Real-World Data of Trastuzumab Deruxtecan for Advanced Gastric Cancer: A Multi-Institutional Retrospective Study

Toshihiko Matsumoto 1,2,* , Shogo Yamamura 1 , Tatsuki Ikoma 3 , Yusuke Kurioka 4 , Keitaro Doi 3 , Shogen Boku 2 , Nobuhiro Shibata 2 , Hiroki Nagai 1 , Takanobu Shimada 3 , Takao Tsuduki 4 , Takehiko Tsumura 3 , Masahiro Takatani 4 , Hisateru Yasui 1 and Hironaga Satake 1,2,5

1 Department of Medical Oncology, Kobe City Medical Center General Hospital, 2-1-1, Minatojimaminamimachi, Kobe 6500047, Japan; yamamura_shogo@kcho.jp (S.Y.); hiroki_nagai@kcho.jp (H.N.); hyasui@kcho.jp (H.Y.); takeh1977@gmail.com (H.S.)
2 Cancer Treatment Center, Kansai Medical University, 2-3-1, Shimachi, Hirakata 5731191, Japan; shogen9820@gmail.com (S.B.); shibanob.kmu@gmail.com (N.S.)
3 Department of Clinical Oncology, Osaka Red Cross Hospital, 5-30, Tenoji-ku, Fudegasakicho, Osaka 5438555, Japan; quouqbnmb@gmail.com (T.I.); kdoi0160@osaka-med.jrc.or.jp (K.D.);
shimadatakano@osaka-med.jrc.or.jp (T.S.); t-tsumura@osaka-med.jrc.or.jp (T.T.)
4 Department of Internal Medicine, Himeji Red Cross Hospital, 1-12-1, Shimoteno, Himeji 6708540, Japan; sage3221592@gmail.com (Y.K.); tsuzuoka@gmail.com (T.T.); takatamash@gmail.com (M.T.)
5 Department of Medical Oncology, Kochi Medical School, Nankoku 7838505, Japan

* Correspondence: makoharutaro2015@gmail.com; Tel.: +81-78-302-4321

Citation: Matsumoto, T.; Yamamura, S.; Ikoma, T.; Kurioka, Y.; Doi, K.; Boku, S.; Shibata, N.; Nagai, H.; Shimada, T.; Tsuduki, T.; et al. Real-World Data of Trastuzumab Deruxtecan for Advanced Gastric Cancer: A Multi-Institutional Retrospective Study. J. Clin. Med. 2022, 11, 2247. https://doi.org/10.3390/jcm11082247

Abstract: Trastuzumab deruxtecan (T-DXd) has shown promising efficacy against HER2-positive advanced gastric cancer (AGC). However, data on its real-world efficacy in AGC patients are insufficient, and the predictive marker of T-DXd is unclear. In this multi-center retrospective study, we collected clinical information of 18 patients with HER2-positive AGC who received T-DXd after intolerant or refractory responses to at least two prior regimens and analyzed predictive factors. The median age was 71 years (range: 51–85), 13 men were included, and ECOG performance status (PS): 0/1/2/3 was 9/6/2/1. A total of 11 patients (61%) received prior immune checkpoint inhibitors (ICIs), 14 patients were HER2 3+, and 4 patients were HER2 2+/FISH positive. The median trastuzumab (Tmab)-free interval was 7.7 months (range: 2.8–28.6). The overall response rate was 41%, and the disease control rate was 76%. Median progression-free survival (PFS) was 3.9 months (95% CI: 2.6–6.5), and median overall survival (OS) was 6.1 months (95% CI: 3.7–9.4). PFS (6.5 vs. 2.9 months, p = 0.0292) and OS (9.2 vs. 3.7 months, p = 0.0819) were longer in patients who received prior ICIs than in those who had not. PFS (6.5 vs. 3.4 months, p = 0.0249) and OS (9.4 vs. 5.7 months, p = 0.0426) were longer in patients with an 8 month or longer Tmab-free interval. In patients with ascites, PFS (6.5 vs. 2.9 months, p = 0.0139) and OS (9.4 vs. 3.9 months, p = 0.0460) were shorter. T-DXd showed promising efficacy in HER2-positive AGC patients in a real-world setting. Pre-administration of ICIs and a sufficient Tmab-free interval may be predictive factors of T-DXd efficacy.

