharmacokinetic. [a]The patient was administered systemic steroid therapy ≤14 days before enrollment. [b]The patient had pulmonary fibrosis on imaging at screening.

TABLE 1. Baseline Characteristics (FAS; n = 30)

Characteristic	HER2-Positive (n = 22)	HER2-Low (n = 8)	FAS (n = 30)
Age, years, median (range)	67.5 (39-78)	68 (43-80)	68 (39-80)
Male, No. (%)	13 (59.1)	5 (62.5)	18 (60.0)
ECOG PS, No. (%)			
0	15 (68.2)	6 (75.0)	21 (70.0)
1	7 (31.8)	2 (25.0)	9 (30.0)
Primary tumor location, No. (%)			
Intrahepatic cholangiocarcinoma	3 (13.6)	3 (37.5)	6 (20.0)
Extrahepatic cholangiocarcinoma	6 (27.3)	2 (25.0)	8 (26.7)
Gallbladder cancer	11 (50.0)	2 (25.0)	13 (43.3)
Cancer of the ampulla of Vater	2 (9.1)	1 (12.5)	3 (10.0)
Disease status, No. (%)			
Unresectable	13 (59.1)	4 (50.0)	17 (56.7)
Recurrent	9 (40.9)	4 (50.0)	13 (43.3)
Disease extent, No. (%)			
Locally advanced	2 (9.1)	1 (12.5)	3 (10.0)
Metastatic	20 (90.9)	7 (87.5)	27 (90.0)
No. of previous regimens, No. (%)			
1	6 (27.3)	3 (37.5)	9 (30.0)
≥2	16 (72.7)	5 (62.5)	21 (70.0)
HER2 expression, No. (%)			
IHC3+/ISH+	10 (45.5)	0	10 (33.3)
IHC2+/ISH+	12 (54.5)	0	12 (40.0)
IHC2+/ISH−	0	6 (75.0)	6 (20.0)
IHC1+/ISH−	0	1 (12.5)	1 (3.3)
IHC0/ISH+	0	1 (12.5)	1 (3.3)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

Table 3. Treatment-related ≥grade 3 adverse events were observed in 81.3% (26/32) of patients. Discontinuation of the study treatment and dose reduction because of treatment-related adverse events occurred in 25.0% and 18.8% of patients, respectively. Treatment-related deaths were observed in two patients (6.3%). The most common ≥grade 3 treatment-related adverse events were anemia (53.1%), neutropenia (31.3%), decreased WBC count (31.3%), and decreased lymphocyte count (21.9%). Eight patients (25.0%) developed ILD, and four (12.5%) were ≥grade 3, including two grade 5 cases (treatment-related deaths). Details of ILD are summarized in Appendix Table A5.

PKs and Human Antihumanized Antibody

The PK profiles of T-DXd, total antibody, and MAAA-1181a in serum concentrations and the incidence of HAHA were assessed in the samples obtained from seven patients. Appendix Figure A2 and Appendix Table A6 summarize the serum concentrations of T-DXd, the total antibody, and MAAA-1181a. The median serum concentrations of T-DXd on day 1 of cycles 2, 3, and 4 were 1,860, 4,660, and 5,070 ng/mL, respectively. These exposures were consistent with those previously reported in patients with breast cancer.[27] All the patients were HAHA-negative.

DISCUSSION

In this phase II trial, the primary cohort of HER2-positive BTC achieved a confirmed ORR of 36.4% (90% CI, 19.6 to 56.1) with a lower limit of 90% CI exceeding the threshold of 15%, resulting in the primary end point being met. Because this threshold was set well above the previously reported ORR for second-line chemotherapy, T-DXd is likely to be at least more effective than chemotherapy.[5] This response rate was higher than the 23% indicated in a clinical trial of another HER2 inhibitor combination, trastuzumab plus pertuzumab.[19] In addition, as a leading success in the development of targeted therapy for BTC, the ORR of the recently approved *FGFR* inhibitors is also 20%-40%; thus, the efficacy of T-DXd is comparable with that of these agents. Notably, while this trial actually included more than 70% of patients in the third-line treatment and beyond, this percentage was only 49%-54% in each of the *FGFR2* inhibitors trials.[11-13] It should be emphasized that two of the responders showed complete responses (CRs; 9.1%), and CR

TABLE 2. Confirmed Tumor Response (FAS; n = 30)

Response	HER2-Positive (n = 22)	HER2-Low (n = 8)	FAS (n = 30)
BICR			
ORR, %	36.4	12.5	30.0
90% CI	19.6 to 56.1[a]		
95% CI	17.2 to 59.3	0.3 to 52.7	14.7 to 49.4
DCR, % (95% CI)	81.8 (59.7 to 94.8)	75.0 (34.9 to 96.8)	80.0 (61.4 to 92.3)
Best response, No. (%)			
CR	2 (9.1)	0	2 (6.7)
PR	6 (27.3)	1 (12.5)	7 (23.3)
SD	10 (45.5)	5 (62.5)	15 (50.0)
PD	3 (13.6)	1 (12.5)	4 (13.3)
NE	1 (4.5)	1 (12.5)	2 (6.7)
LIR, % (95% CI)			
ORR	36.4 (17.2 to 59.3)	12.5 (0.3 to 52.7)	30.0 (14.7 to 49.4)
DCR	86.4 (65.1 to 97.1)	62.5 (24.5 to 91.5)	80.0 (61.4 to 92.3)
Best response, No. (%)			
CR	0	0	0
PR	8 (36.4)	1 (12.5)	9 (30.0)
SD	11 (50.0)	4 (50.0)	15 (50.0)
PD	3 (13.6)	3 (37.5)	6 (20.0)
NE	0	0	0

Abbreviations: BICR, blinded independent central review; BTC, biliary tract cancer; CR, complete response; DCR, disease control rate; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; LIR, local investigator review; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]The threshold ORR of the primary end point, confirmed ORR among patients with HER2-positive BTC, was 15% with a one-sided alpha error of .05.

was seldom observed in advanced BTC. Similar to the trend observed in breast and gastric cancer trials, the ORR increased to 40% in the IHC3+ subset (Appendix Table A2).[28,29] The confirmed ORR for any of the subgroups by primary tumor location was >30%; thus, efficacy could be expected regardless of the primary site. In terms of response durability, the median DoR of 7.4 months was consistent with that of 5-9 months observed in trials of *FGFR* inhibitors.[11-13] In the exploratory cohort of HER2-low disease, one patient (12.5%) achieved a partial response, suggesting that HER2-low may be beneficial for BTC as it proved to be in breast cancer.[24]

