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Patritumab Deruxtecan (HER3-DXd; MK-1022) in Non–Small Cell Lung Cancer After Platinum-Based Chemotherapy and Immunotherapy

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ABSTRACT

PURPOSE Patritumab deruxtecan (HER3-DXd; MK-1022) is an investigational HER3-directed antibody-drug conjugate composed of a human immunoglobulin G1 monoclonal antibody to HER3 (patritumab) covalently linked via a stable tetrapeptide-based cleavable linker to a topoisomerase I inhibitor payload that has shown durable antitumor activity in previously treated patients with *EGFR*-mutated advanced non–small cell lung cancer (NSCLC). We extend these observations to patients with advanced NSCLC with other/no identified driver genomic alterations.

METHODS Patients with advanced squamous or nonsquamous NSCLC without a common *EGFR*-activating mutation whose disease had progressed on previous therapies including platinum-based chemotherapy, immune checkpoint inhibitors, and targeted therapy (for patients with known actionable genomic alterations) received HER3-DXd 5.6 mg/kg intravenously once every 3 weeks. The primary end point was confirmed objective response rate (cORR).

RESULTS Forty-seven patients were treated with HER3-DXd (median treatment duration, 4.2 [range, 0.7-19.8] months). The cORR was 27.7% (95% CI, 15.6% to 42.6%), and the median duration of response was 8.1 (95% CI, 4.2 to not evaluable) months. The median progression-free survival was 5.5 (95% CI, 4.0 to 11.2) months, and the median overall survival was 15.2 (95% CI, 10.8 to 17.7) months. Similar efficacy was observed in patients with NSCLC harboring identified driver genomic alterations and in those without such genomic features. The rate of study drug discontinuation associated with treatment-emergent adverse events (TEAEs) was 12.8%. Study drug–related grade ≥3 TEAEs occurred in 51.1% of patients and were serious in 12.8% (none were associated with death). Adjudicated treatment-related interstitial lung disease occurred in five patients (10.6%; all grade 1 or 2).

CONCLUSION The previously reported efficacy and safety of HER3-DXd in heavily pretreated patients with *EGFR*-mutated NSCLC are also observed in those with other NSCLC subtypes and warrant further clinical evaluation.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

The standard of care for patients who have non–small cell lung cancer (NSCLC) without an actionable genomic alteration (AGA), as well as for those whose disease has progressed on first-line targeted therapy (eg, an epidermal growth factor receptor [EGFR] tyrosine kinase inhibitor [TKI] or anaplastic lymphoma kinase [ALK] inhibitor), is platinum-based chemotherapy (PBC) alone or in combination with other agents.[1] Such therapies provide a median progression-free survival (PFS) in the range of 6.8 to 8.8 months.[2-6] For treatments administered after the failure of PBC, responses are limited and transient, and the median PFS is in the range of 3.0 to 4.5 months.[7,8]

Expression of human EFGR 3 (HER3) has been reported in 83% of NSCLC tumors and is associated with metastatic progression.[9,10] HER3 expression has been implicated in

CONTEXT

Key Objective

To evaluate the efficacy of patritumab deruxtecan (HER3-DXd) in patients with advanced non–small cell lung cancer without common *EGFR*-activating mutations.

Knowledge Generated

HER3-DXd therapy demonstrated clinically meaningful efficacy across a broad range of tumor HER3 membrane expression in a heterogeneous group of previously treated patients. HER3-DXd showed efficacy and a tolerable safety profile irrespective of the presence of specific driver genomic alterations or genomic alterations associated with resistance to targeted drugs.

Relevance *(T.E. Stinchcombe)*

Patritumab deruxtecan demonstrated activity in a molecularly heterogeneous patient population that had received previous treatment. Larger, confirmatory studies are warranted.*

*Relevance statement written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

resistance to a variety of therapies, including targeted therapies for NSCLC. Patritumab deruxtecan (HER3-DXd; MK-1022) is an investigational HER3-directed antibody-drug conjugate (ADC) that is composed of a human immunoglobulin G1 monoclonal antibody to HER3 (patritumab) covalently linked via a stable tetrapeptide-based cleavable linker to a topoisomerase I inhibitor payload (MAAA-1181a, an exatecan derivative), with an approximately 8:1 drug-to-antibody ratio.[11-14] HER3-DXd binds to membrane HER3 and is internalized by the cell, where intracellular lysosomal enzymes typically upregulated in tumor cells cleave the tetrapeptide-based linker, freeing the cytotoxic payload to enter the nucleus and induce DNA damage and apoptosis.[9,11,15,16] Efflux from the cell of the membrane-permeable payload can exert a potential bystander antitumor effect in surrounding cells in the tumor microenvironment.[12,17]

We previously reported data from the ongoing phase I U31402-A-U102 (ClinicalTrials.gov identifier: NCT03260491) and phase II HERTHENA-Lung01 (ClinicalTrials.gov identifier: NCT04619004) trials showing the efficacy and safety of HER3-DXd in heavily pretreated patients with advanced *EGFR*-mutated NSCLC after disease progression on EGFR TKI therapy and PBC.[18-20] In these studies, HER3-DXd treatment provided durable antitumor activity. The median PFS was 6.4 (95% CI, 4.9 to 8.3) months and 5.5 (95% CI, 5.1 to 5.9) months in U31402-A-U102 and HERTHENA-Lung01, respectively; the median overall survival (OS) was 15.8 (95% CI, 10.8 to 21.5) months and 11.9 (95% CI, 11.2 to 13.1) months, respectively.[19,20] In both trials, HER3-DXd was associated with a manageable and tolerable safety profile.[18-20]

Here, we extend these observations and report the efficacy and safety of HER3-DXd therapy, as well as accompanying translational analyses, in patients with squamous or nonsquamous NSCLC with driver genomic alterations other than the common *EGFR*-activating mutations (Ex19del, L858R, L861Q, or G719X) or without identified driver genomic alterations. Enrolled patients in cohort 2 of study U31402-A-U102 had disease progression on PBC and, unless contraindicated, an anti–PD-[L]1 antibody–based therapy (Appendix Fig A1, online only).