Keywords: gastric cancer; trastuzumab deruxtecan; T-DXd; chemotherapy; real-world data

1. Introduction

Gastric cancer is known to be one of the most common cancers, and the frequency of occurrence is the fifth highest among cancers, and cancer-related deaths are the third...
highest [1]. Globally, multimodal treatments including surgery and perioperative/adjuvant chemotherapy have improved the treatment outcome of patients with early-stage disease. However, the treatment outcomes of patients with advanced gastric cancer (AGC) are still poor.

Recently, targeted treatments have demonstrated a significant benefit in gastric cancer. Human epidermal growth factor receptor-2 (HER2) is currently the most useful therapeutic biomarker for patients with AGC, because HER2 overexpression in AGC cases ranges from 6% to 30% [2]. The phase III trial of trastuzumab (ToGA trial) for HER2-positive AGC patients demonstrated a significant efficacy as a first-line chemotherapy [3]. In the ToGA trial, chemotherapy plus trastuzumab (Tmab) significantly prolonged median overall survival (OS) (13.8 vs. 11.1 months, hazard ratio (HR): 0.74, \( p = 0.0046 \)) compared with chemotherapy alone. In an exploratory post hoc analysis, OS improved more (16.0 vs. 11.8 months, HR: 0.65, \( p = 0.036 \)) in the HER2-positive group (defined as immunohistochemical (IHC) 2+ and a FISH-positive result, or IHC 3+, regardless of FISH status). Based on these results, chemotherapy plus Tmab became the standard chemotherapy for chemo-naïve HER2-positive AGC.

Trastuzumab deruxtecan (T-DXd) is an antibody–drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase inhibitor [4]. In a dose expansion phase I study, T-DXd showed 43.2% of confirmed RR, 5.6 months of PFS, and 12.8 months of OS in HER2-positive AGC [5]. Following this trial, a randomized phase II trial (DESTINY-Gastric01) was conducted. This study was open label study compared with the physician’s choice therapy (docetaxel or irinotecan), and the primary endpoint was the response rate (RR). T-DXd showed significantly higher RR (51% vs. 14%, \( p < 0.001 \)) and prolonged OS (12.5 vs. 8.4 months, hazard ratio (HR): 0.59, \( p = 0.01 \)) and median progression-free survival (PFS) (5.6 vs. 3.5 months, HR: 0.47) [6]. Based on these results, T-DXd was approved in Japan, the United States, and the European Union.

There were no HER2-positive AGC patients with poor general health conditions in the clinical trial [3,5]. In the DESTINY-Gastric01 trial, 50% of patients had PS 0 and 50% had PS 1, and the proportion of cases with ascites was unknown. In the real world, T-DXd is also administered to AGC patients with poor PS, the elderly, and ascites. There are no efficacy and safety data for T-DXd in patients with those conditions. In the DESTINY-GC01 study, the pre-specified subgroup analysis reported that HER2 immunohistochemical (IHC) analysis score 3+ cases showed a better response rate than HER2 IHC 2+ cases (58% vs. 29%), but other predictive factors and prognosis factors are not yet clear. Therefore, we planned this study to explore the efficacy, toxicity, and prognostic factors of T-DXd in the real world.

2. Materials and Methods

2.1. Patients

This was a multi-institution study. The subjects were AGC patients received T-DXd between August 2018 and January 2021 at four institutions. Clinical information was retrospectively collected based on the electronic medical records. This study was performed in accordance with institutional and national standards on human experimentation, as confirmed by the ethics committee of all participating institutions and with the principles of the Declaration of Helsinki.