Regarding survival, the median PFS in the HER2-positive and HER2-low BTC was 5.1 months and 3.5 months, respectively. These might be clinically meaningful durations considering that there is no standard of care after third-line treatment, and the PFS is generally reported to be approximately 4 months even with second-line chemotherapy.[6] Furthermore, the most frequent primary site of the study population was gallbladder cancer (43.3% of FAS), which has a poor prognosis[30,31] and an extremely short PFS.[9] The OS was reversed compared with the PFS; 7.1 months of HER2-positive was shorter than 8.9 months of HER2-low, which might have occurred because of biases in background factors. In fact, the HER2-low BTC had better PS, fewer previous regimens, and more intrahepatic cholangiocarcinomas. The observed selection bias could be attributable to the higher prevalence of HER2-low status compared with HER2-positive status, coupled with a tendency to select patients in better condition. Both survival rates were comparable with approximately 6 months of standard second-line chemotherapy.[6]

Overall, the adverse events observed in this study were manageable and consistent with those reported in previous clinical trials of T-DXd. The most common treatment-related adverse events of ≥grade 3 were hematologic toxicities, including anemia and neutropenia. However, febrile neutropenia occurred in only two patients. Compared with the previously reported clinical trial results of T-DXd, the incidence of ILD was slightly higher, although it was not adjudicated to be drug-related, and those of all grades and ≥grade 3 were 25.0% and 12.5%, respectively. Notably, there were two grade 5 cases in this trial. ILD has been recognized as an important risk factor for T-DXd treatment. This trial, as well as other T-DXd trials, followed recent ILD management guideline of T-DXd, including careful monitoring of symptoms, laboratory data, and imaging for immediate management with early treatment interruption and adequate administration of steroids. The principal investigator with the coordinating committee members of the trial reviewed each case in detail, but all rescue interventions for

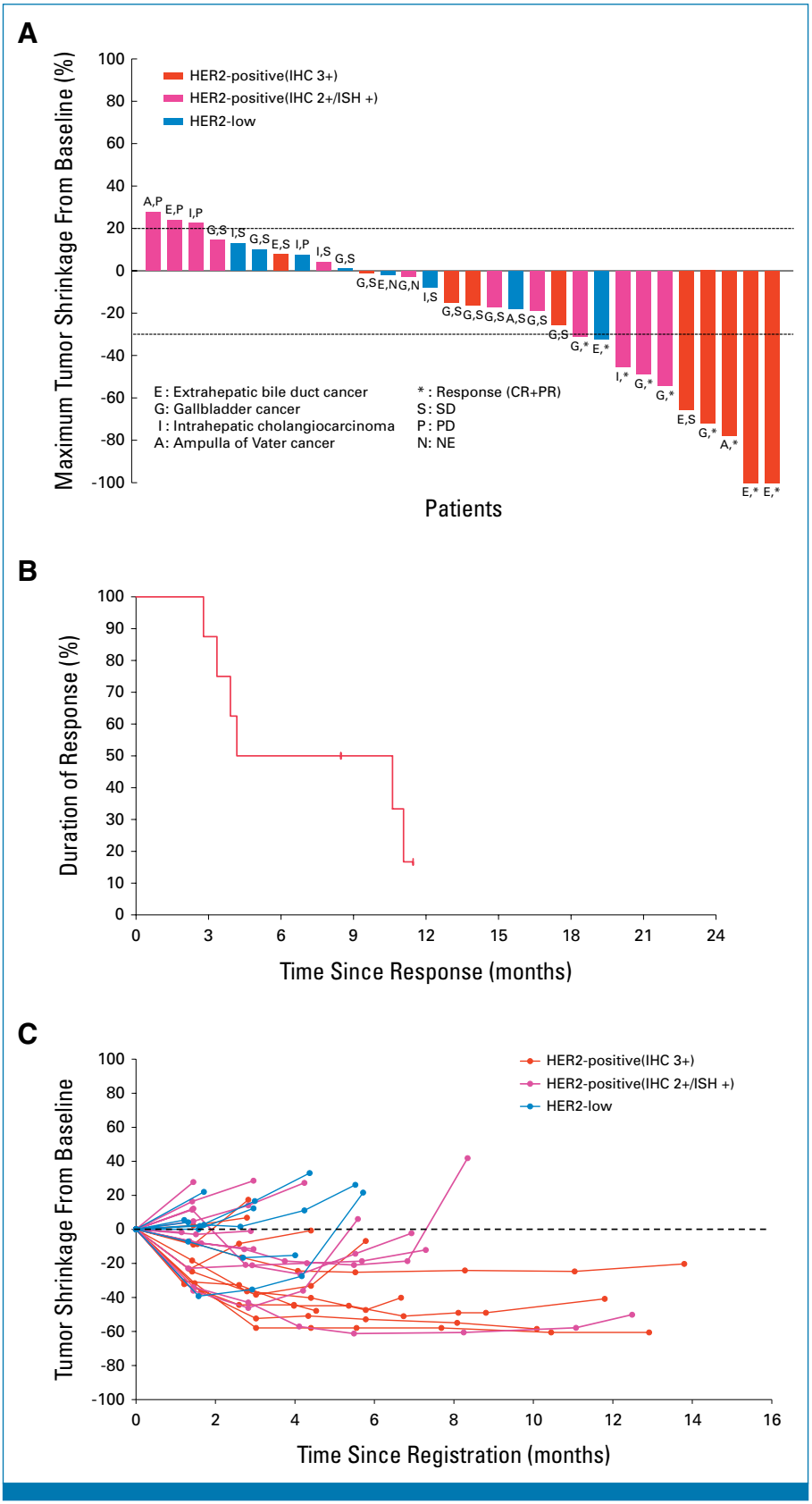

FIG 2. Tumor shrinkage and response durability. (A) Waterfall plots of maximum tumor shrinkage from the baseline by BICR among HER2-positive and HER2-low patients. (B) Duration of response in HER2-positive patients who responded to study treatment by LIR. (C) Spider plots of tumor shrinkage at each time point by LIR among HER2-positive and HER2-low patients. BICR, blinded independent central review; CR, complete response; HER2, (continued on following page)

FIG 2. (Continued). human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LIR, local investigator review; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

