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Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer

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Abstract

BACKGROUND—Human epidermal growth factor receptor 2 (HER2)–targeted therapies have not been approved for patients with non–small-cell lung cancer (NSCLC). The efficacy and safety of trastuzumab deruxtecan (formerly DS-8201), a HER2 antibody–drug conjugate, in patients with *HER2*-mutant NSCLC have not been investigated extensively.

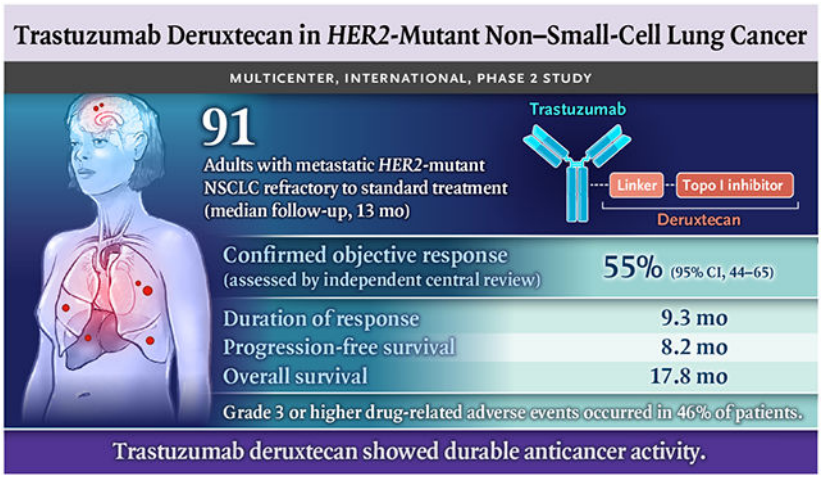
METHODS—We conducted a multicenter, international, phase 2 study in which trastuzumab deruxtecan (6.4 mg per kilogram of body weight) was administered to patients who had metastatic *HER2*-mutant NSCLC that was refractory to standard treatment. The primary outcome was objective response as assessed by independent central review. Secondary outcomes included the duration of response, progression-free survival, overall survival, and safety. Biomarkers of HER2 alterations were assessed.

RESULTS—A total of 91 patients were enrolled. The median duration of follow-up was 13.1 months (range, 0.7 to 29.1). Centrally confirmed objective response occurred in 55% of the patients (95% confidence interval [CI], 44 to 65). The median duration of response was 9.3 months (95% CI, 5.7 to 14.7). Median progression-free survival was 8.2 months (95% CI, 6.0 to 11.9), and median overall survival was 17.8 months (95% CI, 13.8 to 22.1). The safety profile was generally consistent with those from previous studies; grade 3 or higher drug-related adverse events occurred in 46% of patients, the most common event being neutropenia (in 19%). Adjudicated drug-related interstitial lung disease occurred in 26% of patients and resulted in death

in 2 patients. Responses were observed across different *HER2* mutation subtypes, as well as in patients with no detectable HER2 expression or *HER2* amplification.

CONCLUSIONS—Trastuzumab deruxtecan showed durable anticancer activity in patients with previously treated *HER2*-mutant NSCLC. The safety profile included interstitial lung disease that was fatal in two cases. Observed toxic effects were generally consistent with those in previously reported studies. (Funded by Daiichi Sankyo and AstraZeneca; DESTINY-Lung01 ClinicalTrials.gov number, NCT03505710.)

Graphical Abstract



THE MAJORITY OF NON–SMALL-CELL lung cancers (NSCLCs) are caused by oncogenic alterations, and the development of targeted therapies has contributed to a substantial reduction in mortality from NSCLC in recent years.[1,2] Mutations in the gene encoding human epidermal growth factor receptor 2 (*HER2*, also called *ERBB2*) drive approximately 3% of nonsquamous NSCLCs and are associated with female sex, never-smoking history, and a poor prognosis, as well as with a slightly younger age and higher incidence of brain metastases than NSCLC without *HER2* mutations or with other mutations.[3-7]