METHODS

Study Design and Participants

The overall study design and methods for study U31402-A-U102 have been described previously.[18,19]

In brief, U31402-A-U102 is a global, open-label, multiple-dose, multipart, phase I study in adult patients with advanced NSCLC (Appendix Fig A1). Patients with squamous or nonsquamous NSCLC tumors without the common *EGFR*-activating Ex19del, L858R, L861Q, or G719X mutations (cohort 2) were enrolled at 14 sites in North America, Europe, and East Asia. Patients had disease progression on or after the most recent therapy. Prior therapies must have included ≥1 PBC regimen in the locally advanced or metastatic setting. Patients must have also received prior anti–PD-(L)1 antibody–based therapy unless contraindicated or refused by the patient; those with known AGAs must have received appropriate targeted therapy, if available. Patients with inactive or treated asymptomatic brain metastases were eligible. Patients were ineligible if they had any history of interstitial lung disease (ILD) or evidence of ILD on imaging at screening. An Eastern Cooperative Oncology Group performance status of 0 or 1 was required at screening. Patients were required to provide a pretreatment tumor biopsy taken after disease progression that occurred during or after the

patient's most recent prior therapy or an archival tumor biopsy if obtained within 6 months of study entry.

Patients received HER3-DXd 5.6 mg/kg intravenously (IV) once every 3 weeks on day 1 of each 21-day cycle. Tumor assessments were carried out every 6 weeks until week 24 on study, then every 12 weeks.

The study was approved by the institutional review board or ethics committee for each site and was conducted in compliance with the ethical principles of the Declaration of Helsinki, the International Council of Harmonization consolidated Guidelines for Good Clinical Practice, and applicable regulatory requirements. All patients provided written informed consent before participating in this study.

Biomarker Analyses

Tumor HER3 membrane expression was evaluated in formalin-fixed, paraffin-embedded tissue from the pretreatment tumor samples using immunohistochemistry (IHC).[19] HER3 IHC staining used an anti-HER3 recombinant rabbit monoclonal antibody (clone SP438; Ventana Medical Systems, Oro Valley, AZ).

Genomic alterations known to be oncogenic drivers or those associated with resistance to relevant targeted therapies were identified in circulating tumor DNA (ctDNA) from pretreatment blood samples using the approximately 500-gene GuardantOMNI assay (Guardant Health AMEA, Singapore). When available, information regarding identified tumor driver genomic alterations was also obtained from local testing results.

Objectives and End Points

The primary end point of confirmed objective response rate (ORR; complete response [CR] or partial response [PR], confirmed at ≥4 weeks) per RECIST version 1.1[21] was assessed by blinded independent central review (BICR).

Secondary end points were confirmed ORR by the investigator per RECIST 1.1; duration of response, PFS, disease control rate, time to response, and best percentage change from baseline in the sum of diameters of target lesions by BICR and by investigator; OS; and safety. Antidrug antibodies for HER3-DXd and the correlation of baseline HER3 expression with efficacy measures were exploratory end points.

Safety

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

ILD is considered an important identified risk with HER3-DXd, and potential incidents of ILD were reviewed by an independent central adjudication committee.

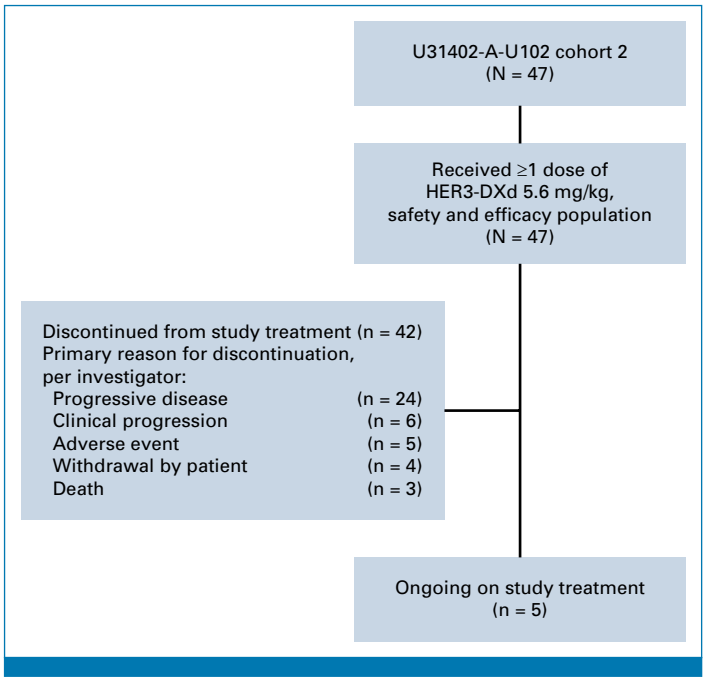

FIG 1. Flow diagram of patient disposition at data cutoff (January 28, 2022). HER3, human epidermal growth factor receptor 3.

TABLE 1. Patient Demographics and Clinical Characteristics at Baseline

Parameter	All Patients (N = 47)
Age at informed consent	
Median, years (range)	62 (29-79)
<65 years, No. (%)	28 (59.6)
≥65 years, No. (%)	19 (40.4)
Sex, No. (%)	
Male	22 (46.8)
Female	25 (53.2)
Race, No. (%)	
American Indian or Alaskan Native	0
Asian	25 (53.2)
African American	2 (4.3)
Native Hawaiian or other Pacific Islander	1 (2.1)
White	18 (38.3)
Other	1 (2.1)
Smoking history, No. (%)	
Never	16 (34.0)
Ever	31 (66.0)
Histology, No. (%)	
Adenocarcinoma	35 (74.5)
Squamous	8 (17.0)
Large cell	1 (2.1)
Other[a]	3 (6.4)
Identified driver genomic alterations, No. (%)[b]	
Any	21 (44.7)
EGFR Ex20ins	4 (8.5)
KRAS G12X	4 (8.5)
ROS1 fusion	3 (6.4)
ALK fusion	2 (4.3)
Other[c]	8 (17.0)
Tumor stage at study entry, No. (%)	
IIIA	1 (2.1)
IIIB	1 (2.1)
IIIC	0
IV	2 (4.3)
IVA	21 (44.7)
IVB	22 (46.8)
ECOG performance status, No. (%)	
0	16 (34.0)
1	31 (66.0)
History of CNS metastases, No. (%)	
Yes	15 (31.9)
No	32 (68.1)
Baseline lesion location by BICR, No. (%)	
Adrenal	1 (2.1)
Bone	2 (4.3)
Brain	8 (17.0)
Liver	10 (21.3)

(continued in next column)

TABLE 1. Patient Demographics and Clinical Characteristics at Baseline (continued)

