HER3-DXd in EGFR TKI-resistant EGFR-mutated NSCLC
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Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, EGFR-Mutated Non-Small Cell Lung Cancer

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ABSTRACT (150/150 words)
HER3 is expressed in the majority of EGFR-mutated lung cancers but is not a known mechanism of resistance to EGFR inhibitors. HER3-DXd is an antibody drug conjugate consisting of a HER3 antibody attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. This phase 1, dose escalation/expansion study included patients with locally advanced or metastatic EGFR-mutated NSCLC with prior EGFR TKI therapy. Among 57 patients receiving HER3-DXd 5.6 mg/kg IV Q3W, the confirmed ORR by BICR (RECIST v1.1) was 39% (95% CI, 26.0-52.4), and median PFS was 8.2 (4.4-8.3) months. Responses were observed in patients with known and unknown EGFR TKI resistance mechanisms. Clinical activity was observed across a broad range of HER3 membrane expression. The most common grade ≥3 TEAE were hematologic toxicities. HER3-DXd has clinical activity in EGFR TKI-resistant cancers independent of resistance mechanisms, providing an approach to treating a broad range of drug-resistant cancers.

STATEMENT OF SIGNIFICANCE (49/50 words)
In metastatic EGFR-mutated NSCLC, after disease progression on EGFR TKI therapy, treatment approaches include genotype-directed therapy targeting a known resistance mechanism or chemotherapy. HER3-DXd demonstrated clinical activity spanning known and unknown EGFR TKI resistance mechanisms. HER3-DXd could present a future treatment option agnostic to the EGFR TKI resistance mechanism.
INTRODUCTION

For a subset of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), initial and subsequent therapy is guided by the identification of oncogenic driver mutations. Approximately 10 to 15% of patients with NSCLC in the United States and Europe and 30 to 40% of those in Asia have an EGFR-activating mutation (termed EGFR-mutated) (1). In these patients, EGFR-targeted tyrosine kinase inhibitors (TKI) result in high response rates (objective response rate [ORR], 76%-80%) (2) and can provide extended disease control (3). Third-generation EGFR TKIs, such as osimertinib, overcome some resistance mechanisms and have been shown to confer improved overall survival (OS) compared with that of first-generation EGFR TKIs (median OS, 38.6 vs 31.8 months (4)); however, relapse is typical with the development of resistance to EGFR TKI treatment (5-7). Mechanisms associated with EGFR TKI resistance are diverse and include EGFR, MET, PIK3CA, or BRAF genomic alterations, among other resistance mechanisms (7,8); alterations commonly associated with resistance to osimertinib are the EGFR C797S mutation and amplifications of HER2 or MET (8-10). However, a significant portion of patients who develop clinical EGFR TKI resistance have tumor genomic alterations associated with EGFR TKI resistance that are yet undefined (11).

After disease progression on EGFR TKI therapy (which may include sequential EGFR TKIs), patients are commonly treated with chemotherapy or investigational genotype-directed therapies targeting an identified resistance mechanism (eg, MET amplification), if known. Several studies have reported successful treatment (response rates, 30%-47%) of patients with MET amplification as an EGFR TKI resistance mechanism with a combination of an EGFR TKI and MET TKI (12,13). The recent CHRYSALIS study combined the EGFR-MET bispecific antibody amivantamab with the third-generation EGFR TKI lazertinib in patients with EGFR-mutated NSCLC: the ORR was 40% in patients with disease progression on platinum-based chemotherapy (14) and 36% in chemotherapy-naive patients with disease progression on osimertinib (median progression-free survival [PFS] was 4.9 months) (15). For platinum-based chemotherapy in EGFR-mutated NSCLC following disease progression on first-generation EGFR TKI, response rates of 25% to 44% have been reported, with median PFS of 2.7 to 6.4 months and a median OS of 8.1 to 19.2 months (16). Salvage therapies after EGFR TKI and platinum-based chemotherapy have limited efficacy (median PFS, 2.8-3.2 months; median OS, 7.5-10.6 months) (17). Given that resistance mechanisms to EGFR TKIs are diverse and that the efficacy of chemotherapy is limited, there is a need to develop novel treatment approaches...
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for previously treated EGFR-mutated NSCLC that provide salvage therapy across a broad spectrum of resistance-associated genomic alterations.

Receptor tyrosine-protein kinase erbB-3 (HER3) is expressed across a variety of malignant solid tumors and has been found in 83% of primary NSCLC tumors (18,19). HER3 overexpression is associated with metastatic progression and decreased relapse-free survival in patients with NSCLC (19). EGFR-mutated NSCLC is associated with higher expression of HER3 compared with EGFR wild-type NSCLC (20). Although increases in HER3 expression have been observed in cell lines that have developed acquired resistance to an EGFR TKI in vitro (21), genomic alterations in HER3 are not known to constitute a mechanism of resistance to EGFR TKI in EGFR-mutated NSCLC. Given the broad overexpression of HER3 in NSCLC, this membrane protein provides an attractive molecular target for the treatment of advanced EGFR-mutated NSCLC.