ILD were appropriately timed and did not lead to the identification of any obvious risk factors, including potential risks. In this trial, the median time to onset of ILD was 124 days (range, 35-247 days), which was shorter than that in breast cancer trials and longer than that in gastric cancer trials.[22,28] Some logical explanations can be made because of the relatively high frequency and severity of ILD in this study. BTC itself could be a risk factor for ILD because the payload is excreted through the bile. The PK profiles of patients in this trial, including those who developed ILD, were similar to those of other cancer types.[26] However, PK profiles were investigated for up to four cycles, and it was unclear whether the concentration of the drug or payload was elevated at the time of the occurrence of ILD. The fact that the severity of ILD was higher in early trials during the development of T-DXd for breast cancer suggests that familiarity with the drug by investigators in a certain area may reduce its severity.[22,23,25,29] The incidence of ILD is reported to be higher in the Japanese subpopulation than in other populations.[32] Additionally, the previously heavily treated status might have increased its frequency.[23,28] Thus, same caution is required when using T-DXd in clinical practice for BTC and heavily treated patients as for other cancer types.

This trial adopted conventional IHC and ISH testing to identify BTC with HER2-positive and HER2-low status, and complied with the guidelines of gastroesophageal cancer for HER2 testing.[26] We reported the HER2 expression status in 454 cases and found that the patterns of expression were similar to those of gastroesophageal cancer rather than breast cancer.[31]

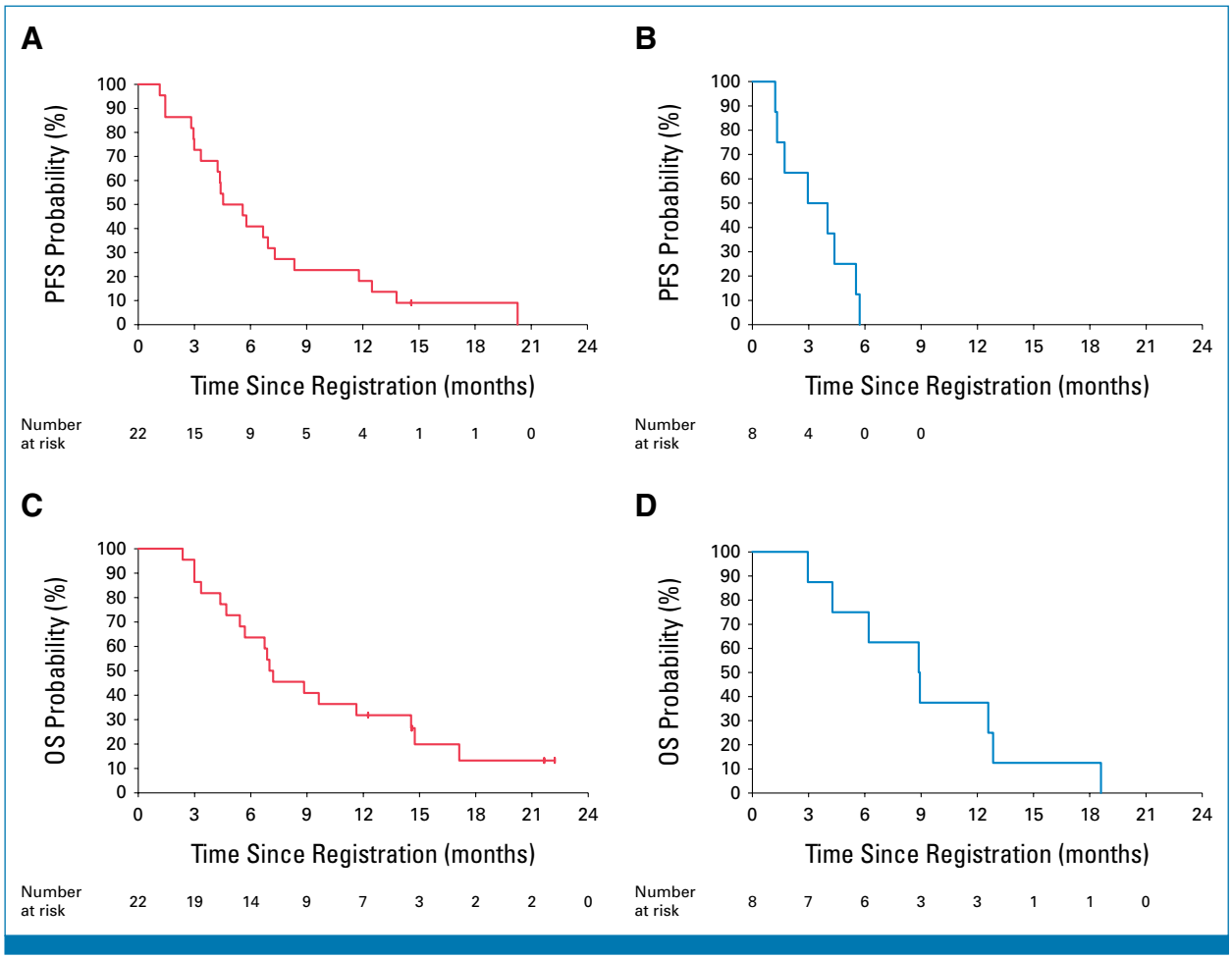

FIG 3. PFS and OS. (A) PFS by LIR among HER2-positive patients. (B) PFS by LIR among HER2-low patients. (C) OS among HER2-positive patients. (D) OS among HER2-low patients. HER2, human epidermal growth factor receptor 2; LIR, local investigator review; OS, overall survival; PFS, progression-free survival.

TABLE 3. Treatment-Related Adverse Events Occurring in ≥10% of Patients (SAS; n = 32)

Safety Summary	SAS (n = 32), No. (%)
Any TRAEs	32 (100)
Grade ≥3 TRAEs	26 (81.3)
Serious TRAEs	6 (18.8)
TRAEs leading to treatment interruption	12 (37.5)
TRAEs leading to treatment discontinuation	8 (25.0)
TRAEs leading to dose reduction	6 (18.8)
Deaths associated with TRAEs	2 (6.3)

Event	Any Grade, No. (%)	Grade ≥3, No. (%)
Anemia	22 (68.8)	17 (53.1)
Neutrophil count decreased	18 (56.3)	10 (31.3)
WBC count decreased	18 (56.3)	10 (31.3)
Platelet count decreased	14 (43.8)	3 (9.4)
Nausea	14 (43.8)	0
Alopecia	13 (40.6)	0
Anorexia	12 (37.5)	1 (3.1)
Lymphocyte count decreased	11 (34.4)	7 (21.9)
Fatigue/malaise	11 (34.4)	0
Interstitial lung disease/pneumonitis	8 (25.0)	4 (12.5)[a]
Hypoalbuminemia	7 (21.9)	1 (3.1)
Vomiting	7 (21.9)	0
Mucositis oral	5 (15.6)	0

Abbreviations: SAS, safety analysis set; TRAEs, treatment-related adverse events.
[a]Two cases were grade 5.