The inclusion criteria of this study were as follows: (1) unresectable gastric cancer, (2) histologically proven gastroesophageal adenocarcinoma, (3) refractory or intolerant to at least two regimens, and (4) HER2 levels were documented as high (score of 3+ on immunohistochemical (IHC) analysis or score of 2+ and positive results on fluorescence in situ hybridization (FISH)). This study was approved by the Institutional Review Board of the Kobe City Medical Center General Hospital (Examination number: zn211018) and all other institutions. All participants were given with opportunities to decline agreement for this study by the ‘opt-out’ option on our hospital homepage.
2.2. Treatment

The patients were administrated T-DXd 6.4 mg/kg infusion every 3 weeks until disease progression or intolerance.

2.3. Evaluation and Statistical Analysis

Tumor response was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events were defined with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.1. Analysis of OS and PFS were performed using the Kaplan–Meier method. OS was defined as the time from date of initiation of treatment with T-DXd until death. Patients who were alive or for whom data were missing at the data cut-off point were censored. PFS was defined as the time from the date of initiation of treatment with T-DXd until disease progression or death from any cause. Censored cases were defined as the patients with no information of tumor progression. Univariate Cox proportional hazards models were performed to investigate the risk factors correlated with PFS and OS. Adverse events were evaluated by the Common Terminology Criteria for Adverse Events ver. 4.0. JMP version 12 (SAS Institute Inc., Cary, NC, USA), which was used for statistical analysis.

3. Results

Between August 2018 and January 2021, 18 patients were treated T-DXd after the failure of at least two regimens. The patients’ backgrounds are presented in Table 1. All patients had a metastatic site. The median age was 71 (range: 51–85) and 72% were male. There were 15 patients with PS 0 or 1 and 3 patients with PS 2 or 3. In total, 10 patients (56%) had a diffuse-type histology. A total of 14 patients (78%) had HER2 IHC 3+, whereas 4 patients (22%) were HER2 IHC 2+/FISH positive. Overall, 15 patients (83%) had two or more organ metastasis, 11 patients (61%) had peritoneal dissemination, and 7 (39%) had liver metastasis. Furthermore, 14 patients (78%) experienced partial response (PR) in a prior trastuzumab (Tmab)-containing regimen; the median Tmab-free interval was 7.7 months (range: 2.8–28.6 months).

Table 1. Patients’ characteristics of this study.

|                                | All (n = 18) |
|--------------------------------|-------------|
| Age Median (range)             | 71 (51–85)  |
| Sex Male                       | 13 (72%)    |
| ECOG PS                        |             |
| 0                              | 9 (50%)     |
| 1                              | 6 (33%)     |
| 2/3                            | 3 (17%)     |
| Primary site                   |             |
| Gastric                        | 14 (78%)    |
| EGJ                            | 4 (4%)      |
| Histology                      |             |
| Diffuse type                   | 10 (56%)    |
| Intestinal type                | 8 (44%)     |
| HER2 status                    |             |
| IHC 3+                         | 14 (78%)    |
| IHC 2+, FISH (+)               | 4 (22%)     |
| Prior gastrectomy              | Yes         |
| Yes                            | 9 (50%)     |
| Number of metastatic sites     | ≥2          |
| Yes                            | 15 (83%)    |
| Liver metastasis               | Yes         |
| Yes                            | 7 (39%)     |
| Peritoneal dissemination       | Yes         |
| Yes                            | 11 (61%)    |
| Ascites                        | Yes         |
| Yes                            | 8 (44%)     |
| Massive ascites                | Yes         |
| Yes                            | 7 (39%)     |
| Measurable lesion              | Yes         |
| Yes                            | 17 (94%)    |
Table 1. Cont.