Although HER2 targeting has transformed the treatment of patients with breast and gastric cancers, HER2-targeted therapies have not been approved for patients with NSCLC. Therefore, patients with *HER2*-mutant NSCLC are currently treated with standard chemotherapy or immunotherapy, which have limited activity as second- or later-line treatment.[8-13] Furthermore, limited and varied results have been reported for responses to immune-checkpoint inhibitors in this population, with 7 to 27% of patients having an objective response to treatment.[13,14] Clinical trials of the HER2 antibody trastuzumab in combination with chemotherapy showed disappointing outcomes in patients with NSCLC, in part because of difficulties in defining precise molecular criteria for the selection of patients who would benefit from HER2-targeted agents and the rarity of high-level HER2 protein expression or *HER2* amplification in NSCLC in contrast to breast and gastric cancers.[15-17] Other efforts in targeting *HER2*-mutant NSCLC have produced encouraging but inconsistent results, with objective response occurring in 0 to 30% of patients who

receive HER2 tyrosine kinase inhibitors and antibodies and in 44% of those who receive the HER2 antibody–drug conjugate trastuzumab emtansine.[18-26]

Trastuzumab deruxtecan (formerly DS-8201) is an antibody–drug conjugate consisting of a humanized anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor payload through a tetrapeptide-based cleavable linker.[27,28] Its formulation incorporates a potent cytotoxic payload at a high drug-to-antibody ratio of approximately 8 while allowing it to remain stable in plasma until internalized and selectively cleaved by peptides that are overexpressed in cancer cells,[27,28] thus releasing the highly potent payload to induce DNA damage and apoptosis, with bystander-killing effect in neighboring tumor cells.[29] Trastuzumab deruxtecan has been approved in various countries worldwide for the treatment of patients with metastatic HER2-positive breast and gastric cancers on the basis of the results from pivotal trials.[30,31] Results from its first-in-human study (ClinicalTrials.gov number, NCT02564900) showed preliminary antitumor activity in 11 patients with *HER2*-mutant NSCLC, with a confirmed objective response occurring in 72.7% of the patients (95% confidence interval [CI], 39.0 to 94.0).[32] Translational studies showed that *HER2*-mutant NSCLC may preferentially internalize the HER2 receptor antibody–drug conjugate complex regardless of HER2 protein expression and overcome resistance to other HER2-targeted agents, which supports the further development of trastuzumab deruxtecan for treatment in this population.[33]

We evaluated trastuzumab deruxtecan in patients with NSCLC, and in this report we describe the results from the primary analysis involving the fully enrolled cohort of patients with a *HER2* mutation.

METHODS

TRIAL DESIGN

We conducted DESTINY-Lung01, a multicenter, open-label, two-cohort, phase 2 study, at 21 sites in North America, Japan, and Europe to evaluate the efficacy and safety of trastuzumab deruxtecan in patients with HER2-overexpressing or *HER2*-mutant NSCLC. To be eligible for participation, patients had to be adults with unresectable or metastatic nonsquamous NSCLC whose disease had relapsed during standard treatment or was refractory to standard treatment, to have at least one measurable lesion as defined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and to have an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (scores range from 0 to 5, with higher scores reflecting greater disability). Standard treatment was chosen at the investigator's discretion, and some patients could be enrolled while receiving an earlier line of treatment. Patients with asymptomatic brain metastases who were not receiving ongoing glucocorticoid or anticonvulsant therapy could be enrolled. Patients with activating *HER2* mutations (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) as detected in a tumor tissue sample and confirmed by local laboratory assessment in accordance with Clinical Laboratory Improvement Amendment standards or equivalent were included. Tumor samples were centrally and retrospectively analyzed for exploratory biomarker assessment. The Oncomine Dx Target Test (Thermo Fisher Scientific) was used for local confirmation of *HER2* mutation status and to determine

HER2 amplification status. A copy-number gain was called when the lower limit of the 95% confidence interval for the copy number was greater than 4. HER2 protein expression status was determined by means of immunohistochemical analysis with the use of the PATHWAY anti-HER2 (4B5) assay (Ventana Medical Systems) along with the lung-staining protocol and the American Society of Clinical Oncology–College of American Pathologists gastric HER2 scoring method (possible scores are 0 [no detectable expression], 1+ [faint or barely detectable expression], 2+ [weak to moderate expression], and 3+ [strong expression]).[34]

Patients who had previously been treated with a HER2 antibody or an antibody–drug conjugate were ineligible for participation, but those who had previously received a HER2 tyrosine kinase inhibitor such as afatinib, pyrotinib, or poziotinib were eligible. Patients with a history of noninfectious interstitial lung disease treated with glucocorticoids or current or suspected interstitial lung disease that could not be ruled out by imaging at screening were ineligible. Details regarding the eligibility criteria are provided in the Supplementary Appendix. Trastuzumab deruxtecan was administered intravenously every 3 weeks at a dose of 6.4 mg per kilogram of body weight.