Antibody drug conjugates (ADCs) are a class of cancer therapy in which antibodies specific for tumor-associated antigens are used to selectively target the delivery of cytotoxic drugs (22). Patritumab deruxtecan (U3-1402, HER3-DXd) is a novel, investigational, HER3-directed ADC composed of a human immunoglobulin G1 monoclonal antibody to HER3 (patritumab) covalently linked to a topoisomerase I inhibitor payload (MAAA-1181a, an exatecan derivative) via a tetrapeptide-based cleavable linker with a drug-to-antibody ratio of approximately 8 (23-26). After trafficking of the ADC to the lysosome, the linker is cleaved by lysosomal enzymes that are upregulated in tumor cells, allowing the cytotoxic payload to be released and to enter the nucleus, leading to cell death (21,23,26,27). The payload is cell membrane permeable, which enables a bystander antitumor effect resulting in elimination of both target and surrounding tumor cells (25,28). An ADC using the same linker-payload technology but directed against HER2 (trastuzumab deruxtecan [T-DXd]) was recently approved for the treatment of HER2+ metastatic breast and gastric cancers (29,30).

The antitumor activity of HER3-DXd was shown in multiple solid tumor murine xenograft models, including EGFR-mutated NSCLC patient-derived xenograft models with known resistance to EGFR TKI therapy (31). On the basis of these nonclinical data, a phase 1, dose escalation/expansion study was initiated, and patients with locally advanced or metastatic NSCLC were enrolled (study U31402-A-U102; clinicaltrials.gov NCT03260491; EudraCT 2017-000543-41; JapicCTI 194868). Here, we report the safety, clinical activity, biomarker analyses,
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and pharmacokinetics of HER3-DXd in patients with advanced or metastatic EGFR-mutated NSCLC treated in this study.
RESULTS

U31402-A-U102 is a phase 1, global, multicenter, dose escalation and dose expansion study evaluating HER3-DXd in patients with locally advanced or metastatic NSCLC, including patients with NSCLC harboring an *EGFR* activating mutation and prior EGFR TKI therapy. The dose escalation part enrolled 36 patients with *EGFR*-mutated NSCLC (adenocarcinoma) that had acquired resistance to at least 1 EGFR TKI; the patients were treated in 1 of 4 dose groups (intravenous [IV] Q3W): 3.2 mg/kg (N=4), 4.8 mg/kg (N=15), 5.6 mg/kg (N=12), and 6.4 mg/kg (N=5) (*Supplementary Figure S1*). In the dose escalation part, the recommended dose for expansion (RDE) of HER3-DXd was determined to be 5.6 mg/kg IV Q3W. Cohort 1 of the dose expansion part enrolled 45 patients with *EGFR*-mutated NSCLC (adenocarcinoma), prior EGFR TKI treatment, and prior platinum-based chemotherapy, who all received a dose of 5.6 mg/kg IV Q3W. Safety assessments include data for all patients in the dose escalation and dose expansion parts (N=81); efficacy measures are presented for the pooled population of patients who received HER3-DXd 5.6 mg/kg (N=57) (*Supplementary Figure S1*). Safety and efficacy data for each dose group in the dose escalation part are presented in *Supplementary Tables S1, S2, and S3*. At the data cutoff date (September 24, 2020), 22% of all patients (18/81) treated were continuing study treatment. Data for dose expansion Cohort 2 (squamous or nonsquamous NSCLC without *EGFR* activating mutations) and Cohort 3 (squamous or nonsquamous *EGFR*-mutated NSCLC with any histology other than combined small and non-small cell; uptitration study) will be presented in the future.

**Patient Demographics and Baseline Characteristics**

For dose escalation and dose expansion Cohort 1, reported here, study eligibility criteria required that all patients had advanced or metastatic *EGFR*-mutated NSCLC with adenocarcinoma histology. Fifty-three percent of enrolled patients (43/81) had a history of stable central nervous system (CNS) metastases, and 19% of patients (15/81) had received prior treatment for CNS metastases (*Table 1*). Patients had a median of 4 (range, 1-9) prior lines of systemic therapy for locally advanced or metastatic NSCLC (*Table 1*). All patients had been previously treated with an EGFR TKI, with 89% of patients (72/81) having received prior osimertinib, and 80% of patients (65/81) having received prior platinum-based chemotherapy (*Table 1*).
Genomic alterations known to be associated with EGFR TKI resistance were identified in 78% of patients (62/80) (identified in assays of tumor tissue or circulating tumor DNA [ctDNA] in blood collected prior to treatment with HER3-DXd for 80 of 81 patients or identified by local testing as captured by electronic case report forms). The most commonly occurring genomic alterations were additional mutations in \textit{EGFR} (61 instances, including T790M [28 instances] and C797X [12 instances]), mutations in \textit{PIK3CA} (17 instances), and mutations in \textit{KRAS} (7 instances). There were 24 instances of amplification (including 10 instances of EGFR amp) and 5 instances of fusion.