Parameter	All Patients (N = 47)
Baseline SOD of target lesions by BICR	
Median, mm (range)	67.0 (18-205)
Time since initial NSCLC diagnosis	
Months, median (range)	26.3 (6.6-124.9)
Prior PBC, No. (%)	47 (100.0)
Prior immunotherapy, No. (%)	
Any	45 (95.7)
Anti–PD-1/anti–PD-L1	45 (95.7)
Anti-CTLA-4	1 (2.1)
Prior targeted therapy, No. (%)	
Any	9 (19.1)
Crizotinib	3 (6.4)
Mobocertinib	3 (6.4)
Alectinib	2 (4.3)
Entrectinib	2 (4.3)
Lorlatinib	2 (4.3)
Poziotinib	2 (4.3)
Brigatinib	1 (2.1)
Ceritinib	1 (2.1)
Selpercatinib	1 (2.1)
Prior lines of systemic therapy in the locally advanced or metastatic setting	
No., median (range)	3 (1-8)
1, No. (%)	8 (17.0)
2, No. (%)	7 (14.9)
≥3, No. (%)	32 (68.1)
Time since last prior therapy	
Months, median (range)	1.7 (0.2-16.9)

Abbreviations: AMP, amplification; BICR, blinded independent central review; ctDNA, circulating tumor DNA; CTLA-4, cytotoxic T-lymphocyte protein 4; ECOG, Eastern Cooperative Oncology Group; GTPase; NSCLC, non–small cell lung cancer; PBC, platinum-based chemotherapy; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1; SOD, sum of diameters.

[a]Adenosquamous, neuroendocrine, NSCLC with neuroendocrine features (n = 1 each).

[b]Identified in ctDNA from blood or local testing data when available.

[c]*EGFR* L861R, *EGFR* T751_I759delinsN, *ERBB2* A775_G776insYVMA, *ERBB2* D769Y, *NRAS* Q61L, *RET* fusion, *MET* AMP, *ERBB2* AMP.

Statistical Analysis

The 95% CIs for response end points were calculated using the Clopper-Pearson method; time-to-event end points, including duration of response, PFS, and OS, were estimated using the Kaplan-Meier method; and 95% CIs for the median were calculated using the Brookmeyer and Crowley method.

Additional analyses of response and efficacy outcomes were performed in the subsets of patients with tumors with and

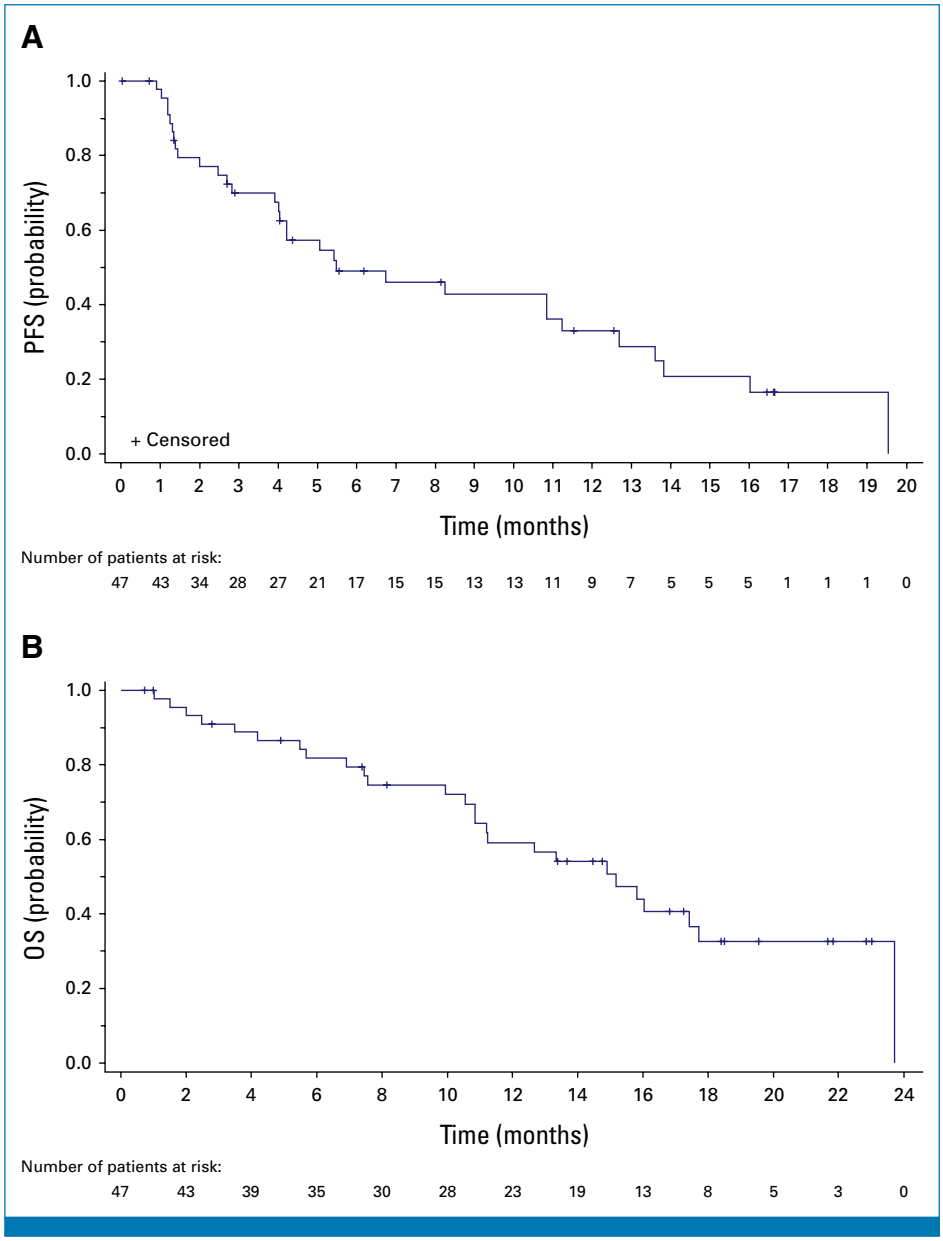

FIG 2. Kaplan-Meier plots of (A) PFS by BICR per RECIST 1.1 and (B) overall survival. BICR, blinded independent central review; OS, overall survival; PFS, progression-free survival.

without identified driver genomic alterations (inclusion of patients in the subset with identified tumor driver genomic alterations did not require those alterations to be actionable with available targeted therapies).

RESULTS

Patient Disposition, Demographics, and Disease Characteristics

Between August 23, 2019, and December 4, 2020, 47 patients with squamous or nonsquamous NSCLC with driver genomic alterations other than the common *EGFR*-activating mutations or without identified driver genomic alterations were enrolled in U31402-A-U102 cohort 2 and treated with HER3-DXd 5.6 mg/kg IV once every 3 weeks (Fig 1). At the time of data cutoff, treatment was ongoing for 5 (10.6%) patients, and 42 (89.4%) had discontinued treatment. Treatment discontinuations were primarily due to progressive disease or clinical progression (totaling 63.8% [30/47] of patients); AEs were the primary reason for treatment discontinuation in 10.6% (5/47) of patients. The median treatment duration was 4.2 (range, 0.7-19.8) months, and the median study follow-up duration was 19.7 (range, 13.8-29.2) months.