STUDY OVERSIGHT

The study was funded by Daiichi Sankyo and AstraZeneca. The study was designed by Daiichi Sankyo, which also oversaw the conduct of the study, and was approved by the institutional review board at each site and conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations regarding the conduct of clinical research. All the patients provided written informed consent before participation. Data were analyzed and interpreted by the funders and authors. The authors vouch for the accuracy and completeness of the data and for the adherence of the study to the protocol, which is available at NEJM.org. Editorial assistance with an earlier version of the manuscript was financially supported by Daiichi Sankyo.

END POINTS

The primary end point was confirmed objective response as assessed by independent central review on the basis of RECIST, version 1.1. Secondary end points included the duration of response, disease control (defined as complete response, partial response, or stable disease at 6 weeks with no progression), progression-free survival, and overall survival. Exploratory end points included time to response and potential biomarkers of response.

SAFETY

Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 23.0, and were graded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Potential cases of interstitial lung disease or pneumonitis were evaluated by an independent adjudication committee and were treated according to protocol-specified guidelines (see Supplementary Methods and Table S2).

STATISTICAL ANALYSIS

Efficacy and safety were assessed in all enrolled patients who received at least one dose of trastuzumab deruxtecan. We originally planned to enroll 40 patients in the *HER2*-mutation cohort of the study. After a protocol amendment to expand this cohort, we planned to enroll 50 additional patients with *HER2* mutations. A sample of 90 patients ensured that the mean distance from the limits of a 95% confidence interval to the observed percentage of patients with an objective response was approximately 9 percentage points, under the assumption that 30% of the patients would have an objective response. This 30% threshold was derived by benchmarking against the estimate of the upper limit of 20% for the current standard-of-care treatment, docetaxel, and allowing a further increment of 10 percentage points to account for the sparseness of data.[35]

Categorical variables (including binary outcomes) were summarized with the use of frequency counts and percentages. Time-to-event outcomes were analyzed with the Kaplan–Meier method. For time-to-event end points for which censoring was not performed, descriptive summaries are reported.

RESULTS

PATIENTS

Between May 30, 2018, and July 21, 2020, a total of 91 patients with *HER2*-mutant NSCLC were enrolled and treated with trastuzumab deruxtecan. The median number of previous cancer therapies among the enrolled patients was two (range, zero to seven). A total of 95% of the patients had received previous platinum-based therapy, and 66% had received anti–programmed death 1 or anti–programmed death ligand 1 treatment. Additional demographic and clinical characteristics of the patients are shown in Table 1. At the time of data cutoff (May 3, 2021), the median duration of treatment was 6.9 months (range, 0.7 to 26.4) and treatment was ongoing for 15 patients (16%) (Fig. S1). The median duration of follow-up was 13.1 months (range, 0.7 to 29.1).

EFFICACY

Among the 91 patients, 50 patients (55%; 95% CI, 44 to 65) had a confirmed objective response as assessed by independent central review. One patient (1%) had a confirmed complete response, and 49 patients (54%) had a confirmed partial response (Table 2). Most patients (92%; 95% CI, 85 to 97) had disease control and had a reduction in tumor size (Fig. 1A). Responses were also observed in patients who had received a variety of previous cancer treatments, including immunotherapy, and in patients who had central nervous system (CNS) metastasis at baseline (Fig. S2). Changes in tumor size from baseline over time are shown in Figure 1B. Among the 33 patients with CNS metastases at baseline, 14 had previously received radiotherapy to the brain and 19 had not; of these patients, 8 and 10, respectively, had a partial response.

The median duration of response was 9.3 months (95% CI, 5.7 to 14.7), median progression-free survival was 8.2 months (95% CI, 6.0 to 11.9), and median overall survival was 17.8 months (95% CI, 13.8 to 22.1) (Table 2 and Fig. 2). A total of 47 patients (52%) had died as

of the data cutoff, and the other patients continue to be followed for survival. Among the 33 patients with CNS metastases at baseline, median progression-free survival was 7.1 months (95% CI, 5.5 to 9.8) and median overall survival was 13.8 months (95% CI, 9.8 to 20.9).

