Targeting HER2 with Trastuzumab Deruxtecan: A Dose-Expansion, Phase I Study in Multiple Advanced Solid Tumors

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Abstract

HER2-targeted therapies are approved only for HER2-positive breast and gastric cancers. We assessed the safety/tolerability and activity of the novel HER2-targeted antibody–drug conjugate trastuzumab deruxtecan (T-DXd) in 60 patients with pretreated, HER2-expressing (IHC 1+), non-breast/non-gastric or *HER2*-mutant solid tumors from a phase I trial (NCT02564900). Most common (>50%) treatment-emergent adverse events (TEAE) were nausea, decreased appetite, and vomiting. Two drug-related TEAEs were associated with fatal outcomes. The confirmed objective response rate (ORR) was 28.3% (17/60). Median progression-free survival (PFS) was 7.2 [95% confidence interval (CI), 4.8–11.1] months. In *HER2*-mutant non–small cell lung cancer (NSCLC), ORR was 72.7% (8/11), and median PFS was 11.3 (95% CI, 8.1–14.3) months. Confirmed responses were observed in six tumor types, including HER2-expressing NSCLC, colorectal cancer, salivary gland cancer, biliary tract cancer, endometrial cancer, and *HER2*-mutant NSCLC and breast cancer. Results suggest T-DXd holds promise for HER2-expressing/mutant solid tumors.

SIGNIFICANCE: T-DXd demonstrated promising activity in a heterogeneous patient population with heavily pretreated HER2-expressing or *HER2*-mutant solid tumors, especially *HER2*-mutant NSCLC. The safety profile was generally acceptable. Interstitial lung disease can be severe and requires prompt monitoring and intervention. Further research of T-DXd is warranted to address these unmet medical needs.

INTRODUCTION

HER2-targeted therapies have greatly improved survival for patients with HER2-positive breast cancer in the adjuvant/neoadjuvant setting and in metastatic disease, as well as for HER2-positive metastatic gastric cancer (1–4). Dual blockade with trastuzumab and pertuzumab, anti-HER2 humanized mAbs, in combination with chemotherapy is the recommended first-line therapy for patients with HER2-positive metastatic breast cancer (5). Other HER2-targeted therapies such as the antibody–drug conjugate (ADC) trastuzumab emtansine (T-DM1) and the HER2 kinase inhibitor lapatinib are approved in later lines of therapy (5). For HER2-positive gastric cancer, a trastuzumab-based regimen is the standard of care for previously untreated metastatic disease (6).

HER2 overexpression and/or mutations are also observed in tumors other than breast and gastric cancers, such as non–small cell lung cancer (NSCLC) and colorectal cancer (7, 8). Despite the presence of HER2 overexpression and/or mutations in these solid tumors, there are no approved HER2-targeted therapies for these patients. HER2 overexpression (IHC 2+ or 3+) occurs in approximately 10% to 30% of NSCLCs, and HER2-activating mutations occur in approximately 1% to 3% of NSCLCs (7, 9, 10). In colorectal cancer, HER2 overexpression is reported in approximately 2% to 11% of tumors (8). HER2 overexpression/mutation is associated with poor prognosis in NSCLC adenocarcinomas, but its prognostic utility in colorectal cancer remains unclear (8, 11, 12).

Trastuzumab deruxtecan (T-DXd; DS-8201a) is a novel ADC with a humanized anti-HER2 antibody, a cleavable, peptide-based linker, and a potent topoisomerase I inhibitor payload (13). T-DXd was designed with the goal of delivering a potent cytotoxic payload to HER2-expressing tumor cells, while limiting off-target toxicity in normal cells. The novel peptide-based linker is stable in plasma and is thought to be selectively cleaved by lysosomal enzymes such as cathepsins that are upregulated in the tumor microenvironment (13). T-DXd has a drug-to-antibody ratio (DAR) of approximately 8 with homogeneous conjugation, which is 2-fold higher than T-DM1 (DAR 3–4), enabling efficient delivery of the payload to targeted cells (13, 14). The released payload is membrane-permeable, allowing it to exhibit a cytotoxic effect on neighboring tumor cells in close proximity to the targeted cell, regardless of their HER2 expression levels (i.e., a cytotoxic bystander effect; ref. 15). The high DAR and the cytotoxic bystander effect may be of particular importance in targeting tumors with heterogeneous HER2 expression, such as NSCLC and colorectal cancer (16, 17). In preclinical studies, T-DXd showed antitumor activity across a wide range of HER2-expressing tumor types (13, 15).

In August 2015, a dose-escalation and -expansion phase I trial was initiated to assess the safety/tolerability and efficacy of T-DXd in patients with advanced HER2-expressing or *HER2*-mutant solid tumors (18). During dose escalation, no dose-limiting toxicities were observed and the MTD for doses ranging from 0.8 to 8.0 mg/kg in patients with advanced breast cancer or gastric cancer was not reached (18). During the dose-expansion phase, T-DXd demonstrated promising antitumor activity with an acceptable safety profile in patients with HER2-positive breast cancer or gastric cancer treated with 5.4 or 6.4 mg/kg doses [investigator-assessed confirmed objective response rates (ORR) of 59.5% and 43.2%, respectively; refs. 19, 20]. In the HER2-expressing non-breast/non-gastric or *HER2*-mutant solid tumor cohort, the MTD during dose escalation was 6.4 mg/kg intravenously once every 3 weeks, and this dose was chosen for dose expansion in this cohort based on the principle of highest tolerated dose without dose-limiting toxicities (18). Here, we present the safety/tolerability and antitumor activity of T-DXd in patients with HER2-expressing non-breast/non-gastric or HER2-mutant solid tumors who received the 6.4 mg/kg dose of T-DXd.

RESULTS

Demographics and Baseline Characteristics

As of February 1, 2019, 60 patients with HER2-expressing non-breast/non-gastric and/or *HER2*-mutant solid tumors were enrolled (colorectal cancer, $n = 20$; NSCLC, $n = 18$; and other, $n = 22$); 59 patients received ≥1 dose of 6.4 mg/kg T-DXd (colorectal cancer, $n = 20$; NSCLC, $n = 18$; and other, $n = 21$). In this analysis, "other cancers" included 8 salivary gland tumors; 2 *HER2*-mutant breast cancers (1 HER2 IHC 2+ and 1 HER2 IHC missing per central laboratory assessment); 2 esophageal cancers; 2 endometrial cancers; 2 cases of Paget disease; 2 cases of biliary tract cancer; and 1 case each of pancreatic cancer, uterine cervix carcinoma, extraskeletal myxoid chondrosarcoma, and small-intestine adenocarcinoma. At the time of this analysis, 10 patients were still on treatment and 49 patients discontinued (Fig. 1). One patient discontinued prior to receiving the first dose of study drug due to the occurrence of an adverse event (AE). The most common reason for

study discontinuation was progressive disease (PD) per RECIST version 1.1 ($n = 34$; 57.6%); 5 (8.5%) patients discontinued due to clinical progression, and 5 (8.5%) patients discontinued due to AEs. On the basis of Kaplan–Meier, the median [95% confidence interval (CI)] treatment duration was 6.3 (3.9–10.8) months; NSCLC, 10.6 (5.5–14.2) months; colorectal cancer, 3.0 (1.4–6.3) months; other, 6.3 (2.2–14.2) months.

Table 1 shows the baseline demographics. The median time from initial diagnosis to the first dose of T-DXd was 28.8 [interquartile range (IQR), 15.9–44.0] months. Overall, 51.7% (31/60) of patients were female. At baseline, all patients had visceral disease. The median number of prior anticancer regimens was 3.0 (IQR, 2–5); 33.3% (20/60) of patients received 5 prior regimens. Among the 18 patients with NSCLC, 27.8% (5/18) had received a prior HER2-targeted regimen, 22.2% (4/18) had received a prior EGFR inhibitor, and 5.6% (1/18) had received a prior anaplastic lymphoma kinase inhibitor. Among the 20 patients with colorectal cancer, no patients had received a prior HER2-targeted therapy, 60.0% (12/20) had received a prior EGFR inhibitor, 80.0% (16/20) had received a prior VEGF inhibitor, and 90% (18/20) had received prior irinotecan. A total of 19 patients had a *HER2* mutation; the specific mutations are listed in Supplementary Table S1.