Patients had a median age of 62 years; 53.2% (25/47) were female, and 34.0% (16/47) were never-smokers (Table 1). The most common histological type of NSCLC was

TABLE 2. Efficacy Summary

Outcome (response-based measures by BICR per RECIST 1.1)	All Patients (N = 47)	By Presence of Identified Driver Genomic Alterations	
		With (n = 21)	Without (n = 26)
Confirmed ORR, % (95% CI)	27.7 (15.6 to 42.6)	28.6 (11.3 to 52.2)	26.9 (11.6 to 47.8)
Complete response, No. (%)	1 (2.1)	0	1 (3.8)
Partial response, No. (%)	12 (25.5)	6 (28.6)	6 (23.1)
Stable disease/non-CR/non-PD, No. (%)	22 (46.8)	10 (47.6)	12 (46.2)
Progressive disease, No. (%)	8 (17.0)	4 (19.0)	4 (15.4)
Not evaluable, No. (%)	4 (8.5)	1 (4.8)	3 (11.5)
Disease control rate, % (95% CI)	74.5 (59.7 to 86.1)	76.2 (52.8 to 91.8)	73.1 (52.2 to 88.4)
Time to response, months, median (range)	2.6 (1.2-6.0)	2.8 (1.3-4.6)	2.1 (1.2-6.0)
Duration of response, months, median (95% CI)	8.1 (4.2 to NE)	9.4 (4.2 to NE)	9.6 (1.6 to NE)
DOR ≥6 months, No./n (%)	7/13 (53.8)	4/6 (66.7)	3/7 (42.9)
Progression-free survival, months, median (95% CI)	5.5 (4.0 to 11.2)	10.8 (2.8 to 16.0)	4.2 (2.5 to 10.8)
Overall survival, months, median (95% CI)	15.2 (10.8 to 17.7)	15.8 (10.8 to NE)	15.2 (5.5 to NE)

Abbreviations: BICR, blinded independent central review; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease.

adenocarcinoma (74.5% [35/47]), followed by squamous cell histology (17.0% [8/47]; Appendix Fig A2). Forty-five of 47 patients had genomic alteration data available from the GuardantOMNI ctDNA assays, and 14 of 47 patients had genomic alterations reported from local testing. Known driver genomic alterations were identified in the tumors of 44.7% (21/47) of patients, and 55.3% (26/47) of patients did not have tumors with an identified driver genomic alteration (Appendix Fig A2). Brain and liver metastases by BICR were observed at baseline in 17.0% (8/47) and 21.3% (10/47) of patients, respectively. A history of CNS metastases was reported in 31.9% (15/47) of patients. Prior brain radiotherapy had been received by 17.0% (8/47) of patients (including four of the eight patients with brain metastases at baseline).

The median number of prior systemic therapies (in the locally advanced/metastatic setting) was 3 (range, 1-8), and the median time since the last prior therapy was 1.7 (range, 0.2-16.9) months. All patients had prior PBC, and 95.7% (45/47) had prior immunotherapy. Prior targeted therapy (approved or investigational) was received by 19.1% (9/47) of patients, all of whom had NSCLC with identified driver genomic alterations (*EGFR* Ex20ins, n = 4; *ALK* fusion and *ROS1* fusion, n = 2 each; and *RET* fusion, n = 1).

Efficacy

In the overall population enrolled into cohort 2, the confirmed ORR (by BICR) was 27.7% (N = 47; 95% CI, 15.6% to 42.6%; Table 2), and the median duration of response was 8.1 (95% CI, 4.2 to not evaluable) months. The median PFS by BICR was 5.5 (95% CI, 4.0 to 11.2) months, and the median OS was 15.2 (95% CI, 10.8 to 17.7) months (Fig 2, Table 2). Most patients (38 of 44 with available baseline and postbaseline target lesion evaluations) had a reduction in the sum of diameters of target lesions by BICR (Fig 3A).

Biomarker-Associated Subgroup Analyses of Efficacy

The efficacy of HER3-DXd in the subsets of patients with tumors with or without identified driver genomic alterations was similar; in these subsets, the cORR was 28.6% (95% CI, 11.3% to 52.2%) and 26.9% (95% CI, 11.6% to 47.8%), respectively. Durable responses were observed in the subset of patients with tumors with identified driver genomic alterations (Table 2, Figs 3B and 4). Three of five patients whose tumors had *KRAS* or *NRAS* mutations had confirmed responses (all PRs). Four patients with *EGFR* Ex20ins mutations all had a confirmed best overall response (BOR) of SD (Figs 3B and 4). Durable responses were also observed in the subset of patients with tumors without identified driver genomic alterations (Table 2, Figs 3C and 4).

Among the 45 patients who had evaluable tumor tissue for HER3 expression, the median pretreatment tumor HER3 membrane IHC H-score was 156 (range, 0-285). Among patients with a confirmed BOR by BICR of CR or PR, pretreatment tumor HER3 membrane H-score was in the range of 90-285 (median, 195; Appendix Fig A3).

The median pretreatment tumor HER3 membrane H-score was higher for tumors with identified driver genomic alterations (190 [range, 65-285]; n = 20) than for those without identified driver genomic alterations (107 [range, 0-234]; n = 25). The efficacy of HER3-DXd in the subsets of patients with tumors with or without identified driver mutations was similar; confirmed ORRs were 28.6% (95% CI, 11.3% to 52.2%) and 26.9% (95% CI, 11.6% to 47.8%), respectively (Table 2).