SAFETY

All 91 patients had at least one adverse event, and 88 patients (97%) had at least one adverse event that was reported by the investigators as being related to trastuzumab deruxtecan (Table S3). Of the adverse events that occurred in 20% or more of patients, most were of grade 1 or 2; common events included gastrointestinal and hematologic events, decreased appetite, and alopecia (Table S4). Grade 3 or higher drug-related adverse events occurred in 42 patients (46%). The most common grade 3 or higher drug-related adverse events were neutropenia (in 19%) and anemia (in 10%) (Table 3). Thirteen patients had grade 5 (i.e., fatal) adverse events, two of which were deemed to be drug-related (Table 3). Serious drug-related adverse events occurred in 18 patients (20%). Twenty-three patients (25%) discontinued treatment because of investigator-reported, drug-related adverse events; these events included pneumonitis in 12 patients (13%) and interstitial lung disease in 5 patients (5%). A total of 31 patients (34%) had drug-related adverse events that led to dose reduction; the most common among these events were nausea (in 10 patients) and fatigue (in 8 patients). Drug-related adverse events led to dose interruption in 29 patients (32%), with the most common being decreased neutrophil count (in 13 patients) and pneumonitis (in 5 patients).

In addition to the above investigator-reported adverse events, adjudicated drug-related interstitial lung disease occurred in 24 patients (26%); the disease was determined to be of grade 1 in 3 patients, grade 2 in 15 patients, grade 3 in 4 patients, and grade 5 in 2 patients (Table S5). Among the patients who had interstitial lung disease, the median time to the onset of first reported interstitial lung disease was 141 days (range, 14 to 462), and the median duration of the disease was 43 days (95% CI, 24 to 94). Adjudicated drug-related interstitial lung disease occurred in 8 of the 20 patients who had previously undergone lung resection. Trastuzumab deruxtecan was withdrawn in 16 patients and interrupted in 8 patients because of adjudicated interstitial lung disease. Of the 24 patients with adjudicated drug-related interstitial lung disease, 21 received at least one dose of glucocorticoids. However, not all glucocorticoid treatment was administered in accordance with the management guidelines for interstitial lung disease. The remaining 3 patients did not receive glucocorticoids. Of these 3 patients, 2 with grade 1 interstitial lung disease were monitored closely per the guidelines and 1 with grade 2 interstitial lung disease was initially treated with antibiotic agents for a suspected infection. At the time of data cutoff, 13 of the patients had fully recovered, 1 patient had recovered with sequelae, 2 patients were still recovering, 7 patients had not recovered and had had interstitial lung disease for 22 to 40 days (including 1 patient with an investigator-reported grade 3 event that was later adjudicated as grade 5 with an outcome of death), and 1 patient had died.

BIOMARKER ANALYSES

All 91 enrolled patients had a tumor with a locally reported *HER2* mutation. Most *HER2* mutations were exon 20 insertions (86%). Other, less common *HER2* mutations were

single-nucleotide variants in exon 19 or 20 of the kinase domain or in exon 8 of the extracellular domain. Tumor tissue was available to evaluate HER2 protein expression and gene-amplification status in 53 and 45 patients, respectively. Any HER2 protein expression (i.e., an immunohistochemical score of 1+ to 3+) was detected in 44 of 53 patients, whereas 9 patients had no detectable HER2 expression (Table S6). *HER2* amplification was found in 2 of 45 patients. Responses to treatment were observed in patients with different *HER2* mutation subtypes across three exon locations, as well as in patients who had no detectable HER2 expression or tested negative for *HER2* amplification (Fig. 1).

DISCUSSION

In this phase 2 study, trastuzumab deruxtecan showed durable anticancer activity in 91 patients with *HER2*-mutant NSCLC: a confirmed objective response occurred in 55% of the patients, the median duration of response was 9.3 months, median progression-free survival was 8.2 months, and median overall survival was 17.8 months. These results support the clinical benefit of trastuzumab deruxtecan in patients with *HER2*-mutant NSCLC, a clinical context in which no targeted agents are currently approved.