|                                      | All (n = 18) |
|--------------------------------------|-------------|
| Number of prior regimens             |             |
| 2                                    | Over 2      |
| Prior 5-FU                           | Yes         |
| Prior Platinum                       | Yes         |
| Prior taxane                         | Yes         |
| Prior irinotecan                     | Yes         |
| Prior ramucirumab                    | Yes         |
| Prior immune checkpoint inhibitors    | Yes         |
| Efficacy of Prior Tmab regimen        | PR/SD/PD    |
| Response rate of prior Tmab           | PR          |
| Tmab Free interval (months)          | Median (range) |

ECOG PS, Eastern Cooperative Oncology Group performance status; EGJ, gastroesophageal junction carcinoma; HER2, human epidermal growth factor receptor; 5-FU, 5-fluorouracil; Tmab, trastuzumab; PR, partial response; SD, stable disease; PD, progressive disease.

3.1. Efficacy

The effect evaluation by the image was possible with 17 patients. PR was observed in 41%, and 35% of patients achieved stable disease (SD); the response rate (RR) was 41% and the disease control rate (DCR) was 76%. The median follow-up time was 5.8 months (range: 0.5–30.5 months) among censored cases. The median PFS was 3.9 months (95% confidence interval (CI), 2.6–7.7), the median OS was 6.5 months (95% CI, 3.7–10.6), and the 1-year survival rate was 16.7% (Figure 1).

Eleven patients (61%) had received prior immune checkpoint inhibitors (ICIs). The median PFS (6.5 vs. 2.9 months, \( p = 0.0292 \)) was longer, whereas the median OS (9.2 vs. 3.7 months, \( p = 0.0819 \)) tended to be better in patients who were treated with prior ICIs than in those who were not. In addition, RR (60% vs. 14%, \( p = 0.0595 \)) and DCR (90% vs. 57%, \( p = 0.1147 \)) tended to be better in patients who received prior ICIs than in those who did not (Figures 2a,b and 3).

Figure 1. (a) Progression-free survival (PFS) and (b) overall survival (OS) among all study population.
patients with a TFI of less than 8 months. In addition, RR (62% vs. 22%,
3.4 months, p = 0.0426) were significantly better in patients with a TFI of 8 months or longer than in patients with a TFI of less than 8 months. (Figures 2c,d and 3). No significant relationship was observed between prior ICI administration and TFI (p = 0.2151).

The median Tmab-free interval (TFI) was 7.7 months, and nine patients (50%) had a TFI of 8 months or longer. PFS (6.5 vs. 3.4 months, p = 0.0249) and OS (9.4 vs. 5.7 months, p = 0.0426) were significantly better in patients with a TFI of 8 months or longer than in patients with a TFI of less than 8 months. In addition, RR (62% vs. 22%, p = 0.0878) tended to be better and DCR (100% vs. 56%, p = 0.0129) was better in patients with a TFI of 8 months or longer than in patients with a TFI of less than 8 months. (Figures 2c,d and 3). No significant relationship was observed between prior ICI administration and TFI (p = 0.2151).

Median Tmab PFS was 7.1 months (range: 0.93–22.3). PFS of T-DXd was significantly better in patients with Tmab PFS > 7 months than in those with Tmab PFS < 7 months (5.9 vs. 3.4 months, p = 0.0426). RR (50% vs. 14%, p = 0.116) and DCR (80% vs. 57%, p = 0.3105)

Figure 2. (a) PFS and (b) OS among study participants classified by prior therapy. Red line: No prior immune checkpoint inhibitor (ICI); blue line: prior ICI; Kaplan–Meier plots of (c) PFS and (d) OS among study participants. Red line: Tmab-free interval (TFI) < 8 months; blue line: TFI ≥ 8 months.

Figure 3. Best rate of change from baseline in total measurable tumor diameter. Blue: Prior use of ICI (n = 10): (RR: 60%), Red: no prior use of ICI (n = 6): (RR: 14%), ●: Tmab-free interval over 8 months (n = 8): (RR: 75%).
also showed a good tendency in patients with Tmab PFS > 7 months than in those with Tmab PFS < 7 months (Figure S1).