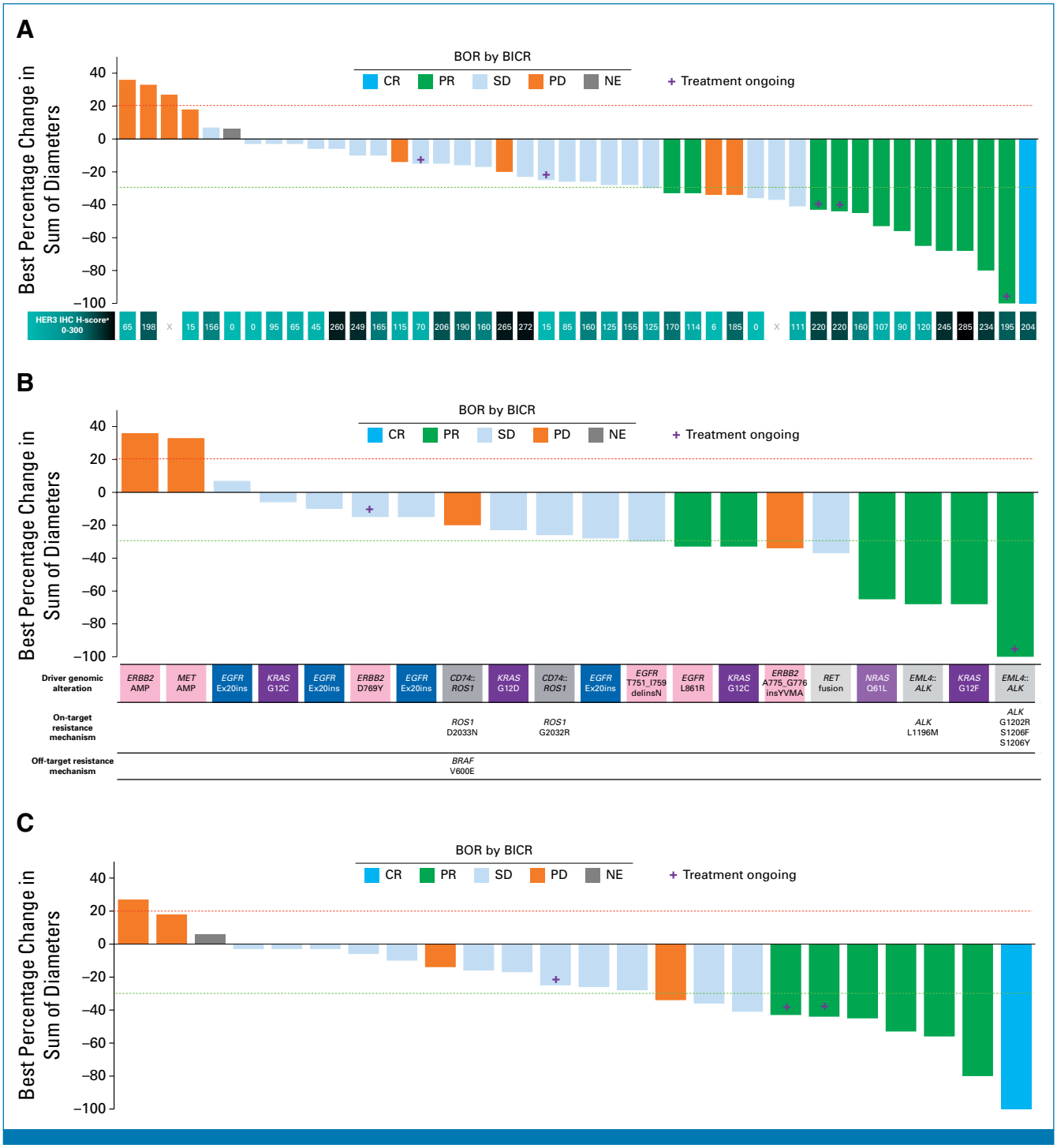

FIG 3. Waterfall plot of best percentage change in the sum of diameters of target lesions from baseline for (A) all patients and for patients (B) with or (C) without identified driver genomic alterations. Below the waterfall plot for all patients, pretreatment tumor HER3 membrane IHC H-score is shown as a heat map; below the waterfall plot for patients with driver genomic alterations prior to treatment with HER3-DXd, identified genomic alterations are shown for each patient. Forty-four patients had evaluable target lesion measurements at both baseline and post-baseline and are included (20 with identified driver genomic alterations and 24 without). [a]Pretreatment (within 6 months before baseline) HER3 membrane IHC H-score. AMP, amplification; BICR, blinded independent central review; BOR, best overall response; CR, complete response; HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