Historically, two distinct types of agents have been evaluated in patients with HER2-mutant NSCLC: HER2 tyrosine kinase inhibitors and HER2 antibodies or antibody–drug conjugates. Earlier trials of afatinib, dacomitinib, and neratinib did not show sufficient clinical activity.[18-20] Pyrotinib and poziotinib have been shown to produce a response in 30% and 28% of patients, respectively. However, these responses have not been consistently durable, with median progression-free survival of 5.5 to 6.9 months and a median duration of response of 4.6 to 6.9 months.[24,25,36] In the MyPathway trial, trastuzumab in combination with pertuzumab produced a response in 21% of patients with *HER2*-mutant NSCLC.[21] A phase 2 basket trial of trastuzumab emtansine showed a response occurring in 44% of patients, which indicated that an antibody–drug conjugate was clinically active in patients with *HER2*-mutant NSCLC.[23] However, the median duration of response of 4 months was relatively short.[23] Taken together, these data suggest that *HER2* mutations in NSCLC can be targeted, with resulting antitumor effects. The results of the present study provide evidence of durable anticancer activity of trastuzumab deruxtecan in this population.

Efficacy was consistently observed across different subgroups, including those who had previously been treated with a HER2 tyrosine kinase inhibitor and those with CNS metastasis, which is particularly prevalent in this population.[7] Unfortunately, CNS surveillance was not performed systematically in all patients, which makes it impossible to assess anti-CNS tumor activity comprehensively. However, among the 33 patients who were known to have CNS disease, the percentages of patients with a response were similar to those among patients without CNS lesions. Responses were seen in patients with different mutation subtypes located across the extracellular and kinase domains of the HER2 protein. Responses were observed in the majority of the small number of patients with no detectable HER2 expression as assessed by immunohistochemical analysis or gene amplification. In contrast to the studies leading to the approvals in HER2-positive breast and gastric cancers, this study involving patients with lung cancer is particularly notable for its targeting of tumors bearing *HER2* mutations.

The exact mechanism by which HER2 antibody–drug conjugates are effective in *HER2*-mutant NSCLC requires further research; however, it has been shown preclinically that activating *HER2* mutations enhance receptor internalization and intracellular uptake of the HER2 receptor antibody–drug conjugate complex.[33] This may provide the mechanistic basis for the high degree of efficacy in patients with *HER2*-mutant NSCLC, in contrast to the lower response rates seen in preliminary observations among patients with HER2-overexpressing NSCLC classified as having an immunohistochemical score of 2+ or 3+.[37] Furthermore, this property of activating *HER2* mutations may explain why efficacy is observed even in *HER2*-mutant cancers with no detectable HER2 expression (i.e., with an immunohistochemical score of 0). Further research is needed to understand the mechanisms of intrinsic and acquired resistance to trastuzumab deruxtecan.[38]

Overall, the safety profile of trastuzumab deruxtecan in patients with *HER2*-mutant NSCLC was generally consistent with that in previously reported studies.[32,39] In total, 49% of patients had drug-related grade 3 or higher adverse events, which were generally hematologic or gastrointestinal in nature. However, 26% of patients had adjudicated drug-related interstitial lung disease; 75% of these events were of grade 1 or 2, but 4 patients had grade 3 pulmonary toxic effects, and 2 patients died. However, the development of this toxic effect was not predictable; as a consequence, patients must be carefully monitored. Adverse events of interstitial lung disease in the present study were actively managed on the basis of the protocol-defined management guidelines for interstitial lung disease, including prompt initiation of glucocorticoid treatment. This resulted in 13 of the patients (>50%) having recovered from interstitial lung disease by the time of data cutoff. Further research is needed to determine which patients are at greatest risk and how to most effectively manage this potentially fatal adverse event.

The lack of a comparator group in this study necessitates further clinical research. In addition, patients who had previously been treated with HER2-directed antibodies or antibody–drug conjugates were excluded from the current study. Whether clinical activity remains similar in such patients, as has been previously observed in breast cancer,[31] remains to be determined. A randomized phase 2 trial is under way to further evaluate the efficacy and safety of trastuzumab deruxtecan, including a lower dose of 5.4 mg per kilogram, the recommended and approved dosage in HER2-positive breast cancer, in patients with *HER2*-mutant NSCLC (DESTINY-Lung02; ClinicalTrials.gov number, NCT04644237). Another trial (DESTINY-PanTumor01; NCT04639219) is also under way to evaluate trastuzumab deruxtecan in targeting *HER2* mutations across other cancer types.