Overall, 36.7% (22/60) of patients were HER2 IHC 3+, 15.0% (9/60) were IHC 2+, 18.3% (11/60) were IHC 1+, and 20.0% (12/60) were IHC 0 as assessed by a central laboratory (Table 1). Among patients with NSCLC evaluated for HER2 expression/amplification by central laboratory assessment, 11.1% (2/18) were HER2 IHC 3+, 5.6% (1/18) were IHC 2+, 44.4% (8/16) were IHC 1+, and 27.8% (5/18) were IHC 0. *HER2* mutations were reported in 61.1% (11/18) of patients with NSCLC; among them 9.1% (1/11) were HER2 IHC 2+, 36.4% (4/11) were HER2 IHC 1+, 36.4% (4/11) were IHC 0, and 18.2% (2/11) were not evaluated/missing for HER2 IHC. The most common *HER2* mutations among patients with NSCLC were exon 20 insertions [44.4% (8/18)]. Among patients with colorectal cancer examined or evaluated for HER2 expression/amplification, 45.0% (9/20) were HER2 IHC 3+, 10.0% (2/20) were IHC2+, 10.0% (2/20) were IHC 1+, and 35.0% (7/20) were IHC 0. *RAS* gene (*KRAS* and *NRAS*) mutations were observed in 35.0% (7/20) of patients with colorectal cancer.

Safety Outcomes

As of February 1, 2019, a total of 59 subjects received one dose of T-DXd and were included in the safety analysis. The median treatment duration overall was 6.3 months (range, 0.7–29.0 months). For patients with NSCLC, median treatment duration was 10.3 (range, 0.7–14.3) months, whereas for patients with colorectal cancer, median treatment duration was 3.0 (range, 0.7–18.5) months. The frequency of all-grade treatment-emergent adverse events (TEAE) was similar among the different tumor types in this analysis. All patients experienced at least 1 TEAE. The most common all-grade TEAEs were gastrointestinal and hematologic (Table 2; Supplementary Table S2). In total, 62.7% (37/59) of patients experienced grade 3 TEAEs (regardless of causality), of which the most common (5%) were anemia (15/59; 25.4%), decreased neutrophil count (12/59; 20.3%), decreased white blood cell count (11/59; 18.6%), decreased platelet count (9/59; 15.3%), decreased appetite (4/59; 6.8%), increased aspartate aminotransferase (3/59; 5.1%), febrile neutropenia (3/59;

5.1%), and hyponatremia (3/59; 5.1%; Table 2). Overall, 30.5% (18/59) of patients experienced serious TEAEs [regardless of causality; NSCLC, 11.1% (2/18); colorectal cancer, 45.0% (9/20); and other, 33.3% (7/21)]. In total, 8.5% (5/59) discontinued treatment due to TEAEs, most frequently (1%) due to pneumonitis (2/59; 3.4%) and interstitial lung disease (ILD; 1/59; 1.7%). Dose reduction associated with TEAEs occurred in 23.7% (14/59) of patients, most commonly (5%) due to platelet count decrease (6/59; 10.2%), anemia (4/59; 6.8%), and fatigue (3/59; 5.1%). Dose interruption associated with TEAEs occurred in 37.3% (22/59) of patients, most commonly (5%) due to decreased neutrophil count (10/59; 16.9%), anemia (6/59; 10.2%), decreased white blood cell count (3/59; 5.1%), and nasopharyngitis (3/59; 5.1%). Five patients experienced an AE associated with a fatal outcome, of which 2 were reported as drug-related by the investigator. Of the 2 patients who experienced an AE associated with a fatal outcome, one of them experienced an AE of respiratory failure summarized in detail below. The other patient was a 58-year-old male with colorectal cancer who experienced events of abnormal hepatic function, disseminated intravascular coagulation, and febrile neutropenia that were associated with a fatal outcome. This patient had a history of hepatic dysfunction and metastases at baseline. These events occurred 64 days after the first dose of T-DXd, and the patient died 14 days after receiving the last dose of the study drug.

In this study, 7 patients (4 NSCLC, 2 colorectal cancer, and 1 other cancer) experienced ILD or pneumonitis as reported by the investigator. There was 1 case of ILD (grade 1), 1 case of respiratory failure (grade 5), and 5 cases of pneumonitis (3 grade 1, 1 grade 2, and 1 grade 3). All 7 cases were sent for adjudication and 5 were adjudicated as drug-related ILD (2 grade 1 pneumonitis, 1 grade 2 pneumonitis, 1 grade 3 pneumonitis, and 1 grade 5 respiratory failure). The remaining 2 cases (1 grade 1 ILD and 1 grade 1 pneumonitis) were adjudicated as not ILD. No history of prior chest/lung radiotherapy was reported in these patients; 3 were from Japan and 2 were from the United States. In patients with NSCLC who experienced ILD, 3 of 4 cases were adjudicated as ILD related to the study drug, and the remaining case was adjudicated as not an ILD. Among the 3 patients with NSCLC with drug-related ILD, 1 patient experienced an AE of respiratory failure which was associated with a fatal outcome. This patient was a 48-year-old male with NSCLC who developed grade 3 respiratory failure 16 days after the first dose of T-DXd, which further worsened, and he died because of respiratory failure 26 days after receiving the first infusion. This patient had a history of ongoing dyspnea and pneumonectomy at baseline. The AE of respiratory failure associated with a fatal outcome was adjudicated as ILD and related to the study drug. The adjudicated onset date was determined to be before the patient started receiving the study drug.

Antitumor Activity Outcomes

As of February 1, 2019, the median (range) duration of follow-up was 7.8 (0.1–28.6) months for the overall cohort [NSCLC, 11.0 (0.9–21.9); colorectal cancer, 3.1 (0.8–18.9); other, 9.5 (0.1–28.6)]. The confirmed ORR based on independent central review in this heterogeneous population of patients with HER2-expressing non-breast/non-gastric and/or HER2-mutant solid tumors treated with T-DXd at the 6.4 mg/kg dose was 28.3% (17/60). The ORR based on investigator assessment was 36.7% (22/60; Table 3). Of the 60 patients, 51 were

evaluable for tumor shrinkage. The median duration of response (DoR) was 11.5 [95% CI, 7.0–not estimable (NE)] months and the time to response (TTR) was 1.4 (95% CI, 1.4–2.9) months. Overall, 63.3% (38/60) of patients had a progression-free survival (PFS) event, and the median PFS was 7.2 (95% CI, 4.8–11.1) months; the median overall survival (OS) was 23.4 (95% CI, 15.6–NE) months (Fig. 2). Patients with NSCLC and other cancers showed better PFS than patients with colorectal cancer (Fig. 2). Tumor shrinkage by independent central review assessment was observed in 80.4% (41/51) of patients, of whom 92.7% (38/41) showed tumor shrinkage at the first assessment 6 weeks post-baseline (Fig. 3). Patients with *HER2*-mutant NSCLC had more pronounced tumor shrinkage than patients with NSCLC without documented mutations, regardless of IHC/ISH status. Among patients with colorectal cancer, the largest antitumor response was observed in those patients with HER2 IHC 3+. In the other cancers group, patients with *HER2*-mutant breast cancer and those with HER2-expressing or *HER2*-mutant endometrial cancer, salivary duct carcinoma, gallbladder cancer, and cholangiocarcinoma had the most pronounced tumor shrinkage (Fig. 3). Of the 19 patients with *HER2* mutations, the most common confirmed response was partial response [PR; 9 (47.4%); Supplementary Table S1].

In the HER2-expressing or *HER2*-mutant NSCLC subgroup, 55.6% (10/18) of patients had a confirmed objective response, with a median DoR of 10.7 (95% CI, 6.9–11.5) months and a TTR of 1.4 (95% CI, 1.2–2.8) months. A total of 50.0% (9/18) of patients with NSCLC had a PFS event, and the median PFS was 11.3 (95% CI, 7.2–14.3) months (Fig. 2). Among the subset of patients with NSCLC with *HER2*-mutant disease, the confirmed ORR was 72.7% (8/11), with a median DoR of 9.9 (95% CI, 6.9–11.5) months. The disease control rate (DCR) was 90.9% (10/11) and the median PFS was 11.3 (95% CI, 8.1–14.3) months (Table 4).