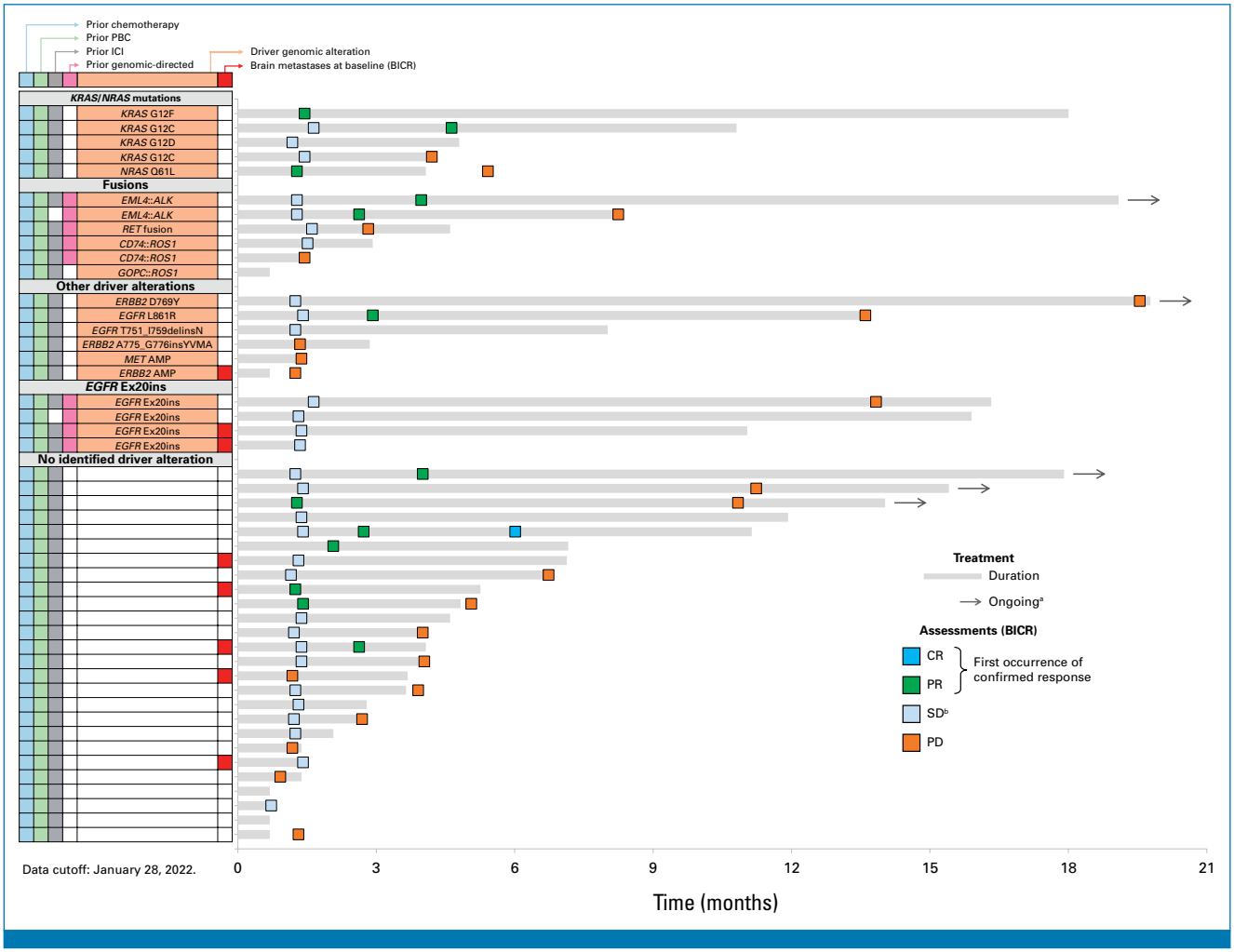

FIG 4. Swimmer plot by identified driver genomic alteration showing treatment duration, tumor assessments, prior therapies, and baseline brain metastases for all patients (N = 47). [a]The protocol allowed treatment after PD if the investigator felt the patient was deriving benefit. [b]Including unconfirmed PR. AMP, amplification; BICR, blinded independent central review; CR, complete response; ICI, immune checkpoint inhibitor; PBC, platinum-based chemotherapy; PD, progressive disease; PR, partial response; SD, stable disease.

Genomic alterations associated with acquired resistance to targeted therapies were found in the pretreatment samples of four patients: Two with *ALK* fusions (*ALK* L1196M and *ALK* G1202R S1206F S1206Y, both with a confirmed BOR of PR) and two with *ROS1* fusions (*ROS1* G2032R with a confirmed BOR of SD and *ROS1* D2033N, progressive disease as BOR in a patient whose tumor also had a *BRAF* V600E mutation [reported to be an off-target mechanism of resistance to ALK/ROS1 TKIs[22,23]]; Fig 3B).

Safety

The safety set comprised patients treated with ≥1 dose of HER3-DXd (N = 47; Table 3). The median treatment duration was 4.2 (range, 0.7-19.8) months, and the median relative dose intensity was 96.2% (range, 63.4%-106.5%).

All patients experienced ≥1 treatment-emergent adverse event (TEAE); the most common were nausea (66.0% [31/47]), anemia (51.1% [24/47]), and decreased appetite (51.1% [24/47]). Grade ≥3 TEAEs occurred in 72.3% of patients (34/47); the most common were neutropenia (25.5% [12/47]), fatigue (17.0% [8/47]), and thrombocytopenia (14.9% [7/47]). Overall, 12.8% (6/47) of patients had treatment discontinuations associated with TEAEs, and 23.4% (11/47) had dose reductions associated with TEAEs (Table 3). TEAEs associated with death occurred in 14.9% (7/47) of patients; none were considered study drug related by the treating investigator. Five patients had ILD (all drug related) as determined by an independent adjudication committee (one grade 1 event and four grade 2 events). The median time to onset of adjudicated treatment-related ILD was 140 (range, 43-331) days (Appendix Table A1).

DISCUSSION

In this phase I trial, HER3-DXd showed efficacy beyond NSCLC with common *EGFR*-activating mutations to include

TABLE 3. Safety Summary

Parameter	All Patients (N = 47)
Any TEAE, No. (%)	47 (100)
CTCAE grade ≥3	34 (72.3)
Serious TEAE	19 (40.4)
Associated with an outcome of death[a]	7 (14.9)
Associated with treatment discontinuation	6 (12.8)
Associated with dose interruption	23 (48.9)
Associated with dose reduction	11 (23.4)
Study drug–related TEAE, No. (%)	47 (100)
CTCAE grade ≥3	24 (51.1)
Serious TEAE	6 (12.8)
CTCAE grade ≥3	6 (12.8)
Associated with an outcome of death	0
Grade ≥3 TEAEs occurring in ≥10% of patients, No. (%)	
Neutropenia (grouped PT)[b]	12 (25.5)
Fatigue	8 (17.0)
Thrombocytopenia (grouped PT)[c]	7 (14.9)
Hypokalemia	6 (12.8)
Anemia (grouped PT)[d]	5 (10.6)
Leukopenia (grouped PT)[e]	5 (10.6)
Pneumonia	5 (10.6)
Treatment duration, months, median (range)	4.2 (0.7-19.8)
Dose intensity, mg/kg/cycle, median (range)	5.4 (3.6-6.0)
Relative dose intensity, %, median (range)	96.2 (63.4-106.5)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; PT, preferred term; TEAE, treatment-emergent adverse event.
[a]Disease progression (n = 2); pneumonia (n = 2); and COVID-19, malignant neoplasm progression, and physical deconditioning (n = 1 each).
[b]Neutropenia, neutrophil count decreased.
[c]Platelet count decreased, thrombocytopenia.
[d]Anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[e]Leukopenia, white blood cell count decreased.

NSCLC with other identified driver genomic alterations and without identified driver genomic alterations. HER3-DXd also showed efficacy in tumors with additional resistance-associated genomic alterations. The standard of care for patients with advanced NSCLC following disease progression on PBC and immunotherapy (and targeted therapy, when appropriate) is chemotherapy, such as docetaxel with or without antiangiogenic therapy. The clinical benefit of available therapies is limited; in phase III trials, docetaxel monotherapy was associated with a median PFS of 3.0-4.0 months and a median OS of 9.1-9.6 months.[7,8] With docetaxel plus ramucirumab, the median PFS was 4.5 months, and the median OS was 10.5 months.[7] In this study, HER3-DXd treatment resulted in a median PFS of 5.5 months and a median OS of 15.2 months in patients with NSCLC harboring identified driver genomic alterations other than common *EGFR*-activating mutations and in those without such identified genomic features. Note that the number of prior therapies was greater in this phase I study population than in the populations of the phase III trials of docetaxel with or without ramucirumab, and therefore, comparisons are tentative. Efficacy was observed across a broad range of pretreatment tumor HER3 membrane expression levels and in patients with brain metastasis at baseline.

In the previously reported cohorts of the phase I U31402-A-U102 and phase II HERTHENA-Lung01 studies, HER3-DXd showed clinically meaningful efficacy in patients with previously treated *EGFR*-mutated NSCLC, independent of the acquired resistance mechanisms to prior EGFR TKI treatment (confirmed ORR, 29.8%-39.2%).[18-20] Here, HER3-DXd showed efficacy and a tolerable safety profile irrespective of the presence of specific driver genomic alterations or genomic alterations associated with resistance to targeted drugs.