In this multicenter international trial, treatment with trastuzumab deruxtecan was shown to produce a response in a high percentage of patients with advanced *HER2*-mutant NSCLC and to provide durable clinical benefit. The observed safety profile was consistent with that in previously reported studies of trastuzumab deruxtecan. Interstitial lung disease remains an important risk that requires careful safety monitoring and management. This study provides clinical evidence of antitumor activity from a HER2-targeted therapy for patients with previously treated *HER2*-mutant NSCLC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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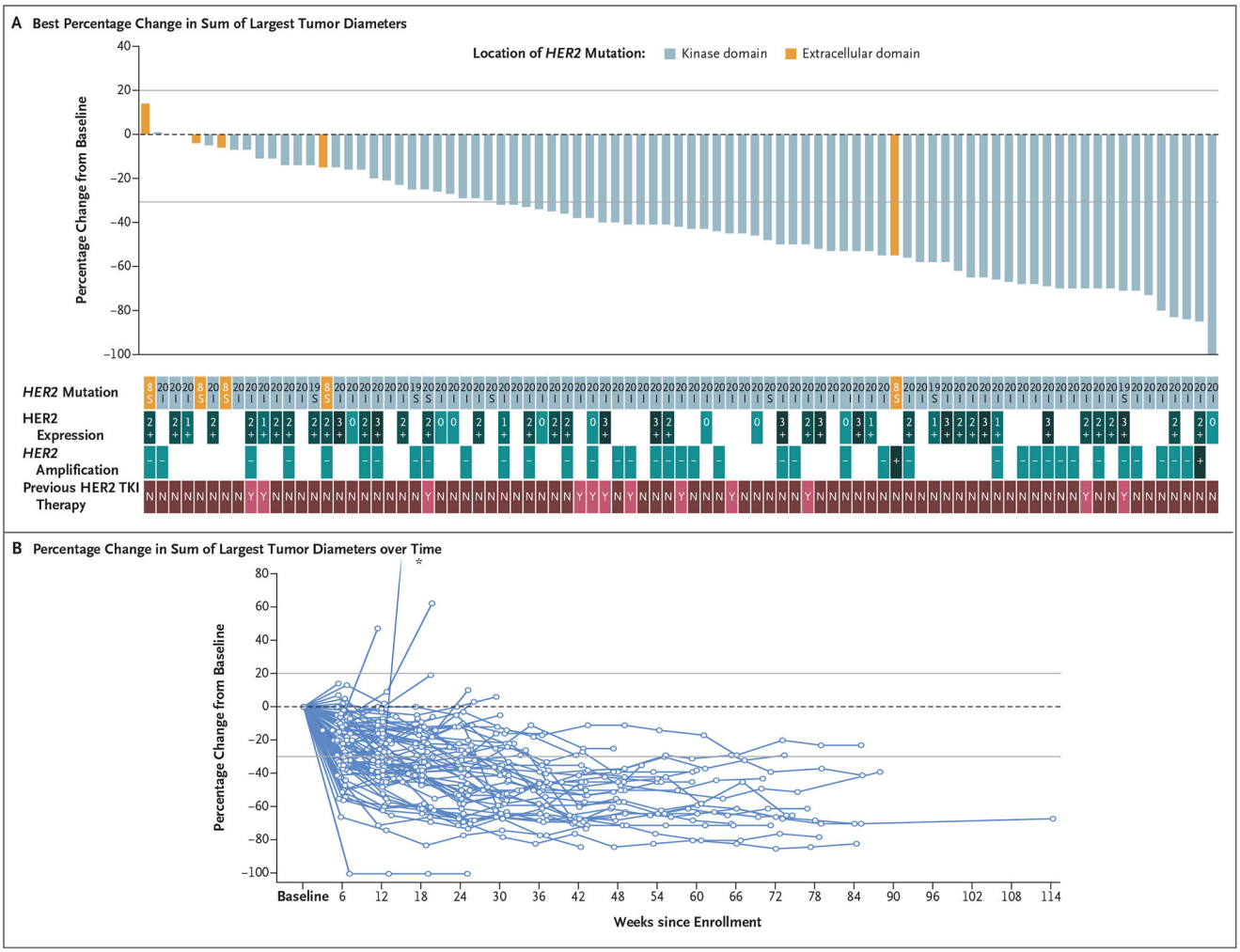

Figure 1. Antitumor Activity.