Circulating tumor DNA was also collected from all patients at multiple points, and the association between the status of genetic alterations and efficacy will be investigated.

Recently, several effective agents or regimens have emerged in the space of HER2-positive BTC. Zanidatamab, a bispecific antibody targeting two HER2 domains, demonstrated an ORR of 41.3% with a favorable safety profile in a global phase IIb trial.[33] Tucatinib and trastuzumab showed an ORR of 46.7% with good tolerability in a phase II basket study.[34] Trastuzumab plus FOLFOX showed an ORR of 29.4% with manageable toxicity in a Korean phase II trial.[35] Our next challenge is to optimize treatments including T-DXd and trastuzumab plus pertuzumab. Clearly, treatments with high efficacy and low toxicity should be used as frontline options. However, as we currently only have data up to phase II trials and cross-trial comparisons, further clinical trial is eagerly awaited.

The main limitations of this study were that it included a small number of Japanese patients and was conducted in a single country. Although our findings may have limited generalizability, previous trials of chemotherapy and targeted therapy for BTC have consistently demonstrated efficacy across different regions and races. Furthermore, T-DXd has shown its efficacy in multiple trials in many countries, and another global trial on the BTC cohort is ongoing (ClinicalTrials.gov identifier: NCT04482309).

In this trial, T-DXd showed promising activity among patients with HER2-positive BTC and signal of efficacy among patients with HER2-low BTC. Although the safety profile was generally manageable, in terms of ILD, there is a probability that their frequency and severity may be high in patients with BTC.

AFFILIATIONS

[1]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan
[2]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan
[3]Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan
[4]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[5]Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan
[6]Division of Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo, Japan

[7]Biostatistics Section, Clinical Research Support Office, National Cancer Center Hospital/Biostatistics Division, Center for Research Administration and Support, National Cancer Center, Tokyo, Japan
[8]Clinical Research Support Office, National Cancer Center Hospital, Tokyo, Japan
[9]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[10]Cancer Treatment Center, Hiroshima University Hospital, Hiroshima, Japan

CORRESPONDING AUTHOR

Chigusa Morizane, MD, PhD; e-mail: cmorizan@ncc.go.jp.

PRIOR PRESENTATION

Presented at the ASCO Annual Meeting, Chicago, IL, June 4-6, 2022.

SUPPORT

Supported in part by Japan Agency for Medical Research and Development (grant numbers: 17lk0201067, 18lk0201067, 19lk0201067, 20lk0201067, and 21lk0201067), and funded by Daiichi Sankyo Co, Ltd. The study drug was donated by Daiichi Sankyo Co, Ltd.

CLINICAL TRIAL INFORMATION

jRCT2091220423

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.02010.

DATA SHARING STATEMENT

The study protocol is provided in the Data Supplement. Individual participant data will not be available.

AUTHOR CONTRIBUTIONS

Conception and design: Akihiro Ohba, Chigusa Morizane, Yasuyuki Kawamoto, Makoto Ueno, Masafumi Ikeda, Junji Furuse, Aya Kuchiba, Ryo Sadachi, Kenichi Nakamura, Naoko Matsui, Yoshiaki Nakamura, Wataru Okamoto, Takayuki Yoshino, Takuji Okusaka
Financial support: Chigusa Morizane
Administrative support: Akihiro Ohba, Chigusa Morizane, Kenichi Nakamura, Naoko Matsui
Provision of study materials or patients: Akihiro Ohba, Chigusa Morizane, Yasuyuki Kawamoto, Yoshito Komatsu, Makoto Ueno, Satoshi Kobayashi, Masafumi Ikeda, Mitsuhito Sasaki, Junji Furuse, Naohiro Okano, Takuji Okusaka
Collection and assembly of data: All authors
Data analysis and interpretation: Akihiro Ohba, Chigusa Morizane, Yasuyuki Kawamoto, Yoshito Komatsu, Makoto Ueno, Satoshi Kobayashi, Masafumi Ikeda, Mitsuhito Sasaki, Junji Furuse, Naohiro Okano, Aya Kuchiba, Ryo Sadachi, Kenichi Nakamura, Naoko Matsui, Yoshiaki Nakamura, Wataru Okamoto, Takayuki Yoshino, Takuji Okusaka
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors thank patients and their families for participating in the trial; Ms Yukari Hoshina for her data management and Mr Masahisa Kamikura for his special technical support for developing Electronic Data Capturing system in the Data Management Section of Clinical Research Support Office, National Cancer Center Hospital; SCRUM-Japan; and all investigators.

REFERENCES

1. Valle JW, Kelley RK, Nervi B, et al: Biliary tract cancer. Lancet 397:428-444, 2021
2. Banales JM, Cardinale V, Carpino G, et al: Expert consensus document: Cholangiocarcinoma: Current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol 13:261-280, 2016
3. Valle J, Wasan H, Palmer DH, et al: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362:1273-1281, 2010
4. Oh D-Y, Ruth He A, Qin S, et al: Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Évid 1:EVIDoa2200015, 2022
5. Kelley RK, Ueno M, Yoo C, et al: Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 401:1853-1865, 2023
6. Lamarca A, Palmer DH, Wasan HS, et al: Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): A phase 3, open-label, randomised, controlled trial. Lancet Oncol 22:690-701, 2021
7. Sasaki T, Isayama H, Yashima Y, et al: S-1 monotherapy in patients with advanced biliary tract cancer. Oncology 77:71-74, 2009
8. Sasaki T, Isayama H, Nakai Y, et al: Multicenter phase II study of S-1 monotherapy as second-line chemotherapy for advanced biliary tract cancer refractory to gemcitabine. Invest New Drug 30: 708-713, 2012
9. Suzuki E, Ikeda M, Okusaka T, et al: A multicenter phase II study of S-1 for gemcitabine-refractory biliary tract cancer. Cancer Chemother Pharmacol 71:1141-1146, 2013
10. Abou-Alfa GK, Macarulla T, Javle MM, et al: Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): A multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 21:796-807, 2020
11. Abou-Alfa GK, Sahai V, Hollebecque A, et al: Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: A multicentre, open-label, phase 2 study. Lancet Oncol 21: 671-684, 2020
12. Javle M, Roychowdhury S, Kelley RK, et al: Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: Mature results from a multicentre, open-label, single-arm, phase 2 study. Lancet Gastroenterol Hepatol 6:803-815, 2021
13. Goyal L, Meric-Bernstam F, Hollebecque A, et al: Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. J Clin Oncol 40, 2022 (suppl 16; abstr 4009)
14. Subbiah V, Lassen U, Élez E, et al: Dabrafenib plus trametinib in patients with BRAF V600E-mutated biliary tract cancer (ROAR): A phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol 21:1234-1243, 2020
15. Valle JW, Lamarca A, Goyal L, et al: New horizons for precision medicine in biliary tract cancers. Cancer Discov 7:943-962, 2017
16. Hechtman JF, Liu W, Sadowska J, et al: Sequencing of 279 cancer genes in ampullary carcinoma reveals trends relating to histologic subtypes and frequent amplification and overexpression of ERBB2 (HER2). Mod Pathol 28:1123-1129, 2015
17. Baselga J, Cortés J, Kim S-B, et al: Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366:109-119, 2012
18. Bang Y-J, Van Cutsem E, Feyereislova A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 376:687-697, 2010