In this study, confirmed responses by BICR were observed among the five patients with *KRAS*/*NRAS*-mutated NSCLC (Figs 3B and 4). None of these patients, including 2 with *KRAS* G12C–mutated NSCLC, had received prior targeted therapy. In addition, treatment with a KRAS G12C inhibitor has previously been shown to increase HER3 expression in vitro.[24] Based on these preliminary findings, the U31402-A-U102 trial has been expanded to include patients with *KRAS* G12C–mutated NSCLC who have had ≥2 prior systemic regimens (including a *KRAS* G12C–targeted therapy) and who have experienced disease progression on previous therapy (Appendix Fig A1).

Although the median of pretreatment tumor HER3 membrane IHC H-scores was lower in the subset of patients with tumors without versus with identified driver genomic alterations, the efficacy of HER3-DXd was similar in both groups. Because of the small subgroup sizes, the difference in HER3 expression should be interpreted with caution. HER3-DXd efficacy across the broad range of tumor HER3 expression was observed previously in patients with *EGFR*-mutated NSCLC. The correlation between the efficacy of HER3-DXd and tumor HER3 expression awaits further evaluation, and additional biomarker studies are needed to help define which patients are most likely to benefit from HER3-DXd.

The overall safety profile of HER3-DXd was manageable and tolerable, similar to that seen in patients with *EGFR*-mutated NSCLC[18-20] and in studies of HER3-DXd in other tumor types.[25] This study saw a low rate of study drug discontinuation associated with AEs. ILD is an important identified risk for HER3-DXd. In this study, in which 95.7% of patients received prior anti–PD-(L)1, adjudicated treatment-related ILD occurred in 10.6% (5/47; all cases were mild in severity [grade 1 or 2]). Guidelines for early detection and management are in place to minimize the risk of ILD and to prevent serious outcomes (Appendix Table A2).

In conclusion, in this heterogeneous group of previously treated patients, HER3-DXd therapy demonstrated clinically meaningful efficacy across a broad range of tumor HER3 membrane expression. This observed efficacy, together with the tolerable safety profile, warrants further clinical evaluation. Additional studies of HER3-DXd are planned in patients with NSCLC with and without common *EGFR*-activating mutations, both as monotherapy and in drug combinations (ClinicalTrials.gov identifiers: NCT03260491, NCT04676477).

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APPENDIX

TABLE A1. Summary of Interstitial Lung Disease Adjudication

	CTCAE Grade by Adjudication Committee/Investigator					
Patient Subset	1	2	3	4	5	All Grade
HER3-DXd 5.6 mg/kg (once every 3 weeks), safety set (N = 47)						
Patients with potential ILD events (investigator-reported grade)	1	4	0	0	0	5
Not adjudicated as of reporting	0	0	0	0	0	0
Adjudicated as not ILD (investigator-reported grade)	0	0	0	0	0	0
Adjudicated as ILD (committee-adjudicated grade)[a]	1	4	0	0	0	5
Adjudicated as drug-related ILD	1	4	0	0	0	5
Adjudicated as not drug-related ILD	0	0	0	0	0	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; HER3-DXd, patritumab deruxtecan; ILD, interstitial lung disease.
[a]Median time to onset of adjudicated ILD event (all drug related) was 140 (range, 43-331) days.

TABLE A2. Protocol Recommendations for Management of Suspected Interstitial Lung Disease

Worst Toxicity Grade Per CTCAE v5.0	Schedule Modification for HER3-DXd
Grade 1	The administration of HER3-DXd must be delayed. HER3-DXd can be restarted only if the event is fully resolved to grade 0: If resolved in ≤28 days from day of onset, maintain dose (once every 3 weeks) If resolved in >28 days from day of onset, reduce dose by 1 level (once every 3 weeks) Toxicity management: Monitor and closely follow-up in 2-7 days for onset of clinical symptoms and pulse oximetry Consider follow-up imaging in 1-2 weeks (or as clinically indicated) Consider starting systemic steroids (eg, ≥0.5 mg/kg total daily dose of prednisone or equivalent) until improvement, followed by gradual taper over ≥4 weeks If diagnostic observations worsen despite initiation of corticosteroids, follow grade 2 guidelines (if patient is asymptomatic, they should still be considered as having toxicity grade 1 even if steroid treatment is given)
Grade 2	Permanently discontinue patient from HER3-DXd Toxicity management: Promptly start systemic steroids (eg, ≥1 mg/kg total daily dose of prednisone or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT scan findings, followed by gradual taper over ≥4 weeks Monitor symptoms closely Reimage as clinically indicated If worsening or no improvement in clinical or diagnostic observations in 5 days: Consider increasing dose of steroids (eg, 2 mg/kg total daily dose of prednisone or equivalent); administration may be switched to IV (eg, methylprednisolone) Reconsider additional workup for alternative etiologies Escalate care as clinically indicated
Grade 3 or 4	Permanently discontinue patient from HER3-DXd Toxicity management: Hospitalization required Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1,000 mg total daily dose for 3 days), followed by ≥1.0 mg/kg total daily dose of prednisone (or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT scan findings, followed by gradual taper over ≥4 weeks Reimage as clinically indicated If still no improvement within 3-5 days: Reconsider additional workup for alternative etiologies Consider other immunosuppressants and/or treat per local practice

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; CT, computed tomography; HER3-DXd, patritumab deruxtecan; IV, intravenous.