In the HER2-expressing or *HER2*-mutant colorectal cancer subgroup, 5.0% (1/20) of patients had a confirmed objective response. A total of 85.0% of patients with colorectal cancer (17/20) had a PFS event, and the median PFS was 4.0 (95% CI, 2.7–5.6) months (Fig. 2). Among 9 patients with HER2 IHC 3+ colorectal cancer, the confirmed ORR was 11.1% (1/9) and the confirmed DCR was 100% (9/9).

In addition to NSCLC and colorectal cancer, responses were also observed across a number of other tumor types, including HER2-expressing or *HER2*-amplified salivary gland cancer, biliary tract cancer, and endometrial cancer, and *HER2*-mutant nonamplified breast cancer (Fig. 3). In this group, the ORR was 6 of 22 (27.3%) and the median DoR was not reached (95% CI, 3.0–not reached). The median PFS was 11.0 months (95% CI, 2.8–NE; Table 3).

DISCUSSION

In this first-in-human clinical study investigating T-DXd for treatment of patients with advanced solid tumors, the 6.4 mg/kg dose demonstrated encouraging preliminary antitumor activity with an acceptable safety profile in patients with heavily pretreated, HER2-expressing and/or *HER2*-mutant solid tumors. In particular, T-DXd showed promising antitumor activity in patients with *HER2*-mutant NSCLC (confirmed ORR 72.7%; median PFS 11.3 months as assessed by an independent central review). The previously reported

clinical activity in the HER2-positive breast cancer and HER2-positive gastric cancer cohorts of this phase I study included investigator-assessed confirmed ORR of 59.5% and 43.2%, respectively (19, 20). In addition, in the phase II DESTINY-BREAST01 trial, T-DXd 5.4 mg/kg demonstrated a confirmed ORR of 60.9% with a PFS of 16.9 months in patients with HER2-positive metastatic breast cancer previously treated with T-DM1 (21).

This study was performed in a heterogeneous population of HER2-expressing or *HER2*-mutant cancers, including NSCLC, colorectal cancer, salivary gland carcinoma, biliary tract cancer, endometrial cancer, small-intestinal adenocarcinoma, chondrosarcoma, and *HER2*-mutant breast cancer. Although sample sizes are too small to draw firm conclusions specific to a tumor type, T-DXd activity appears to be most pronounced in *HER2*-mutant NSCLC.

Beyond HER2-positive breast and gastric cancer, there is a need to develop new treatment options for patients with other HER2-expressing or *HER2*-mutant solid tumors, as conventional therapies (e.g., trifluridine/tipiracil and regorafenib in colorectal cancer, and pemetrexed, platinum, and taxanes in NSCLC) often show limited efficacy with a high frequency of AEs (22–25). HER2-expressing lung, bladder, and endometrial cancers are known to be associated with highly aggressive disease, and these patients carry a poor prognosis (26–28). Prior studies investigating trastuzumab and chemotherapy in patients with uterine and urothelial carcinomas demonstrated high response rates, but are limited by challenges in ascertaining the contribution of HER2-targeted therapy (29, 30). Compared with breast and gastric cancers, the rates of *HER2* amplification are lower in NSCLC, colorectal cancer, and the other solid tumors examined in this study. However, mutations or amplification in *HER2* are becoming more readily identified in these cancers in part due to the increasing use of next-generation sequencing (NGS; ref. 31).

The increasing use of NGS in lung cancers routinely identifies *HER2* mutations, which are known oncogenic drivers in NSCLC (7). However, there are no HER2-targeted agents approved in patients with *HER2*-mutant NSCLC (32). HER2 mutations in advanced lung adenocarcinomas are associated with worse prognosis compared with patients with other oncogene-driven advanced lung adenocarcinomas (12). Analyses of mutations in the kinase and extracellular domains of HER2 found in lung and breast cancers indicate that these *HER2* mutations have potential oncogenic activity and confer sensitivity to HER2-targeted therapies *in vitro* (33, 34).

There is limited clinical evidence to support the efficacy of HER2-targeted therapy in patients with *HER2*-mutant lung adenocarcinomas. The antitumor activity of trastuzumab in *HER2*-mutant lung adenocarcinomas has largely been demonstrated in case studies, and the evidence in support of the use of pan-HER family tyrosine kinase inhibitor (TKI), including afatinib, dacomitinib, and neratinib, is modest at best (35–40). Poziotinib and pyrotinib are two novel irreversible HER TKIs that showed promising activity in NSCLC with *HER2* exon 20 insertions (41–43). Another HER2-targeted ADC, trastuzumab duocarmazine, has shown activity in a phase I study of HER2 low-expressing solid tumors, including endometrial and urothelial cancers (44). Although HER2-targeted ADCs have shown promising results, the number of patients studied is still quite limited (45). For instance, a recent phase II basket study reported an ORR of 44% and a median PFS of 5 months with T-

DM1 in 18 heavily pretreated patients with *HER2*-mutant lung adenocarcinomas (45). Given this context, the ORR of >70% with T-DXd reported here in 11 patients with *HER2*-mutant NSCLC is particularly promising, with responders observed across *HER2* mutation subtypes including exon 20 insertions and extracellular domain point mutations. However, these results need to be confirmed in larger studies.

In addition to NSCLC, the current results demonstrated preliminary activity for T-DXd in other HER2-expressing solid tumors, including colorectal cancer. There is limited data to support the efficacy of HER2-targeted therapies in HER2-expressing colorectal cancer. Here, we report an ORR of 5% with T-DXd in patients with colorectal cancer, of whom 35% had a *KRAS/NRAS* mutation. Among the patients with HER2 IHC 3+ colorectal cancer, the confirmed ORR was 11.1% (1/9) and the confirmed DCR was 100%. In this study, 45% of patients with colorectal cancer were HER2 IHC 1 or 0, which is disproportionately a low-expressing population compared with studies of trastuzumab in metastatic colorectal cancer (46, 47). In our study, the lower levels of HER2 expression, the advanced stage of treatment (50% had 5 prior regimens), and the increased genetic heterogeneity with concurrent *RAS* mutations for patients with colorectal cancer may have contributed to the low response rate observed. Furthermore, 90% of patients with colorectal cancer in this study progressed on prior irinotecan. Although topoisomerase I inhibition may be more targeted with T-DXd than with irinotecan, many of the patients with colorectal cancer had low HER2 expression, and the targeting provided by T-DXd may not be enough to overcome topoisomerase I resistance in these patients. It is important to note that the small sample size of patients with colorectal cancer precludes any conclusions on efficacy. Further studies in a HER2-overexpressing population of patients with colorectal cancer are warranted.

The observed antitumor response in the heterogeneous populations investigated in this study, particularly in patients with *HER2*-mutant NSCLC independent of HER2 IHC status, may relate to the unique mechanism of action of T-DXd. Unlike other anti-HER2–targeted antibody treatments that act through antibody-dependent cell-mediated cytotoxicity or inhibition of the signaling pathway, the HER2 antibody of T-DXd mainly functions to target HER2-expressing cells that then internalize the toxic payload. The high DAR and the bystander effect caused by the membrane permeability of the cytotoxic payload may contribute to enhanced targeting of HER2-expressing or *HER2*-mutant cancer cells (13, 15). It can be hypothesized that the activating *HER2* mutations may lead to enhanced internalization by forming homodimers or heterodimers, which could increase the antitumor activity of ADCs (45, 48). This theory is supported by the enhanced response to trastuzumab that was first observed in patients with NSCLC with extracellular and transmembrane domain mutations (V659E or S310F) known to activate dimers (33, 49). The conformational change of the HER2 receptor caused by *HER2* mutations may provide opportunities for newer anti-HER2 agents with high potency (45, 50).