19. Javle M, Borad MJ, Azad NS, et al: Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): A multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol 22:1290-1300, 2021
20. Ogitani Y, Aida T, Hagihara K, et al: DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin Cancer Res 22:5097-5108, 2016
21. Ogitani Y, Hagihara K, Oitate M, et al: Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody–drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. Cancer Sci 107:1039-1046, 2016
22. Shitara K, Bang Y-J, Iwasa S, et al: Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 382:2419-2430, 2020
23. Cortés J, Kim S-B, Chung W-P, et al: Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med 386:1143-1154, 2022
24. Modi S, Jacot W, Yamashita T, et al: Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 387:9-20, 2022
25. Raghav KPS, Siena S, Takashima A, et al: Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified (HER2+) metastatic colorectal cancer (mCRC): Primary results from the multicenter, randomized, phase 2 DESTINY-CRC02 study. J Clin Oncol 41, 2023 (suppl 16; abstr 3501)
26. Bartley AN, Washington MK, Colasacco C, et al: HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: Guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. J Clin Oncol 35:446-464, 2017
27. Doi T, Shitara K, Naito Y, et al: Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody–drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: A phase 1 dose-escalation study. Lancet Oncol 18:1512-1522, 2017
28. Modi S, Saura C, Yamashita T, et al: Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 382:610-621, 2020
29. Shitara K, Iwata H, Takahashi S, et al: Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: A dose-expansion, phase 1 study. Lancet Oncol 20:827-836, 2019
30. Okusaka T, Nakachi K, Fukutomi A, et al: Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: A comparative multicentre study in Japan. Br J Cancer 103: 469-474, 2010
31. Morizane C, Okusaka T, Mizusawa J, et al: Randomized phase II study of gemcitabine plus S-1 versus S-1 in advanced biliary tract cancer: A Japan Clinical Oncology Group trial (JCOG 0805). Cancer Sci 104:1211-1216, 2013
32. Powell CA, Modi S, Iwata H, et al: Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open 7:100554, 2022
33. Harding JJ, Fan J, Oh D-Y, et al: Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): A multicentre, single-arm, phase 2b study. Lancet Oncol 24:772-782, 2023
34. Nakamura Y, Mizuno N, Sunakawa Y, et al: Tucatinib and trastuzumab for previously treated human epidermal growth factor receptor 2–positive metastatic biliary tract cancer (SGNTUC-019): A phase II basket study. J Clin Oncol 41:5569-5578, 2023
35. Lee C, Chon HJ, Cheon J, et al: Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: A multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19–14). Lancet Gastroenterol Hepatol 8:56-65, 2023

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Trastuzumab Deruxtecan in Human Epidermal Growth Factor Receptor 2–Expressing Biliary Tract Cancer (HERB; NCCH1805): A Multicenter, Single-Arm, Phase II Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Akihiro Ohba
Honoraria: Ono Pharmaceutical, Yakult Honsha, Guardant Health, AstraZeneca, Eisai, Servier, Taiho Pharmaceutical
Consulting or Advisory Role: Zymeworks
Research Funding: Ono Pharmaceutical (Inst), Chugai Pharma (Inst), Novartis (Inst)

Chigusa Morizane
Honoraria: Novartis, Yakult Honsha, Teijin Pharma, Taiho Pharmaceutical, Eisai, MSD K.K, AstraZeneca, Incyte Japan
Consulting or Advisory Role: Yakult Honsha, MSD K.K, Servier, AstraZeneca, Taiho Pharmaceutical, Merck, Boehringer Ingelheim
Research Funding: Eisai (Inst), Yakult Honsha (Inst), Ono Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), J-Pharma (Inst), AstraZeneca (Inst), Merck (Inst), Daiichi Sankyo RD Novare, Hitachi (Inst), Boehringer Ingelheim (Inst)

Yasuyuki Kawamoto
Honoraria: Taiho Pharmaceutical, Merck, Yakult Honsha, Ono Pharmaceutical, Incyte, AstraZeneca, Lilly Japan, Nihon Servier
Consulting or Advisory Role: Taiho Pharmaceutical
Research Funding: Japan Agency for Medical Research and Development, Takeda

Yoshito Komatsu
Honoraria: Lilly Japan, Taiho Pharmaceutical, Chugai Pharma, Takeda, Bayer Yakuhin, Bristol Myers Squibb Co, Sanofi/Aventis, Merck, Yakult Honsha, Ono Pharmaceutical, Nipro Corporation, Moroo Co, Asahi Kasei, Mitsubishi Tanabe Pharma, Otsuka, Medical Review Co, Ltd, Daiichi Sankyo
Research Funding: MSD K.K, Taiho Pharmaceutical, Yakult Honsha, Bayer Yakuhin, Daiichi Sankyo Co, Ltd, Ono Pharmaceutical, NanoCarrier, Eisai, Sanofi/Aventis, Sysmex, Shionogi, IQvia, Parexel International Corporation, Astellas Pharma, Mediscience Planning, Sumitomo Dainippon Pharma Co, Ltd, A2 Healthcare, Incyte, Lilly (Inst), Nipro Corporation (Inst), BeiGene (Inst)