Eleven patients (61%) had peritoneal dissemination, whereas eight patients (44%) had ascites. PFS (6.5 vs. 2.75 months, \( p = 0.0139 \)) and OS (9.4 vs. 3.9 months, \( p = 0.0460 \)) were shorter in patients with ascites than in patients without ascites (Figure 4). Further, a decrease in ascites was observed in 25% of the patients with ascites after T-DXd administration.

Seventeen patients (94%) discontinued T-DXd, and six patients (35%) received post-treatment. Four patients received nivolumab, and two patients received paclitaxel + ramucirumab.

Figure 4. (a) PFS and (b) OS curve classified by ascites. Red line: with ascites; blue line: without ascites.

3.2. Safety

Table 2 shows adverse events of this study. Most of the grade 3 or higher adverse events were neutropenia (17%), anemia (11%), anorexia (6%), and nausea (6%). Grade 2 pneumonia and grade 2 heart failure were observed in one patient each (6% each). Treatment was discontinued in 17 patients: 16 patients discontinued treatment due to tumor progression, whereas 1 patient discontinued treatment due to grade 2 heart failure. No treatment-related deaths occurred.

Table 2. Distribution of drug-related adverse events.

|                | ALL  | G1/2 | G3/4 |
|----------------|------|------|------|
| Neutropenia    | 5 (28%) | 2 (11%) | 3 (17%) |
| Anemia         | 6 (33%) | 4 (22%) | 2 (11%) |
| Platelet decreased | 2 (11%) | 2 (11%) | 0 |
| Fatigue        | 11 (61%) | 11 (61%) | 0 |
| Anorexia       | 7 (39%) | 6 (33%) | 1 (6%) |
| Nausea         | 5 (28%) | 4 (22%) | 1 (6%) |
| Diarrhea       | 3 (20%) | 3 (20%) | 0 |
| Heart failure  | 2 (11%) | 2 (11%) | 0 |
| Pneumoniae     | 1 (6%) | 1 (6%) | 0 |
| Rush           | 1 (6%) | 1 (6%) | 0 |
| Constipation   | 1 (6%) | 1 (6%) | 0 |
| Fever          | 1 (6%) | 1 (6%) | 0 |

4. Discussion

In the DESTINY-Gastric01 study, T-DXd showed promising efficacy as the third- or later-line treatment for HER2-positive AGC patients [6]. In our real-world study, T-DXd showed a 41% RR, and the median PFS and OS were 3.9 months and 6.5 months, respectively. Similar PFS and RR were observed despite the inclusion of 17% PS2 in three cases in the
present study. This result suggests that T-DXd is a useful treatment for HER2-positive AGC patients not only in clinical trials, but also in real-world patients.

This study showed that PFS was longer in patients who received prior ICIs than that in other patients, whereas OS tended to be longer. This result has not been reported in previous studies, including the DESTINY-GC01 trial. These results suggest the possibility of a synergistic action between T-DXd and ICIs. Osa et al. previously reported that binding to nivolumab and T cells was observed more than 20 weeks after the last dose, regardless of the total dose of nivolumab [7]. Previous preclinical studies showed that tumor recognition by T cells is enhanced by T-DXd. T-DXd increases tumor infiltrative CD8+ T cells, and the expression of PD-L1 and major histocompatibility complex class I in tumor cells is also enhanced by T-DXd [8]. Therefore, several studies are currently underway to explore the efficacy of a combination of multiple T-DXd and immune checkpoint inhibitors. In our study, PFS was longer in patients with ICIs free interval <20 weeks than in patients with ICIs free interval >20 weeks (Figure S2). This result suggests that combination or sequential therapy with T-DXd and ICIs may be useful for AGC patients.