Although not every patient had sufficient archival tissue for comprehensive genomic and proteomic testing, the biomarker analyses conducted in this trial have shed some light on the clinical development of HER2-targeted ADCs. First, *HER2* mutations in NSCLC seem to be the most promising biomarker for predicting T-DXd activity, and responses occurred regardless of HER2 protein expression by IHC 0, 1, 2, or 3. Second, responses to T-DXd

occurred in a variety of HER2-activating mutation subtypes in NSCLC, which is consistent with results from recent trials of T-DM1 (refs. 45, 51, 52; Supplementary Table S1). Third, *HER2* amplification by ISH or NGS seems to predict responses across a variety of tumor types.

Treatment with T-DXd resulted in an acceptable safety profile that was observed to be consistent across other study cohorts (patients with HER2-positive breast cancer and gastric cancer), as described previously (19, 20). Our experience of pulmonary toxicity draws parallels with many EGFR-targeting agents, which have also been associated with an increased risk of drug-induced ILD, yet the specific mechanism remains unknown. Preclinical research directed by the TRISTAN consortium is under way to determine a general mechanism by which drug-induced ILD occurs (53). On the basis of a pooled analysis of ILD across multiple studies (multiple tumor types) of T-DXd, Japanese ethnicity and higher dose were associated with a higher risk factors for developing ILD (54). ILD is an important identified risk associated with T-DXd. ILD was managed per-protocol with dose reductions or discontinuation, corticosteroids, and supportive care (see Supplementary Data A). Close monitoring for signs and symptoms of ILD is recommended for early detection, and, once diagnosed, interruption of T-DXd and prompt intervention with steroids when appropriate may help reduce severity of this complication (20, 54). However, more research is needed to further characterize the risk.

There were several aspects of this study that could limit the generalizability of the results. This was a nonrandomized, phase I study with a heterogeneous patient population and a relatively limited sample size. Therefore, the results of this study should be viewed as exploratory, with results to be confirmed in ongoing, larger, tumor type–specific phase II studies, including in NSCLC and colorectal cancer. In addition, the biomarker selection was heterogeneous (HER2 IHC status and *HER2* mutation status were locally assessed using archival samples). The full spectrum of concomitant mutations was not captured, and thus it was not possible to fully assess their impact on response to T-DXd.

In summary, T-DXd demonstrated promising antitumor activity with an acceptable safety profile in patients with heavily pretreated HER2-expressing or *HER2*-mutant solid tumors, especially in *HER2*-mutant NSCLC. If the results of this trial are replicated in subsequent trials, T-DXd may represent a promising option for patients with a variety of HER2-expressing or *HER2*-mutant cancers, for which there are no approved HER2-targeted therapies. Future directions include ongoing cancer type–specific phase II studies in HER2-overexpressing or *HER2*-mutant advanced NSCLC (NCT03505710), and HER2-expressing recurrent or metastatic colorectal cancer (NCT03384940). More clinical trials are needed to develop HER2-targeted agents for other solid tumors such as biliary tract, endometrial, and salivary gland cancers. The encouraging results of this clinical trial and the exploratory biomarker analyses conducted may serve to propel innovative trial designs and accelerate the clinical development of T-DXd and other HER2-targeted ADCs so that the substantial therapeutic benefits brought by HER2-targeted agents may be extended to patients with tumors other than breast or gastric cancer.

METHODS

Study Design and Participants

This was a first-in-human, phase I, nonrandomized, open-label, multiple-dose, two-part study conducted at six sites in Japan and eight in the United States (ClinicalTrials.gov NCT02564900; ClinicalTrials.jp 152978). This study complies with the ethical standards established by the Declaration of Helsinki, the International Council for Harmonisation, Good Clinical Practice consolidated Guideline E6, and applicable local regulations including those out-lined by FDA and Japanese Ministry of Health, Labor, and Welfare. Patients were required to provide written informed consent prior to study enrollment.

Detailed methods were reported previously (18–20). In brief, in the dose-escalation phase safety/tolerability and the MTD/recommended dose for expansion (RDE) were assessed in patients with advanced breast cancer or gastric cancer who had failed prior therapy in doses ranging from 0.8 to 8.0 mg/kg. In dose expansion, safety/tolerability and clinical activity of T-DXd at the RDE (5.4 or 6.4 mg/kg intravenous every 3 weeks) were assessed in five dose-expansion cohorts: post–T-DM1 HER2-positive (IHC 3+ or ISH+) breast cancer (part 2a); post-trastuzumab HER2-positive (IHC 3+ or IHC 2+/ISH+) gastric cancer (part 2b); HER2 low-expressing (IHC 1+ or 2+, ISH−) breast cancer (part 2c); other HER2-expressing (IHC 1+ or amplified by ISH or NGS) or *HER2*-mutant solid tumors (part 2d); and HER2-expressing (IHC 3+, 2+, 1+, and/or ISH+) advanced/unresectable or metastatic breast cancer for pharmacokinetic analysis (part 2e). The design for parts 1 and 2 of this study are shown in Fig. 1.

Study Population

This analysis included patients with HER2-expressing (IHC 1+ or amplified by ISH or NGS) or *HER2*-mutant (as determined by NGS or other analysis techniques as appropriate) advanced solid tumors (part 2d), including NSCLC, colorectal cancer, and other solid cancers. Patient HER2 status at enrollment was defined on the basis of local laboratory testing data. A retrospective analysis of HER2 IHC and ISH of archived formalin-fixed, paraffin-embedded tumor tissue sections was done after enrollment by a central laboratory (HercepTest, Dako). Key inclusion/exclusion criteria are presented in Supplementary Table S3.

Procedures

The study drug was provided by the sponsor (Daiichi Sankyo Inc.; Daiichi Sankyo Co. Ltd.) and was supplied in single-use glass vials. In patients with HER2-expressing non-breast and non-gastric or *HER2*-mutant solid tumors, the 6.4 mg/kg dose of T-DXd was administered once every 3 weeks until withdrawal of patient consent, PD, death, or loss to follow-up. Dosage interruptions of up to 4 weeks from the planned study drug administration date were permitted.

Tumor assessments and response to treatment measures have been described previously (18). In brief, assessments (CT or MRI) were performed every 6 weeks for the first 24 weeks, and every 12 weeks thereafter. RECIST version 1.1 was used by investigators, and by an

independent central imaging facility to evaluate tumor response. TEAEs were recorded at every visit and graded according to the Common Terminology Criteria for Adverse Events version 4.03. Cardiac evaluations (echocardiography or multigated acquisition scanning) were performed at screening, before infusion on cycles 2 and 3, and thereafter at every other cycle until treatment termination. Reported cases of ILD (including pneumonitis and organizing pneumonia and additional preferred terms agreed to with the ILD adjudication committee including respiratory failure and acute respiratory failure) were reviewed by an independent adjudication committee.

Outcomes

Efficacy endpoints include ORR [rate of complete response (CR) plus rate of PR], DoR (first time CR or PR criteria were met to the first date of objectively documented PD or any cause of death), TTR (measured from registration to the time when criteria for CR or PR were first met), DCR [the sum of CR, PR, and stable disease (SD; neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD) per RECIST v1.1 for at least 5 weeks from the date of the first dose], percent change in a target lesion, duration of SD, PFS (time from the date of registration to the first objective documentation of radiographic PD or death due to any cause, whichever was earlier), and OS (time from registration to death from any cause).

Safety endpoints include TEAEs and TEAEs of special interest (ILD, ejection fraction decrease, electrocardiogram QT prolongation, and infusion-related reactions). An independent ILD adjudication committee was responsible for providing ongoing review of all potential ILD cases throughout the study (including cases of pneumonitis and organizing pneumonia). Cases were sent for adjudication from the trigger event based on 42 preferred terms (all from the ILD Standardized Med-DRA Query) and two additional preferred terms of respiratory failure and acute respiratory failure (44 preferred terms total) to identify cases eligible for adjudication. Additional data collected for cases brought to adjudication included an in-depth relevant medical history (smoking history, chronic obstructive pulmonary disease, and other chronic lung conditions), diagnostic evaluation, treatment, and outcome.