Makoto Ueno
Honoraria: Taiho Pharmaceutical, Yakult Honsha, AstraZeneca, MSD, Ono Pharmaceutical, Servier, Chugai Pharma, Incyte, Takeda, Novartis, Daiichi Sankyo/UCB Japan, J-Pharma, Boehringer Ingelheim, Eisai
Consulting or Advisory Role: Novocure, Boehringer Ingelheim
Research Funding: Taiho Pharmaceutical (Inst), Eisai (Inst), AstraZeneca (Inst), Ono Pharmaceutical (Inst), MSD (Inst), Incyte (Inst), Astellas Pharma (Inst), Chugai Pharma (Inst), Delta-Fly Pharma (Inst), JPH Clinical Development (Inst), Chiome Bioscience (Inst), Novartis (Inst), Boehringer Ingelheim (Inst), J-Pharma (Inst), Novocure (Inst), Chio (Inst)

Satoshi Kobayashi
Honoraria: Taiho Pharmaceutical, Bayer Yakuhin, Eisai, Yakult Honsha, Chugai Pharma, Lilly, Takeda, AstraZeneca, Zymeworks, Otsuka
Research Funding: Taiho Pharmaceutical (Inst), Chugai Pharma (Inst), AstraZeneca (Inst), Ono Pharmaceutical (Inst), MSD Oncology (Inst), Eisai (Inst), Takeda (Inst), Lilly (Inst), Incyte (Inst), Daiichi Sankyo/UCB Japan (Inst)

Masafumi Ikeda
Honoraria: Taiho Pharmaceutical, Eisai, Lilly Japan, MSD, Yakult Pharmaceutical, Servier, Chugai Pharma, Takeda, AstraZeneca, Novartis, Bristol Myers Squibb, Ono Pharmaceutical, AbbVie, Fujifilm, Incyte, Taisho Pharmaceutical Holdings, Nihonkayaku, Teijin Pharma, Guardant Health, Nobelpharma
Consulting or Advisory Role: Eisai, Novartis, Chugai Pharma, AstraZeneca, Servier, MSD, Boston Scientific, Guardant Health, Roche, Boehringer Ingelheim, Astellas Pharma
Research Funding: Bayer Yakuhin (Inst), Lilly Japan (Inst), Ono Pharmaceutical (Inst), Eisai (Inst), AstraZeneca (Inst), Chugai Pharma (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), MSD (Inst), J-Pharma (Inst), Merck (Inst), Delta-Fly Pharma (Inst), Chiome Bioscience (Inst), Merus NV (Inst), Nihon Servier (Inst), Syneos Health (Inst), InVitae (Inst), Nobelpharma (Inst), Boehringer Ingelheim (Inst), Rakuten Medical Japan (Inst)

Junji Furuse
Honoraria: Taiho Pharmaceutical, Chugai Pharma, Yakult Honsha, Lilly Japan, Astellas Pharma, Ono Pharmaceutical, Bayer Yakuhin, Novartis, Takeda, Daiichi Sankyo, Eisai, EA Pharma, MSD, Teijin Pharma, AstraZeneca, Nihon Servier, Fujifilm, Incyte Japan
Consulting or Advisory Role: Eisai, Astellas Pharma, Ono Pharmaceutical, Fujifilm, AstraZeneca, MSD, J-Pharma, OncoTherapy Science, Delta-Fly Pharma

Naohiro Okano
Honoraria: Taiho Pharmaceutical, Bayer Yakuhin, Lilly Japan, Chugai Pharma, Ono Pharmaceutical, Takeda, Eisai, Daiichi Sankyo, AstraZeneca, Incyte Japan, MSD

Aya Kuchiba
Honoraria: Chugai Pharma

Kenichi Nakamura
Honoraria: Chugai Pharma, Taiho Pharmaceutical, AstraZeneca, Lilly, Takeda
Research Funding: Astellas Pharma (Inst), Eisai (Inst), Otsuka (Inst), Ono Pharmaceutical (Inst), Daiichi Sankyo (Inst), Taiho Pharmaceutical (Inst), Takeda (Inst), Chugai/Roche (Inst), Novartis (Inst), Pfizer (Inst), Bristol Myers Squibb Japan (Inst), Boehringer Ingelheim Seiyaku (Inst), SymBio Pharmaceuticals (Inst), Merck (Inst), Servier (Inst)

Yoshiaki Nakamura
Consulting or Advisory Role: Natera, Inc, Roche Ltd/, Seagen, Inc, Premo Partners, Inc, Daiichi Sankyo Co, Ltd, Takeda, Exact Sciences, Gilead Sciences, Guardant Health Pte Ltd
Speakers' Bureau: MSD K.K, Eisai, Zeria Pharmaceutical, Miyarisan Pharmaceutical, Merck, CareNet, Inc, Hisamitsu Pharmaceutical, Taiho Pharmaceutical, Daiichi Sankyo Co, Ltd, Chugai Pharma, Becton Dickinson, Guardant Health Japan Corp, Guardant Health Pte Ltd
Research Funding: Seagen, Inc (Inst), Genomedia (Inst), Guardant Health AMEA, Inc (Inst), Guardant Health (Inst), Tempus (Inst), Roche Diagnostics K.K (Inst), Daiichi Sankyo Co, Ltd (Inst), Chugai Pharma (Inst)

Wataru Okamoto
Honoraria: Chugai Pharma, Ono Pharmaceutical, Bristol Myers Squibb Japan, Yakult Honsha, Takeda, Novartis, Taiho Pharmaceutical, Eisai, AstraZeneca, Bayer Yakuhin, Daiichi Sankyo, MSD K.K, Guardant Health
Consulting or Advisory Role: Daiichi Sankyo, Chugai Pharma
Research Funding: Janssen Oncology (Inst), Daiichi Sankyo (Inst), Agios (Inst)
Travel, Accommodations, Expenses: Guardant Health

Takayuki Yoshino
Honoraria: Chugai Pharma, MSD K.K, Takeda, Merck
Consulting or Advisory Role: Sumitomo Corp
Research Funding: MSD (Inst), Daiichi Sankyo Company, Limited (Inst), Ono Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), Amgen (Inst), Sanofi (Inst), Pfizer (Inst), Sysmex (Inst), Chugai Pharma (Inst), Eisai (Inst), Molecular Health (Inst), Roche (Inst), FALCO Biosystems Ltd (Inst), Merus (Inst), Bristol Myers Squibb Japan (Inst), Medical & Biological Laboratories Co, Ltd (Inst), Takeda (Inst)

Takuji Okusaka
Honoraria: Ono Pharmaceutical, Taiho Pharmaceutical, Chugai Pharma, Yakult Honsha, Daiichi Sankyo, Incyte, Nihon Servier, AstraZeneca, Eisai, Novartis, Myriad Genetics, Kyowa Kirin International
Consulting or Advisory Role: Dainippon Sumitomo Pharma, AstraZeneca, Eisai, Nihon Servier, FUJIFILM Toyama Chemistry
Research Funding: Eisai (Inst), Bristol Myers Squibb (Inst), AstraZeneca (Inst), Syneos Health/Immunocore (Inst), Incyte, Sysmex (Inst), Chiome Bioscience

No other potential conflicts of interest were reported.