Further, in our study, the efficacy of T-DXd was significantly better in patients with a TFI of 8 months or longer. There are no data on the correlation between TFI and the effect of T-DXd. Makiyama et al. reported a randomized, phase II study exploring efficacy of trastuzumab beyond progression for AGC patients who were HER2 positive (WJOG7112G: T-ACT Study) [9]. In the T-ACT study, no additional effect of Tmab on paclitaxel was observed in the entire population. However, in patients with a long TFI (30 or more days), the administration of Tmab showed significant improvement of PFS (HR, 0.45; 95%CI, 0.21–0.96; interaction test, \( p = 0.022 \)). Makiyama et al. also reported that the HER2 copy number is high in cases with long Tmab-free intervals. Pietrantonio et al. reported that HER2 overexpression was decreased in 32% of patients who previously received trastuzumab-based chemotherapy [10], and Wang et al. reported that patients with acquired resistance of Tmab have reduced HER2 somatic copy number alterations [11]. Similarly, the therapeutic effect of T-DXd may also be enhanced by prolonging the TFI and increasing the HER2 copy number. In the DESTINY-GC01 trial, patients with high plasma HER2 copies number and high HER2 extracellular domain (ECD) tended to be more effective with T-DXd [12]. If TFI is extended, HER2 amplification may occur, and the effect of T-DXd may be enhanced. However, data on the relationship between TFI and T-DXd efficacy are limited, and further investigations are needed. In addition, in our study, the efficacy of T-DXd tended to be higher in patients with longer PFS after prior therapies with a Tmab combination. Since T-DXd is used after third-line therapy, re-biopsy is often difficult in clinical practice. Therefore, in cases where re-biopsy is not possible, PFS and TFI of pretreatment Tmab may be useful to predict the efficacy of T-DXd.

Moreover, exploratory cohorts in DESTINY-Gastric01 trial, T-DXd improved RR (26.3% vs 9.5%) and PFS (4.4 vs. 2.8 months) in HER2 IHC 1+ or HER2 IHC 2+ and FISH-negative patients [12]. This result suggested that T-DXd had modest efficacy in HER2 low AGC. Although this result was only a small number exploratory analysis, and further prospective studies for HER2-low AGC patients are warranted.

In a real-world setting, many cases of AGC have peritoneal dissemination or ascites. The DESTINY-Gastric 01 study does not reveal the proportion of cases with peritoneal dissemination or ascites, nor does it reveal efficacy data. In our study, 61% had peritoneal dissemination and 44% had ascites. In patients with ascites, PFS and OS were significantly worse than patients without ascites. However, in patients with ascites, only 25% of patients showed a decrease in ascites. This result is similar to the therapeutic effect of nivolumab [13]. In our study, there was no difference in the frequency of serious toxicity by T-DXd with or without ascites. These results indicate that, although T-DXd shows a modest effect for HER2-positive gastric cancer with ascites, careful use is required.

The mechanism of resistance after T-DXd administration is not yet clear. Reports of treatment with trastuzumab suggest that ERBB2 exon 16 and mutations in the receptor tyrosine kinase, PI3K, and RAS pathways are related to resistance of anti-HER2 therapy [14].
In our study, genome profiling using next-generation sequencing was conducted in only two cases before and after T-DXd administration. In one case, the HER2 amplification observed before treatment disappeared after progressive disease and the PIK3CA E542K mutation appeared. This suggests that a known Tmab resistance mechanism may be involved in the resistance to T-DXd, but there are still few reports of biomarkers involved in T-DXd resistance, including changes in HER2 amplification. Further research is needed.

5. Conclusions

Some limitations were found in our trial. First, the study was a retrospective study with small sample size of only Japanese patients, but it nevertheless indicated that T-DXd has promising effects and is tolerable as a third- or later-line therapy for HER2-positive AGC patients. It is suggested that the administration history of immune checkpoint inhibitors, short ICI intervals, long TFI, and long-term tumor control with Tmab may be predictors of the therapeutic effect of T-DXd. However, in patients with ascites, our study suggests that the effect may not be sufficient. Further investigations to explore efficacy, safety, and more convenient predictive factors of T-DXd are needed.

Supplementary Materials: Supplementary figures can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11082247/s1, Figure S1: (a) PFS and (b) OS classified by efficacy of prior Tmab containing regimen; Figure S2: (a) PFS and (b) OS classified by ICI free interval.