Statistical Analysis

The dose-escalation phase did not include formal statistical assessments for sample size. Cohort 2d had a planned enrollment of 60 patients, providing at least 80% power to exclude an ORR   15% at the 5% type I error (one-sided), when the true ORR is 30% based on a binomial distribution using SAS version 9.2.

The enrolled analysis set includes all patients with HER2-expressing non-breast/non-gastric solid tumors or *HER2*-mutant solid tumors who provided informed consent and were enrolled in the dose escalation or expansion. The response-evaluable set includes all patients with HER2-expressing non-breast/non-gastric solid tumors or *HER2*-mutant solid tumors who received at least one dose of T-DXd, and baseline measurable tumors assessed by independent central review. The safety analysis set includes all HER2-expressing non-breast/

non-gastric solid-tumor patients or all *HER2*-mutant solid-tumor patients who received at least one dose of T-DXd.

Point estimates and exact binomial 95% CIs are provided for ORR and DCR. Descriptive summaries using the Kaplan–Meier method are provided with CIs based on the Brookmeyer–Crowley method for time to event variables (PFS, TTR, and DoR). Descriptive statistics are used to summarize demographic and safety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure of Potential Conflicts of Interest

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Part 1 dose escalation

Enrolled 27 patients with BC, GC, or gastroesophageal junction adenocarcinoma

Dose level increment by mCRM with EWOC

T-DXd dose cohorts: 0.8 mg/kg, $n = 3$; 1.6 mg/kg, $n = 3$; 3.2 mg/kg, $n = 3$; 5.4 mg/kg, $n = 6$; 6.4 mg/kg, $n = 6$; 8.0 mg/kg, $n = 6$

5.4 and 6.4 mg/kg were the recommended part 2 doses

Part 2 dose-expansion cohorts

2a, $N = 103$
T-DM1-treated
HER2-positive BC
5.4 or 6.4 mg/kg

2b, $N = 41$
Trastuzumab-treated
HER2-positive GC
5.4 or 6.4 mg/kg

2c, $N = 40$
HER2-low BC
5.4 or 6.4 mg/kg

2d, $N = 60$
HER2-positive or -mutated
non-BC/GC solid tumors
6.4 mg/kg

2e (PK cohort), $N = 21$
HER2-positive or -low BC
6.4 mg/kg

Enrolled HER2-expressing or HER2-mutated solid tumors, $N = 60$
NSCLC, $n = 18$; CRC, $n = 20$; Other, $n = 22$

Received ≥1 dose T-DXd, $n = 59$

Discontinued treatment $n = 49$
Progressive disease per RECIST, $n = 34$
Clinical progression, $n = 5$
Adverse event, $n = 5$
Death, $n = 2$
Withdrawal by patient, $n = 2$
Lost to follow-up, $n = 0$
Protocol violation, $n = 0$
Other, $n = 1$
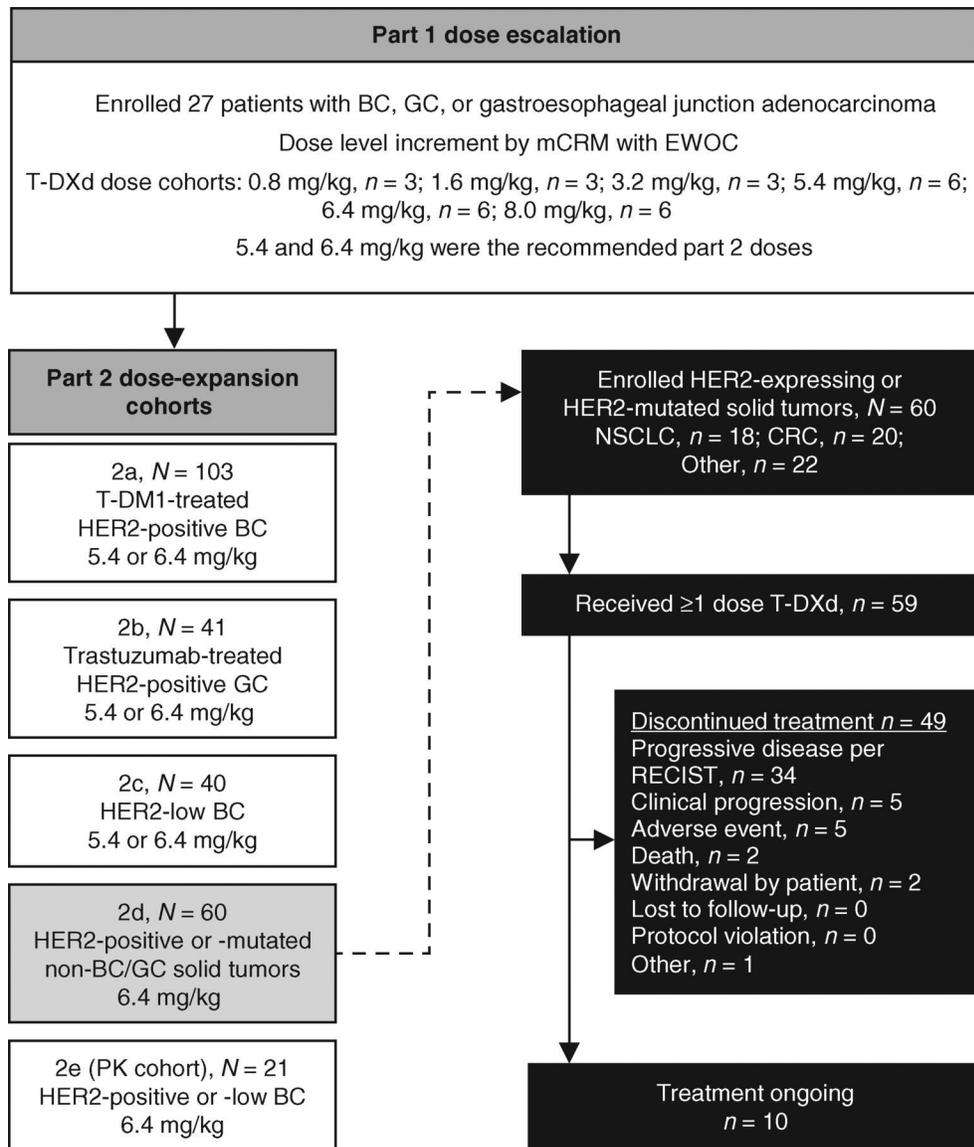
Treatment ongoing
$n = 10$