APPENDIX

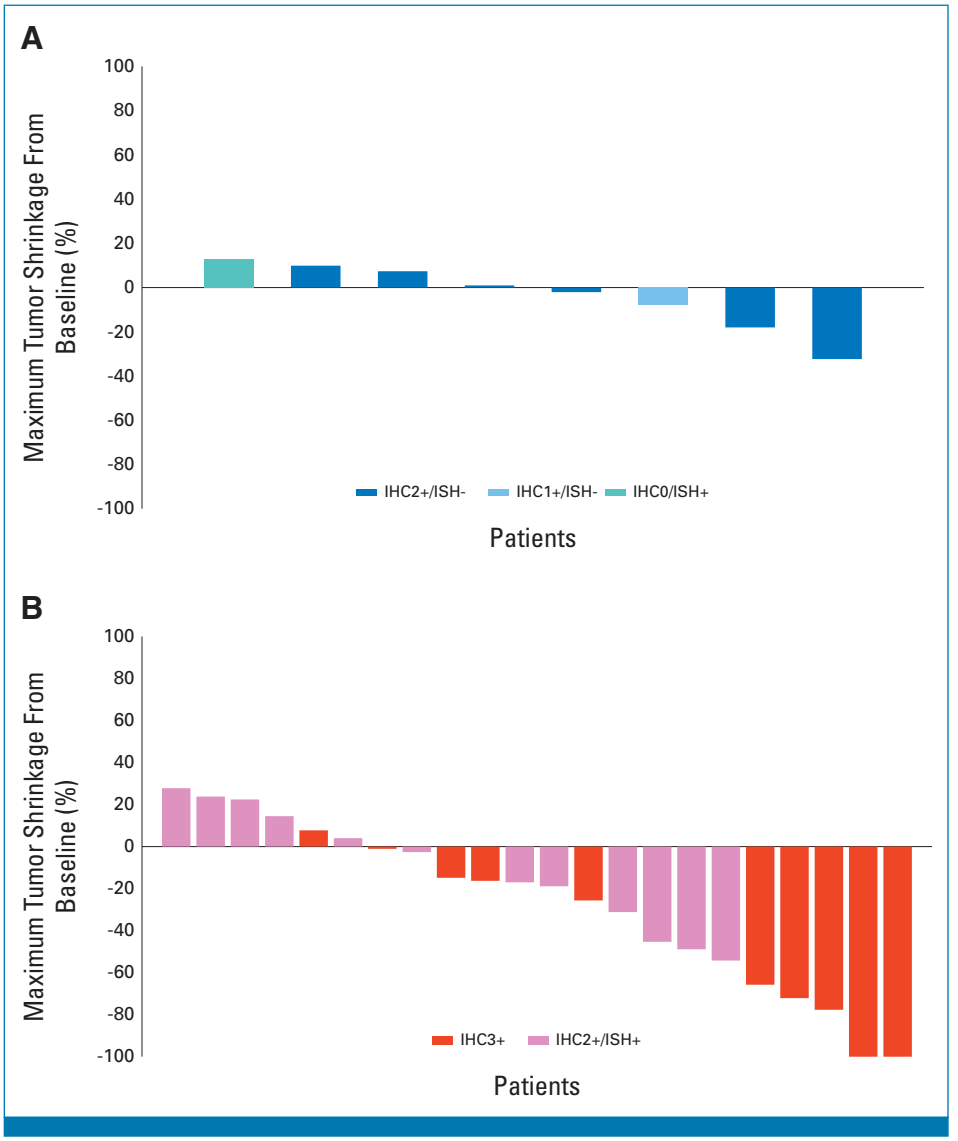

FIG A1. Waterfall plots by HER2 status of maximum tumor shrinkage from baseline by BICR among (A) HER2-positive and (B) HER2-low. BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

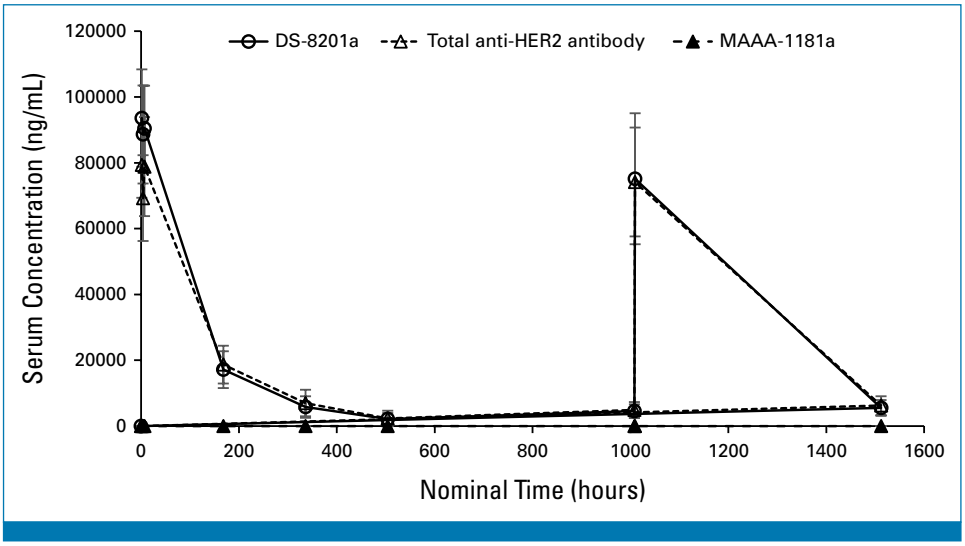

FIG A2. PK profile in PK/HAHA analysis set (n = 7). HAHA, human anti-human antibody; HER2, human epidermal growth factor receptor 2; PK, pharmacokinetic.