Panel A shows the best percentage change from baseline in the sum of the largest diameters of measurable tumors in 85 of 91 patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available. The upper horizontal line indicates a 20% increase in tumor size in the patients who had disease progression, and the lower horizontal line indicates a 30% decrease in tumor size (partial response). Below the graph, blank cells indicate patients whose tumor samples could not be evaluated or were not assessed. In the *HER2* mutation row, numbers indicate the exon in which the mutation is located (8, 19, or 20). In the HER2 expression row, numbers indicate the immunohistochemical scores (0 [no detectable expression], 1+ [faint or barely detectable expression], 2+ [weak to moderate expression], or 3+ [strong expression]). HER2 denotes human epidermal growth factor receptor 2, I insertion, N no, S substitution, TKI tyrosine kinase inhibitor, and Y yes. Panel B shows the percentage change from baseline in the sum of the largest diameters of measurable tumors from baseline over time. The asterisk indicates a patient outlier with an increase of 236% in tumor diameter from baseline at week 18.

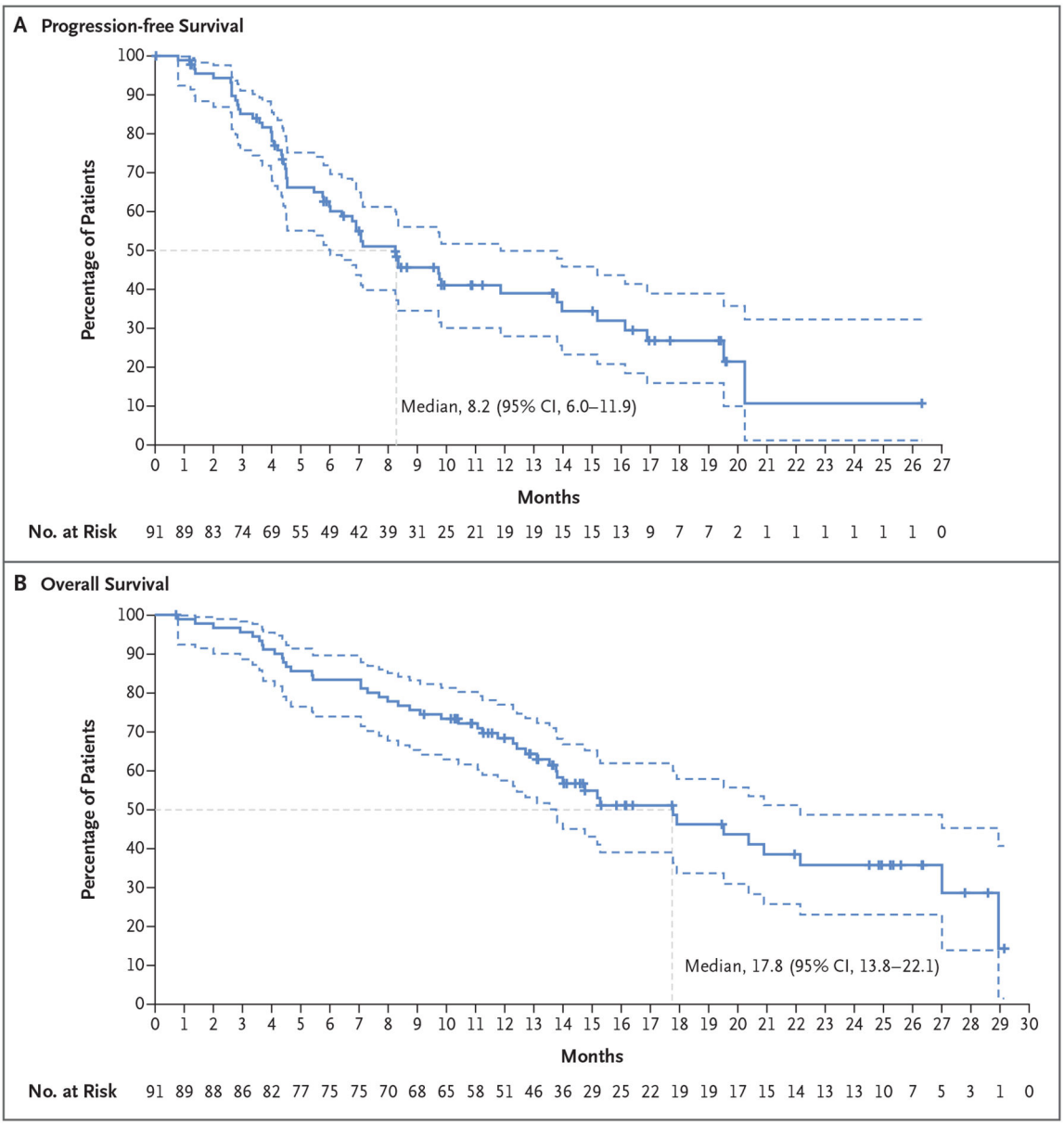

Figure 2. Kaplan–Meier Analysis of Progression-free Survival and Overall Survival.