Figure 1.
Study design and patient disposition. Data cutoff for this analysis was February 2019. BC, breast cancer; CRC, colorectal cancer; EWOC, escalation with overdose control; GC, gastric cancer; mCRM, modified continuous reassessment method; PK, pharmacokinetics.
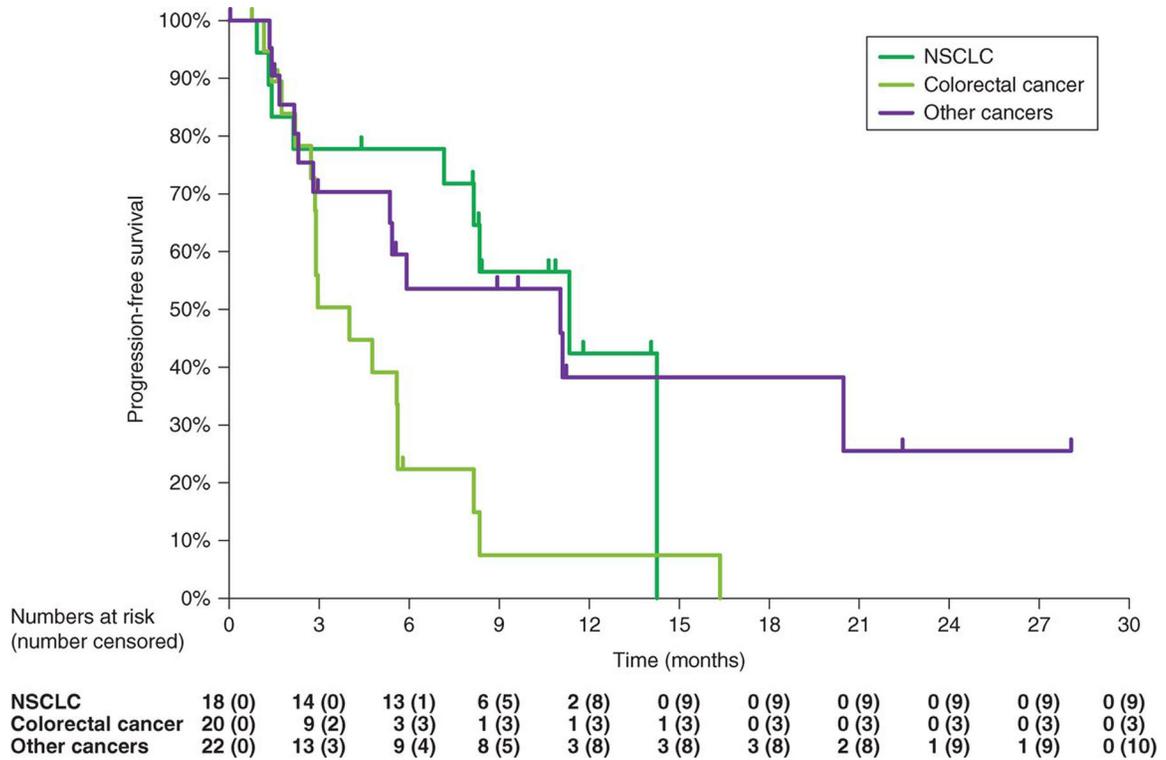
Figure 2.
Kaplan–Meier estimate for PFS for T-DXd (6.4 mg/kg) in patients with HER2-expresssing non-breast, non-gastric cancers or *HER2*-mutant advanced solid tumors. Data cutoff for this analysis was February 2019.
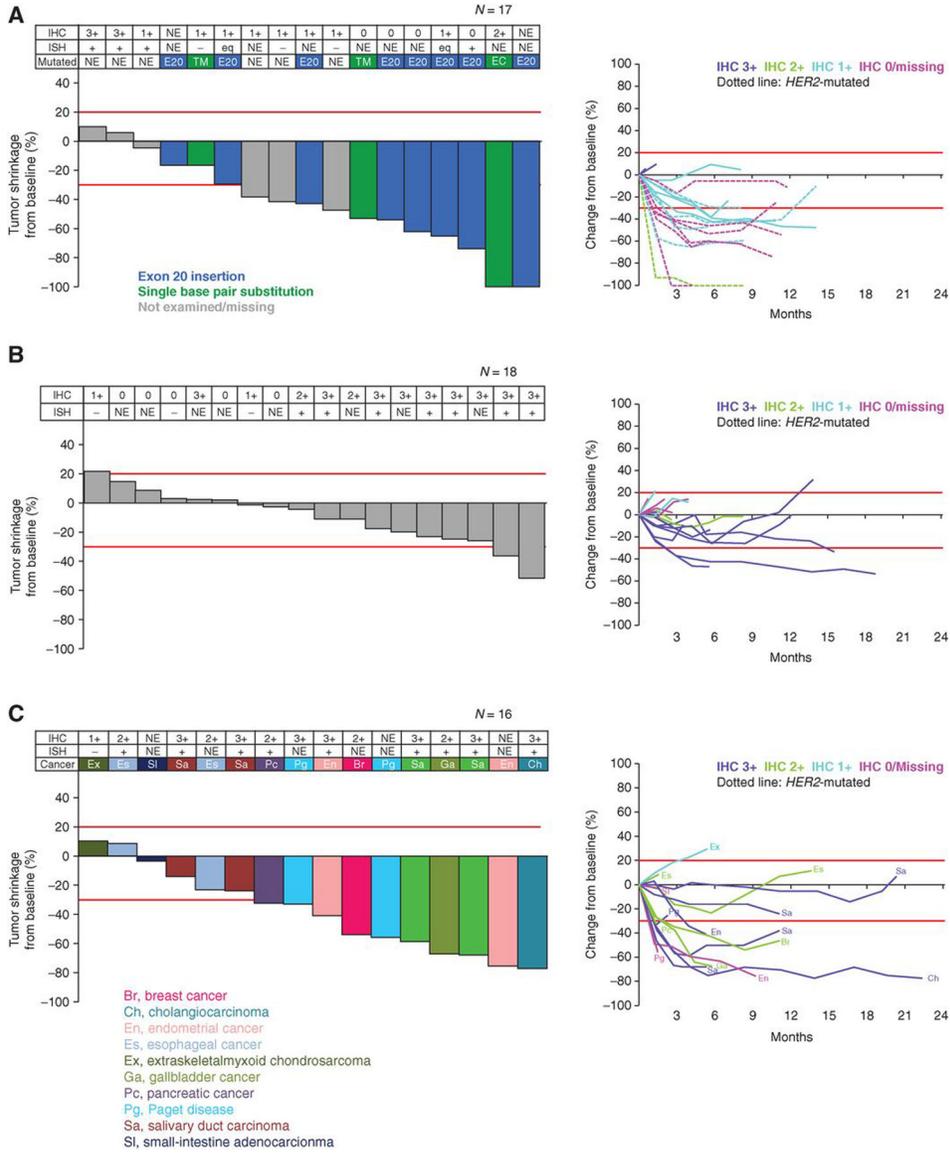
Figure 3.
Best percentage change in tumor size and tumor shrinkage over time (based on central laboratory assessment) after T-DXd in patients with NSCLC (**A**), colorectal cancer (**B**), or other cancers (**C**). HER2 expression and mutation values shown are based on central laboratory assessment. HER2 expression and mutation status at enrollment was determined via local assessment. Of the 60 patients, 51 were evaluable for tumor shrinkage. Eight patients did not have baseline measurable disease and 1 patient did not have a post-baseline tumor assessment. Data cutoff for this analysis was February 2019. Red lines denote 20% increase or 30% reduction in tumor size, respectively. Br, breast cancer; Ch, cholangiocarcinoma; E20, exon 20 insertion; En, endometrial cancer; Es, esophageal cancer; Ex, extraskeletal myxoid chondrosarcoma; Ga, gallbladder cancer; NE, not evaluated; Pc,

pancreatic cancer; Pg, Paget disease; Sa, salivary duct carcinoma; SI, small-intestine adenocarcinoma; TM, single base pair substitution at transmembrane domain.

Table 1.

Patient demographics and baseline characteristics (enrolled analysis set)

Characteristic	NSCLC n = 18	CRC n = 20	Other cancers n = 22[a]	Total (part 2d) N = 60
Age, median (range), years	58.0 (23–83)	59.5 (35–75)	58.0 (44–76)	58.0 (23–83)
Sex				
Male	5 (27.8)	11 (55.0)	13 (59.1)	29 (48.3)
Female	13 (72.2)	9 (45.0)	9 (40.9)	31 (51.7)
Country				
Japan	8 (44.4)	17 (85.0)	13 (59.1)	38 (63.3)
United States	10 (55.6)	3 (15.0)	9 (40.9)	22 (36.7)
ECOG performance status				
0	4 (22.2)	13 (65.0)	12 (54.5)	29 (48.3)
1	14 (77.8)	7 (35.0)	9 (40.9)	30 (50.0)
Missing	0	0	1 (4.5)	1 (1.7)
Time from initial diagnosis, median (range), months [b]	22.5 (0.1–111.9)	27.4 (5.6–91.3)	33.6 (2.0–95.2)	28.8 (0.1–111.9)
Prior anticancer regimens, median (range)	4.0 (1–10)	4.5 (1–7)	2.0 (0–7)	3.0 (0–10)
5 prior anticancer regimens	5 (27.8)	10 (50.0)	5 (21.7)	20 (33.3)
Chemotherapy	18 (100)	20 (100)	18 (81.8)	56 (93.3)
Immunotherapy	13 (72.2)	1 (5.0)	2 (9.1)	16 (26.7)
HER2-targeted therapy	5 (27.8)	0	12 (54.5)	17 (28.3)
Hormone therapy	0	1 (5.0)	2 (9.1)	3 (5.0)
VEGF inhibitors	8 (44.4)	16 (80.0)	4 (18.2)	28 (46.7)
EGFR inhibitor	4 (22.2)	12 (60.0)	1 (4.5)	17 (28.3)
ALK inhibitor	1 (5.6)	0	0	1 (1.7)
Previous cancer surgery	6 (33.3)	16 (80.0)	18 (81.8)	40 (66.7)
Previous radiotherapy	11 (61.1)	5 (25.0)	15 (68.2)	31 (51.7)
HER2 expression (IHC): local assessment				
3+	2 (11.1)	5 (25.0)	10 (45.5)	17 (28.3)
2+	4 (22.2)	5 (25.0)	1 (4.5)	10 (16.7)
ISH+	1 (5.6)	3 (15.0)	0	4 (6.7)