TABLE A1. Previous Anticancer Therapy for Unresectable Setting

Regimen	No.
Gemcitabine + cisplatin	27
S-1 monotherapy	20
Gemcitabine + cisplatin + S-1	6
Gemcitabine + S-1	2
Gemcitabine monotherapy	2
Others (clinical trials)	3
Anti-HER2 therapy	0
Irinotecan-based therapy	0

Abbreviation: HER2, human epidermal growth factor receptor 2.

TABLE A2. Treatment Cycles

Cycle	n = 32, No.
1	4
2	5
3	1
4	3
5	2
6	6
7	1
8	2
9	2
10	2
12	1
14	1
17	1
20	1

TABLE A3. Reason for Discontinuation

Reason	SAS (n = 32), No. (%)
Disease progression	20 (62.5)
Adverse event	7 (21.9)
Patient refusal related to adverse event	2 (6.3)
Patient refusal not related to adverse event	1 (3.1)
Death during protocol treatment	1 (3.1)
Other	1 (3.1)

Abbreviation: SAS, safety analysis set.

TABLE A4. Subgroup Analyses of Confirmed ORR by BICR Among HER2-Positive Patients

		HER2-Positive (n = 22)
Subgroup	No. (%)	Confirmed ORR by BICR, % (95% CI)
Age, years		
≥65	13 (59.1)	38.5 (13.9 to 68.4)
<65	9 (40.9)	33.3 (7.5 to 70.1)
Sex		
Male	13 (59.1)	23.1 (5.0 to 53.8)
Female	9 (40.9)	55.6 (21.2 to 86.3)
ECOG PS		
PS 0	15 (68.2)	40.0 (16.3 to 67.7)
PS 1	7 (31.8)	28.6 (3.7 to 71.0)
Primary tumor location		
Intrahepatic cholangiocarcinoma	3 (13.6)	33.3 (0.8 to 90.6)
Extrahepatic cholangiocarcinoma	6 (27.3)	33.3 (4.3 to 77.7)
Gallbladder cancer	11 (50.0)	36.4 (10.9 to 69.2)
Ampulla of Vater cancer	2 (9.1)	50.0 (1.3 to 98.7)
Disease status		
Unresectable	13 (59.1)	38.5 (13.9 to 68.4)
Recurrent	9 (40.9)	33.3 (7.5 to 70.1)
Disease extent		
Locally advanced	2 (9.1)	50.0 (1.3 to 98.7)
Metastatic	20 (90.9)	35.0 (15.4 to 59.2)
HER2 expression		
IHC3+	10 (45.5)	40.0 (12.2 to 73.8)
IHC2+	12 (54.5)	33.3 (9.9 to 65.1)

Abbreviations: BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate.

TABLE A5. Details of ILD or Pneumonitis

Details	Patients With ILD or Pneumonitis (n = 8)
Grade, No. (%)	
1	3 (37.5)
2	1 (12.5)
3	2 (25.0)
4	0
5	2 (25.0)[a]
Time to onset, days, median (range)	124 (35-247)[b]
Age, years, median (range)	73 (51-75)
Male, No. (%)	5 (62.5)
No. of previous regimens, No. (%)	
1	4 (50.0)
≥2	4 (50.0)
Previous administered anticancer agents, No. (%)	
Gemcitabine	8 (100)
Cisplatin	7 (87.5)
S-1	6 (75.0)
Investigational agent	1 (12.5)
HER2 status of IHC/ISH, No. (%)	
3+/+	5 (62.5)
2+/+	3 (37.5)
Lung metastasis, No. (%)	3 (37.5)
Smoking history,[c] No. (%)	3 (37.5)
Biliary drainage, No. (%)	4 (50.0)

Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization.

[a]One patient had recurrent disease with liver and lymph node metastases after surgery for extrahepatic cholangiocarcinoma and underwent one line of previous cancer therapy with gemcitabine alone. The patient was initially diagnosed with grade 2 ILD 183 days after the initiation of trastuzumab deruxtecan and received oral prednisolone at 1 mg/kg once daily. After 1 week, the patient progressed to grade 3 ILD and received intravenous methylprednisolone 1,000 mg once daily for 3 days, followed by gradual tapering of oral prednisolone from 50 mg to 30 mg once daily for 3 weeks. However, the disease worsened again to grade 4, despite the readministration of intravenous methylprednisolone at 1,000 mg once daily, and the patient died 44 days later after the event onset. The other patient had recurrent disease with liver metastases after surgery for intrahepatic cholangiocarcinoma and received two previous cancer therapies with gemcitabine plus cisplatin and S-1. The patient was initially transported to another emergency hospital because of respiratory failure and suspected to be severe COVID-19 disease 127 days after the initiation of trastuzumab deruxtecan. Four days later, the patient received intravenous methylprednisolone 1,000 mg once daily for 3 days at the diagnosis of ILD. However, the patient died 6 days later after the event onset.

[b]All patients developed ILD or pneumonitis during the protocol treatment period.

[c]Smoking history was collected retrospectively.

TABLE A6. PK Properties in PK/HAHA Analysis Set (n = 7)

Property	Trastuzumab Deruxtecan	Total Antibody	MAAA-1181a
C_{max}, μg/mL, mean (SD)	96.8 (13.0)	83.7 (13.5)	11.5 (4.65)[a]
AUC_{last}, μg·day/mL, mean (SD)	410 (106)	406 (110)	24.5 (8.96)[b]
T_{max}, hours, median (range)	6.83 (1.62-7.13)	1.88 (1.62-7.13)	3.88 (1.65-4.07)
AUC_{inf},[c] μg·day/mL, mean (SD)	452 (112)	454 (116)	25.7 (9.47)[b]
$t_{1/2}$,[c] days, mean (SD)	4.83 (0.941)	4.82 (1.28)	4.76 (1.02)

Abbreviations: AUC_{inf}, area under the concentration versus time curve from time zero extrapolated to infinity; AUC_{last}, area under the concentration versus time curve from time zero to the time of the last quantifiable concentration; C_{max}, maximum serum concentration; HAHA, human antihuman antibody; PK, pharmacokinetic; SD, standard deviation; T_{max}, time of observed C_{max}; $t_{1/2}$, terminal elimination half-life.
[a]ng/mL.
[b]ng·day/mL.
[c]n = 6.