Author Contributions: T.M., S.Y., T.I., Y.K., K.D., S.B., N.S., H.N., T.S., T.T. (Takao Tsuzuki), T.T. (Takehiko Tsumura), M.T., H.Y. and H.S. participated in the literature search, data acquisition, data analysis, or data interpretation. T.M. conducted and designed the study, critically revised the manuscript, performed the research, wrote the first draft, and collected and analyzed the data. T.M., S.Y., T.I., Y.K., K.D., S.B., N.S., H.N., T.S., T.T. (Takao Tsuzuki), T.T. (Takehiko Tsumura), M.T., H.Y. and H.S. participated in writing the paper and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was approved by the Institutional Review Board of Kobe City Medical Center General Hospital (Examination number: zn211018), Himeji Red Cross Hospital, Osaka Red Cross Hospital, and Kansai Medical University Hospital. Given that this was an observational study, informed consent was waived. However, we guaranteed the opportunity by opt-out. Obtaining consent in this study was approved by the ethics committee of Kobe City Medical Center General Hospital, Himeji Red Cross Hospital, Osaka Red Cross Hospital, and Kansai Medical University Hospital. Our team acquired administrative permission to access the data used in this research.

Data Availability Statement: All the data and materials supporting the conclusions are included in the main paper. The datasets used in the current study are available from the corresponding author upon request.

Acknowledgments: The authors wish to thank the study participants and their families.

Conflicts of Interest: H.S. received research funding from Ono Pharmaceutical Co. Ltd.; Daiichi Sankyo, Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Sanofi; honoraria from Bayer Co., Ltd.; Bristol-Myers Squibb Co., Ltd.; Chugai Pharmaceutical Co., Ltd.; Daiichi Sankyo Co., Ltd.; Eli Lilly Japan Co., Ltd.; Merck Bio Pharma Co., Ltd.; MSD Co., Ltd.; Ono Pharmaceutical Co., Ltd.; Sanofi Co., Ltd.; Taiho Pharmaceutical Co., Ltd., Takeda Co., Ltd., and Yakult Honsha Co., Ltd. TM received research funding from Ono Pharmaceutical Co. Ltd., Sanofi, honoraria from Bayer Co., Ltd., Bristol-Myers Squibb Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan Co., Ltd., Merck Bio Pharma Co., Ltd., MSD Co., Ltd., Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Co., Ltd., and Yakult Honsha Co., Ltd. All remaining authors declare that they have no competing interests.
References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J. Clin. 2018, 68, 394–424. [CrossRef] [PubMed]

2. Gravalos, C.; Jimeno, A. HER2 in Gastric Cancer: A New Prognostic Factor and a Novel Therapeutic Target. Ann. Oncol. 2008, 19, 1523–1529. [CrossRef] [PubMed]

3. Bang, Y.J.; Van Cutsem, E.; Feyereislova, A.; Chung, H.C.; Shen, L.; Sawaki, A.; Lordick, F.; Ohtsu, A.; Omuro, Y.; Satoh, T.; et al. Trastuzumab in Combination with Chemotherapy Versus Chemotherapy Alone for Treatment of HER2-Positive Advanced Gastric or Gastric-oesophageal Junction Cancer (ToGA): A phase 3, Open-Label, Randomised Controlled Trial. Lancet 2010, 376, 687–697. [CrossRef]

4. Ogitani, Y.; Aida, T.; Hagihara, K.; Yamaguchi, J.; Ishii, C.; Harada, N.; Soma, M.; Okamoto, H.; Oitae, M.; Arakawa, S.; 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. 2016, 22, 5097–5108. [CrossRef] [PubMed]

5. Shitara, K.; Iwata, H.; Takahashi, S.; Tamura, K.; Park, H.; Modi, S.; Tsurutani, J.; Kadowaki, S.; Yamaguchi, K.; Iwasa, S.; et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. Lancet Oncol. 2019, 20, 827–836. [CrossRef]