Characteristic	NSCLC	CRC	Other cancers	Total (part 2d)
	n = 18	n = 20	n = 22[a]	N = 60
ISH– or NE	1 (5.6)	1 (5.0)	0	2 (3.3)
ISH missing	2 (11.1)	1 (5.0)	1 (4.5)	4 (6.7)
1+	0	1 (5.0)	1 (4.5)	2 (3.3)
0	1 (5.6)	0	0	1 (1.7)
NE	0	0	1 (4.5)	1 (1.7)
Not examined	11 (61.1)	9 (45.0)	9 (40.9)	29 (48.3)
HER2 expression (IHC): central laboratory assessment				
3+	2 (11.1)	9 (45.0)	11 (50.0)	22 (36.7)
2+	1 (5.6)	2 (10.0)	6 (27.3)	9 (15.0)
ISH+	0	1 (5.0)	3 (13.6)	4 (6.7)
ISH– or NE	0	0	1 (4.5)	1 (1.7)
ISH missing	1 (5.6)	1 (5.0)	2 (9.1)	4 (6.7)
1+	8 (44.4)	2 (10.0)	1 (4.5)	11 (18.3)
0	5 (27.8)	7 (35.0)	0	12 (20.0)
NE	0	0	0	0
Not examined	0	0	0	0
HER2 mutation	11 (61.1)	6 (30.0)	2 (9.1)[c]	19 (31.7)
Kinase domain mutations	8 (44.4)	5 (25.0)	2 (9.1)	15 (25.0)
Transmembrane domain mutations	2 (11.1)	1 (5.0)	0 (0.0)	3 (5.0)
Extracellular domain mutations	1 (5.6)	0 (0.0)	0 (0.0)	1 (1.7)
RAS mutation	—	7 (35.0)	—	—
KRAS mutation	—	5 (25.0)	—	—
NRAS mutation	—	2 (10.0)	—	—

NOTE: All values are n (%), unless otherwise specified. Data cutoff for this analysis was February 1, 2019. The enrolled analysis set includes all patients with HER2-expressing non-breast/non-gastric solid tumors or HER2-mutant solid tumors who provided informed consent and were enrolled in the dose escalation or expansion. Percentage was calculated using the number of patients in the column heading as the denominator. Baseline was defined as the last nonmissing value taken before the first dose of study drug.

Abbreviations: ALK, anaplastic lymphoma kinase; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group.

[a] Other cancers group includes eight salivary gland tumors; two HER2-mutant breast cancers (one HER2 IHC 2+ and one HER2 IHC missing per central laboratory assessment); two esophageal cancers; two endometrial cancers; two cases of Paget disease; two cases of biliary tract cancer; and one case each of pancreatic cancer, uterine cervix carcinoma, extraskeletal myxoid chondrosarcoma, and small-intestine adenocarcinoma.

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[b] Time from initial diagnosis was calculated as (date of registration − date of initial diagnosis + 1) × 12/365.25.

[c] Both subjects were patients with breast cancer.

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Table 2.

Severity of TEAEs (safety analysis set)

Worst NCI-CTCAE grade	Part 2d total (N = 59)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematologic (>10% total)					
Anemia[a]	1 (1.7)	7 (11.9)	14 (23.7)	1 (1.7)	0
Platelet count decreased[b]	9 (15.3)	4 (6.8)	6 (10.2)	3 (5.1)	0
Neutrophil count decreased[c]	0	9 (15.3)	8 (13.6)	4 (6.8)	0
White blood cell count decreased[d]	1 (1.7)	5 (8.5)	8 (13.6)	3 (5.1)	0
Gastrointestinal (>10% total)					
Nausea	26 (44.1)	16 (27.1)	2 (3.4)	0	0
Vomiting	24 (40.7)	6 (10.2)	1 (1.7)	0	0
Diarrhea	12 (20.3)	7 (11.9)	0	0	0
Constipation	12 (20.3)	3 (5.1)	1 (1.7)	0	0
Stomatitis[e]	7 (11.9)	2 (3.4)	1 (1.7)	0	0
Abdominal pain[f]	4 (6.8)	3 (5.1)	1 (1.7)	0	0
Nervous system disorders (>10% total)					
Dysgeusia	8 (13.6)	1 (1.7)	0	0	0
Dizziness	7 (11.9)	1 (1.7)	0	0	0
Other (>10% total)					
Decreased appetite	15 (25.4)	16 (27.1)	4 (6.8)	0	0
Fatigue	11 (18.6)	9 (15.3)	1 (1.7)	0	0
Alopecia	13 (22.0)	7 (11.9)	0	0	0
Malaise	13 (22.0)	0	0	0	0
Weight decreased	3 (5.1)	6 (10.2)	2 (3.4)	0	0
Pyrexia	5 (8.5)	4 (6.8)	0	0	0
Hypokalemia	8 (13.6)	0	1 (1.7)	0	0
Epistaxis	8 (13.6)	0	0	0	0
Hiccups	6 (10.2)	1 (1.7)	0	0	0
Dehydration	2 (3.4)	5 (8.5)	0	0	0

Worst NCI-CTCAE grade	Part 2d total (*N* = 59)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood alkaline phosphatase increased	6 (10.2)	1 (1.7)	0	0	0
Cough	3 (5.1)	3 (5.1)	0	0	0
Nasopharyngitis	5 (8.5)	1 (1.7)	0	0	0
Dry skin	6 (10.2)	0	0	0	0
Peripheral edema	4 (6.8)	2 (3.4)	0	0	0
AEs of interest					
AST increased	7 (11.9)	2 (3.4)	3 (5.1)	0	0
ALT decreased	5 (8.5)	1 (1.7)	2 (3.4)	0	0
Ejection fraction decreased	1 (1.7)	4 (6.8)	0	0	0
Electrocardiogram QT prolonged	0	1 (1.7)	0	0	0
Interstitial lung disease[g]	1 (1.7)	0	0	0	0
Pneumonitis[g]	3 (5.1)	1 (1.7)	1 (1.7)	0	0
Organizing pneumonia[g]	0	0	0	0	1 (1.7)[h]
Blood bilirubin increased	0	0	0	0	0
Infusion-related reactions	0	0	0	0	0

NOTE: Data are presented as *n* (%). Data cutoff for this analysis was February 1, 2019. Safety analysis set included all patients who received ≥ 1 dose of T-DXd. Although patients may experience more than one event per system organ class and preferred term, each patient is counted once for the worst CTCAE grade. One patient may be counted toward ≥ 2 preferred terms in the same system organ class category. System Organ Class was coded with Medical Dictionary for Regulatory Activities (MedDRA) version 20.1.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

[a] Anemia includes hemoglobin decrease, red blood cell count decrease, and anemia.

[b] Platelet count decrease includes platelet count decrease and thrombocytopenia.

[c] Neutrophil count decrease includes neutrophil count decrease and neutropenia.

[d] White blood cell count decrease includes leukopenia and white blood cell count decrease.

[e] Stomatitis includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

[f] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper.

[g] As assessed by the investigator before independent adjudication.

[h] Drug-related ILD as determined by the independent ILD adjudication committee; includes one grade 5 case of respiratory failure adjudicated as drug related.

Table 3.