Panel A shows progression-free survival in the overall population. Of the 91 patients, 41 had progressive disease and 15 had died by the data cutoff date; data for 35 patients were censored, as indicated by tick marks. Panel B shows overall survival in the overall population. Of the 91 patients, 47 had died by the cutoff date; data for 44 patients were censored, as indicated by tick marks. In each panel, the dashed lines indicate the 95% confidence interval.

Table 1.

Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Patients (N = 91)
Median age (range) — yr	60 (29–88)
Female sex — no. (%)	60 (66)
Race — no. (%)†	
Asian	31 (34)
White	40 (44)
Black	1 (1)
Other	19 (21)
Geographic region — no. (%)	
Asia	23 (25)
North America	35 (38)
Europe	33 (36)
ECOG performance-status score — no. (%)‡	
0	23 (25)
1	68 (75)
Location of *HER2* mutations — no. (%)	
Kinase domain	85 (93)
Extracellular domain	6 (7)
Previous cancer therapy — no. (%)	90 (99)§
No. of lines of previous cancer therapy — median (range)	2 (0–7)
Previous cancer therapy — no. (%)	
Platinum-based therapy	86 (95)
Docetaxel	18 (20)
Anti–PD-1 or anti–PD-L1 treatment	60 (66)
HER2 TKI	13 (14)
Reason for discontinuation of previous cancer therapy — no./total no. (%)	
Disease progression	63/90 (70)
Completed therapy	6/90 (7)
Adverse event	8/90 (9)
Investigator decision	3/90 (3)
Patient choice	1/90 (1)
Unknown	5/90 (6)
Other	4/90 (4)
CNS metastases at baseline — no. (%)	33 (36)
Smoking history — no. (%)	
Current	2 (2)
Former	37 (41)
Never	52 (57)
Previous lung resection — no. (%)	20 (22)

[*] Percentages may not total 100 because of rounding. CNS denotes central nervous system, HER2 human epidermal growth factor receptor 2, PD-1 programmed cell death 1, PD-L1 programmed death ligand 1, and TKI tyrosine kinase inhibitor.

[†] Race was reported by the patients.

[‡] Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores reflecting greater disability.

[§] One patient was enrolled without having received previous cancer therapy.

Table 2.

Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review.

Response Assessment	Patients (N = 91)
Confirmed objective response *	
No. of patients	50
Percentage of patients (95% CI)	55 (44–65)
Best response — no. (%)	
Complete response	1 (1)
Partial response	49 (54)
Stable disease	34 (37)
Progressive disease	3 (3)
Response could not be evaluated	4 (4)
Disease control †	
No. of patients	84
Percentage of patients (95% CI)	92 (85–97)
Median time to response (range) — mo ‡	1.5 (1.2–9.3)
Median duration of response (95% CI) — mo ‡	9.3 (5.7–14.7)

* Confirmed objective response was assessed by independent central review on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1.

† Disease control was defined as complete response, partial response, or stable disease at 6 weeks with no progression.

‡ Analyses of time to response and duration of response included only the patients with a confirmed objective response.

Table 3.

Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).

Event	Grade 1–2	Grade 3	Grade 4	Grade 5	Overall
	number of patients (percent)				
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1) *	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue †	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia ‡	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia §	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia ¶	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

* One patient had grade 5 (i.e., fatal) pneumonitis that was assessed as drug-related by the investigator (subsequently adjudicated as interstitial lung disease). Another patient had grade 3 interstitial lung disease, as reported by the investigator, and died; the reported interstitial lung disease was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee. All adjudicated events of drug-related interstitial lung disease are reported in Table S5.

† This category includes the preferred terms fatigue, asthenia, and malaise.

‡ This category includes the preferred terms neutrophil count decreased and neutropenia.

§ This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased.

¶ This category includes the preferred terms white-cell count decreased and leukopenia.