6. Shitara, K.; Bang, Y.J.; Iwasa, S.; Sugimoto, N.; Ryu, M.H.; Sakai, D.; Chung, H.C.; Kawakami, H.; Yabusaki, H.; Lee, J.; et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N. Engl. J. Med. 2020, 382, 2419–2430. [CrossRef] [PubMed]

7. Osa, A.; Uenami, T.; Koyama, S.; Fujimoto, K.; Okuzaki, D.; Takimoto, T.; Hirata, H.; Yano, Y.; Yokota, S.; Kinehara, Y.; et al. Clinical Implications of Monitoring Nivolumab Immunokinetics in Non-Small Cell Lung Cancer patients. JCI Insight. 2018, 3, e59125. [CrossRef] [PubMed]

8. Iwata, T.N.; Ishii, C.; Ishida, S.; Ogitani, Y.; Wada, T.; Agatsuma, T. A HER2-Targeting Antibody-Drug Conjugate, Trastuzumab Deruxtecan (DS-8201a), Enhances Antitumor Immunity in a Mouse Model. Mol. Cancer Ther. 2018, 17, 1494–1503. [CrossRef] [PubMed]

9. Makiyama, A.; Sukawa, Y.; Kashiwada, T.; Kawada, J.; Hosokawa, A.; Horie, Y.; Tsuji, A.; Moriwaki, T.; Tanioka, H.; Shinozaki, K.; et al. Randomized, phase II Study of Trastuzumab Beyond Progression in Patients with HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer: WJOG7112G (T-ACT Study). J. Clin. Oncol. 2020, 38, 1919–1927. [CrossRef] [PubMed]

10. Wang, D.S.; Liu, Z.X.; Lu, Y.X.; Bao, H.; Wu, X.; Zeng, Z.L.; Liu, Z.; Zhao, Q.; He, C.Y.; Lu, J.H.; et al. Liquid biopsies to track trastuzumab resistance in metastatic HER2-positive gastric cancer. Gut 2019, 68, 1152–1161. [CrossRef] [PubMed]

11. Pietrantonio, F.; Caporale, M.; Morano, F.; Scortozzi, M.; Gloghini, A.; De Vita, F.; Giommoni, E.; Fornaro, L.; Aprile, G.; Melisi, D.; et al. HER2 loss in HER2-positive gastric or gastroesophageal cancer after trastuzumab therapy: Implication for further clinical research. Int. J. Cancer 2016, 139, 2859–2864. [CrossRef] [PubMed]

12. Shitara, K.; Bang, Y.; Iwasa, S.; Sugimoto, N.; Ryu, M.; Sakai, D.; Chung, H.; Omuro, Y.; Kawakami, H.; Yabusaki, H.; et al. O-14 Exploratory Biomarker Analysis of Trastuzumab Deruxtecan in DESTINY-Gastric01, a Randomized, phase 2, Multicenter, Open-Label Study in Patients with HER2-Positive or -Low Advanced Gastric or Gastroesophageal Junction Adenocarcinoma. Ann. Oncol. 2021, 32, S224. [CrossRef]

13. Suzuki, H.; Yamada, T.; Sugaya, A.; Ueyama, S.; Yamamoto, Y.; Moriwaki, T.; Hyodo, I. Retrospective Analysis for the Efficacy and Safety of Nivolumab in Advanced Gastric Cancer Patients According to Ascites Burden. Int. J. Clin. Oncol. 2021, 26, 370–377. [CrossRef] [PubMed]

14. Janjigian, Y.Y.; Sanchez-Vega, F.; Jonsson, P.; Chatila, W.K.; Hechtman, J.F.; Ku, G.Y.; Riches, J.C.; Tuvy, Y.; Kundra, R.; Bouvier, N.; et al. Genetic Predictors of Response to Systemic Therapy in Esophagogastric Cancer. Cancer Discov. 2018, 8, 49–58. [CrossRef]