Clinical activity outcomes (enrolled analysis set)

	NSCLC	CRC	Other cancers	Total (part 2d)
	n = 18	n = 20	n = 22	N = 60
Treatment duration, months, median (range) [a]	10.3 (0.7–14.3)	3.0 (0.7–18.5)	6.3 (0.7–29.0) [b]	6.3 (0.7–29.0) [c]
Duration of follow-up, months, median (range)	11.0 (0.9–21.9)	3.1 (0.8–18.9)	9.5 (0.1–28.6)	7.8 (0.1–28.6)
Investigator-assessed outcomes				
Best overall response with confirmation of CR/PR				
CR	0	0	1 (4.5)	1 (1.7)
PR	10 (55.6)	3 (15.0)	8 (36.4)	21 (35.0)
SD	4 (22.2)	13 (65.0)	9 (40.9)	26 (43.3)
PD	3 (16.7)	3 (15.0)	3 (13.6)	9 (15.0)
Not evaluable	1 (5.6)	1 (5.0)	1 (4.5)	3 (5.0)
ORR with confirmation of CR/PR, n/N (%)	10/18 (55.6)	3/20 (15.0)	9/22 (40.9)	22/60 (36.7)
95% CI	(30.8–78.5)	(3.2–37.9)	(20.7–63.6)	(24.6–50.1)
DCR with confirmation of CR/PR/SD, n/N (%) [d]	14/18 (77.8)	16/20 (80.0)	18/22 (81.8)	48/60 (80.0)
95% CI	(52.4–96.3)	(56.3–94.3)	(59.7–94.8)	(67.7–89.2)
TTR with confirmation, months [e]				
n/N	10/18	3/20	9/22	22/60
Median (95% CI)	2.1 (1.2–2.8)	3.0 (1.4–8.1)	1.6 (1.2–3.0)	1.7 (1.4–2.9)
Min, max	1.2, 5.4	1.4, 8.1	1.2, 5.7	1.2, 8.1
Duration of response with confirmation, months [f]				
n/N	10/18	3/20	9/22	22/60
Median (95% CI)	9.9 (6.9–11.5)	7.4 (2.8–17.5)	12.9 (3.0–NE)	9.9 (9.0–17.5)
Min, max	5.3+, 11.5	2.8, 17.5	3.0, 26.3+	2.8, 26.3+
PFS, months				
Median (95% CI)	11.3 (5.5–14.1)	4.1 (2.1–5.9)	11.1 (5.4–20.5)	8.3 (5.4–11.8)
Assessment by independent central review				
Best overall response with confirmation of CR/PR				
CR	0	0	1 (4.5)	1 (1.7)

	NSCLC	CRC	Other cancers	Total (part 2d)
	n = 18	*n* = 20	*n* = 22	*N* = 60
PR	10 (55.6)	1 (5.0)	5 (22.7)	16 (26.7)
SD	5 (27.8)	15 (75.0)	12 (54.5)	32 (53.3)
PD	2 (11.1)	2 (10.0)	3 (13.6)	7 (11.7)
Not evaluable	1 (5.6)	2 (10.0)	1 (4.5)	4 (6.7)
ORR with confirmation of CR/PR, *n/N* (%)	10/18 (55.6)	1/20 (5.0)	6/22 (27.3)	17/60 (28.3)
95% CI	(30.8–78.5)	(0.1–24.9)	(10.7–50.2)	(17.5–41.4)
DCR with confirmation of CR/PR/SD, *n/N* (%) [d]	15/18 (83.3)	16/20 (80.0)	18/22 (81.8)	49/60 (81.7)
95% CI	(58.6–96.4)	(56.3–94.3)	(59.7–94.8)	(69.6–90.5)
TTR with confirmation, months [e]				
n/N	10/18	1/20	6/22	17/60
Median (95% CI)	1.4 (1.2–2.8)	3.0 (NE)	1.6 (1.4–3.0)	1.4 (1.4–2.9)
Min, max	1.2, 5.8	3.0, 3.0	1.4, 3.0	1.2, 5.8
Duration of response with confirmation, months [f]				
n/N	10/18	1/20	6/22	17/60
Median (95% CI)	10.7 (6.9–11.5)	13.4 (NE)	NR (3.0–NE)	11.5 (7.0–NE)
Min, max	3.3+, 11.5	13.4, 13.4	3.0, 21.1+	3.0, 21.1+
PFS, months				
Median (95% CI)	11.3 (7.2–14.3)	4.0 (2.7–5.6)	11.0 (2.8–NE)	7.2 (4.8–11.1)
OS, months				
Median (95% CI)	NR (17.3–NE)	15.6 (4.8–NE)	23.4 (9.6–NE)	23.4 (15.6–NE)
Min, max	0.9, 21.9+	1.0+, 25.9+	0.1+, 28.6+	0.1+, 28.6+

NOTE: All values are *n* (%), unless otherwise specified. Data cutoff for this analysis was February 2019. The enrolled analysis set includes all patients with HER2-expressing non-breast/non-gastric solid tumors or *HER2*-mutant solid tumors who provided informed consent and were enrolled in the dose escalation or expansion. Min and max include the censored observations; using "+" after value indicates censoring.

Abbreviations: CR, complete response; CRC, colorectal cancer; DCR, disease control rate; max, maximum; min, minimum; NE, not estimable; NR, not reached; PR, partial response; SD, stable disease.

[a] Safety analysis set.

[b] *n* = 21.

[c] *n* = 59.

[d]DCR is calculated as the proportion of patients demonstrating CR, PR, or SD for a minimum of 5 weeks from date of first dose.

[e]TTR was measured from the date of registration to the date at which criteria for CR or PR are first met.

[f]Duration of response was measured from the time at which CR or PR criteria are first met, until the first date of objectively documented PD or death due to any cause.

Table 4.

Clinical activity outcomes in *HER2*-mutant NSCLC (enrolled analysis set)

Outcome	*HER2*-mutant NSCLC *n* = 11
Duration of follow-up, median (range), months[a]	11.5 (5.1–14.6)
Investigator-assessed outcomes	
Best overall response with confirmation of CR/PR	
CR	0
PR	8 (72.7)
SD	2 (18.2)
PD	1 (9.1)
NE	0
Confirmed ORR	8/11 (72.7)
95% CI	(39.0–94.0)
Confirmed DCR[b]	10/11 (90.9)
95% CI	(58.7–99.8)
TTR, months[c]	
n/N	8/11
Median (95% CI)	1.4 (1.2–2.8)
Min, max	1.2, 5.4
Duration of response, months[d]	
n/N	8/11
Median (95% CI)	9.9 (6.9–11.5)
Min, max	5.3+, 11.5
PFS, months	
Median (95% CI)	11.3 (5.5–14.3)
Min, max	2.8, 14.3
Assessment by independent central review	
Best overall response with confirmation of CR/PR	
CR	0
PR	8 (72.7)
SD	2 (18.2)
PD	1 (9.1)
NE	0
Confirmed ORR	8/11 (72.7)
95% CI	(39.0–94.0)
Confirmed DCR[b]	10/11 (90.9)
95% CI	(58.7–99.8)
TTR, months[c]	
n/N	8/11

Outcome	*HER2*-mutant NSCLC
	n = 11
Median (95% CI)	1.4 (1.2–1.4)
Min, max	1.2, 2.8
Duration of response, months[d]	
n/N	8/11
Median (95% CI)	9.9 (6.9–11.5)
Min, max	3.3+, 11.5
PFS, months	
Median (95% CI)	11.3 (8.1–14.3)
Min, max	1.3, 14.3
OS, months	
Median (95% CI)	17.3 (17.3–NE)
Min, max	8.4, 20.9+

NOTE: All values are *n* (%), unless otherwise specified. Data cutoff for this analysis was February 1, 2019. Dashes indicate value not reached. Min and max include the censored observations; using "+" after value indicates censoring. Abbreviations: max, maximum; min, minimum; NE, not evaluable; ORR, objective response rate.

[a] Safety analysis set.

[b] DCR is calculated as the proportion of patients demonstrating CR, PR, or SD for a minimum of 6 weeks (±1 week) from date of first dose.

[c] TTR was measured from the date of registration to the date at which criteria for CR or PR are first met.

[d] Duration of response was measured from the time at which CR or PR criteria are first met until the first date of objectively documented PD.