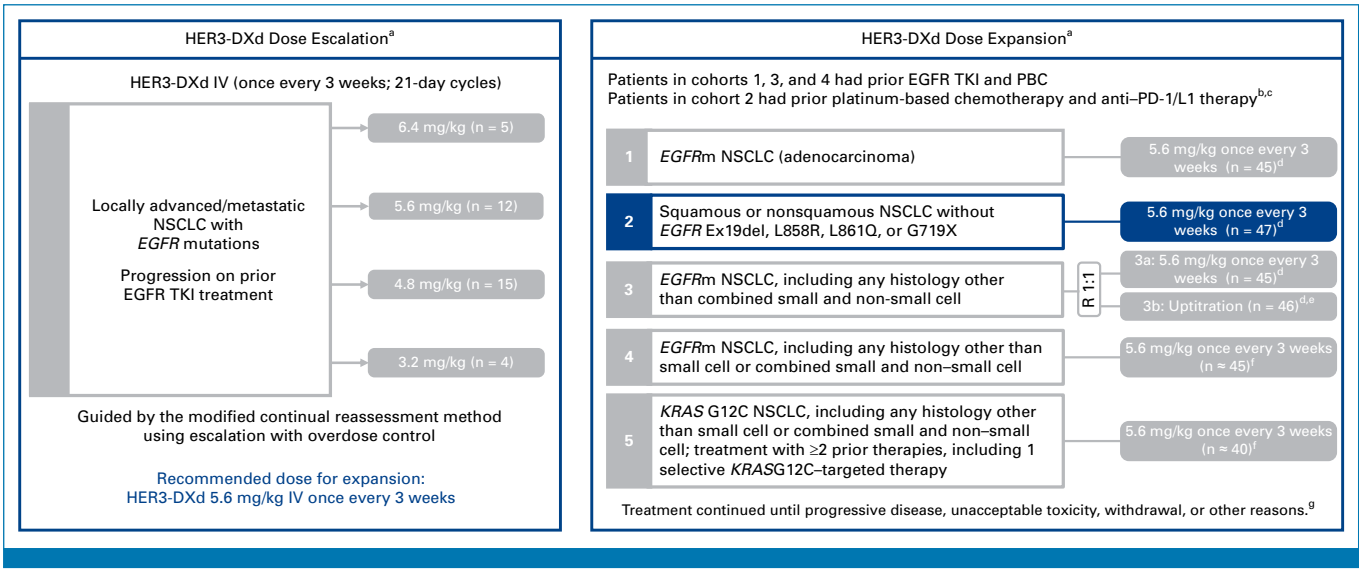

FIG A1. Study design. [a]Patients with stable brain metastases were permitted to enroll. A tumor biopsy was required before study entry, but patients were not selected for inclusion based on measurement of HER3 expression. [b]Unless unable or unwilling to receive immunotherapy. [c]Patients with known targetable genomic alterations (other than *EGFR* mutations), for which therapy was available, must have had ≥1 genomic-directed therapy. [d]Drug product manufactured by the clinical manufacturing sites. [e]Uptitration regimen (21-day cycles; all doses once every 3 weeks): cycle 1, 3.2 mg/kg; cycle 2, 4.8 mg/kg; cycle 3 and subsequent cycles, 6.4 mg/kg. [f]Drug product manufactured by the commercial manufacturing sites. [g]Other reasons for discontinuation may include investigator discretion, death, pregnancy, study termination by sponsor, and loss to follow-up. EGFR, epidermal growth factor receptor; HER3-DXd, patritumab deruxtecan; NSCLC, non–small cell lung cancer; PBC, platinum-based chemotherapy; RDE, recommended dose for expansion; TKI, tyrosine kinase inhibitor.

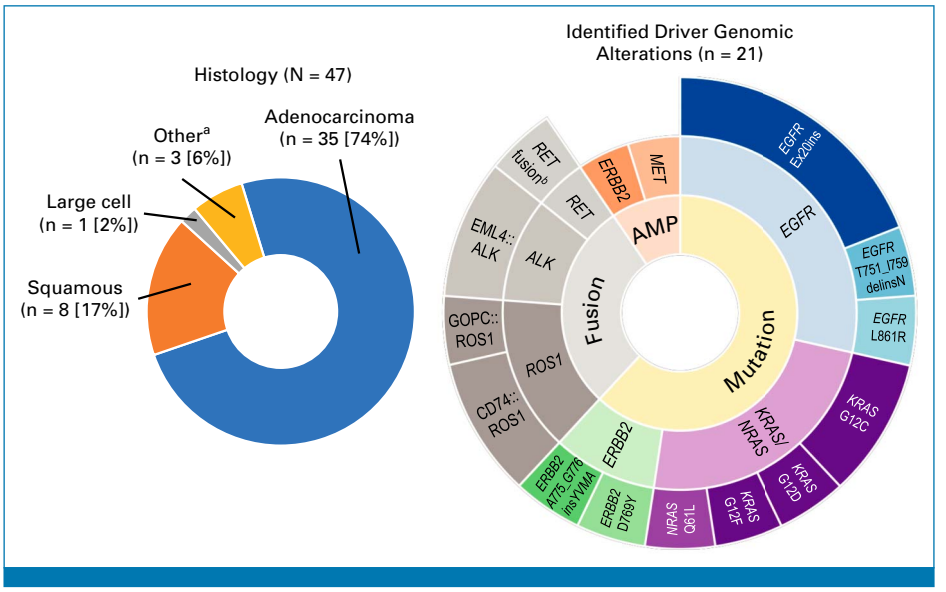

FIG A2. Histology and identified driver genomic alterations. [a]Adenosquamous, neuroendocrine, NSCLC with neuroendocrine features (n = 1 each). [b]RET rearrangement was identified in the case report form. Information on the partner gene was not obtained. EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer.

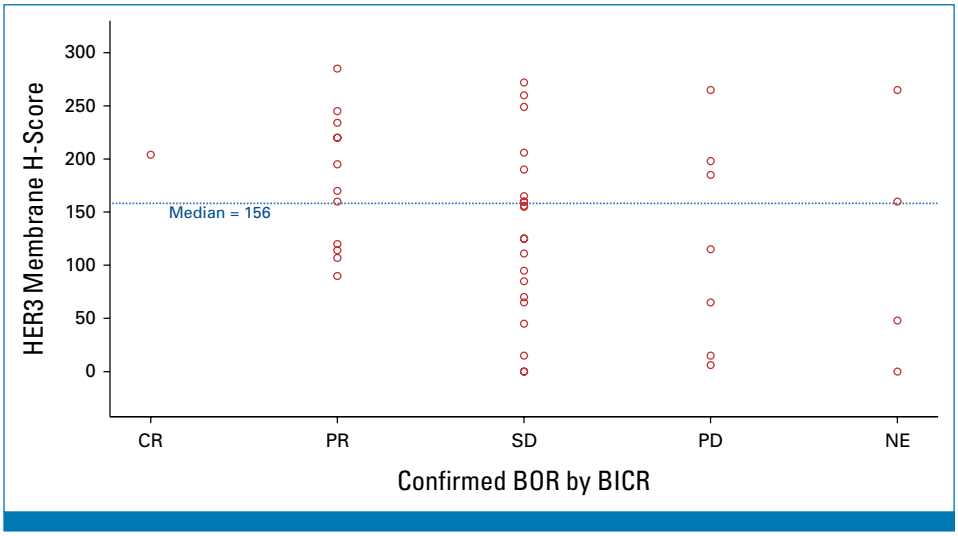

FIG A3. Association of baseline tumor HER3 membrane H-score (in evaluable patients) with confirmed BOR by BICR. Forty-five patients had evaluable samples for tumor HER3 expression. Baseline was the sample on or before the first dose date and not earlier than 180 days before the first dose date. Highest HER3 membrane H-score was used if multiple records were available. BICR, blinded independent central review; BOR, best overall response; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.