\textbf{Dose Determination and Safety}

Among the 36 patients in the dose escalation part, 5 patients experienced dose-limiting toxicities: 1 patient in the 5.6 mg/kg dose group experienced grade 3 febrile neutropenia and grade 4 platelet count decreased; 1 patient in the 4.8 mg/kg dose group experienced grade 3 neutrophil count decreased, grade 4 platelet count decreased and white blood cell count decreased; and 3 patients in the 6.4 mg/kg dose group experienced grade 4 platelet count decreased. Both the maximum tolerated dose and the RDE were determined to be 5.6 mg/kg.

In the combined dose escalation and dose expansion parts, a total of 81 patients received ≥1 dose of HER3-DXd and were included in the safety analysis. The median treatment duration was 5.7 (range, 0.7-28.3) months (\textbf{Supplementary Table S1}; in the pooled group of patients who were treated with HER3-DXd at 5.6 mg/kg IV Q3W [N=57], the median treatment duration was 5.5 months [range, 0.7-18.6 months]). All 81 patients had at least 1 treatment-emergent adverse event (TEAE) (\textbf{Table 2}), with the most common (≥50%) being fatigue (64% [52/81]) and nausea (60% [49/81]) (\textbf{Supplementary Table S4}). Grade ≥3 TEAEs occurred in 64% of patients (52/81), with the most common (≥10%) being thrombocytopenia (26% [21/81]; grade 4, 13.6% [11/81]; grade 5, 0), neutropenia (15% [12/81]; grade 4, 9.9% [8/81]; grade 5, 0), and fatigue (10% [8/81]) (\textbf{Table 2}). Occurrences of grade ≥3 thrombocytopenia and neutropenia were generally early and transient; in the 45 patients in dose expansion Cohort 1 who were treated with prior EGFR TKI and prior platinum-based chemotherapy, the median time to first onset was 8 days for thrombocytopenia and 12 days for neutropenia; the median duration was 8 days for both thrombocytopenia and neutropenia. Treatment was discontinued due to TEAEs in 9% of patients (7/81), and no patient discontinued study treatment due to thrombocytopenia. TEAEs were associated with dose reduction in 22% of patients (18/81) and with dose interruption in 37% of patients (30/81). TEAEs were associated with death in 6% of patients.
(5/81), but none were judged by the investigator to be related to study treatment (disease progression, 2; respiratory failure, 2; and shock [infection induced], 1) (Table 2). Safety outcomes for each dose group are shown in Supplementary Table S2.

Interstitial lung disease (ILD) has been identified as an important risk in previous studies of T-DXd, which is also an ADC with a DXd-based topoisomerase 1 payload (29). In study U31402-A-U102 reported here, a predefined list of adverse events (AEs) suggestive of potential ILD triggered review by an independent adjudication committee to determine ILD diagnosis, grade, time of ILD onset, and relation to study drug. Treatment-related ILDs occurred in 5% of patients (4/81) (Table 2). All cases of adjudicated treatment-related ILD resolved after drug discontinuation. One patient in the dose expansion part experienced a grade 5 ILD event that was adjudicated to be unrelated to study treatment. The protocol recommendations for management of ILD are shown in Supplementary Table S5.

Antitumor Activity
Within the pooled population of patients (N=57) who received the HER3-DXd RDE (5.6 mg/kg IV Q3W), the median follow-up was 10.2 months (range, 5.2-19.9), and 32% of patients (18/57) were continuing study treatment at the time of the analysis (Supplementary Table S1).

The confirmed objective response rate (ORR) by blinded independent central review (BICR) was 39% (95% CI, 26.0-52.4) in patients who received HER3-DXd at a dose of 5.6 mg/kg IV Q3W (Table 3). There was 1 complete response (CR) and 21 partial responses (PR); 19 patients had stable disease (SD) as a best response. The median time to the first documentation of objective response (CR or PR) was 2.6 (range, 1.2-5.4) months. The median DOR was 6.9 (95% CI, 3.1-not evaluable [NE]) months. Among patients who had at least 1 evaluable tumor assessment after the initiation of study treatment (51 of 57 patients), 53% of patients (27/51) had a best reduction in sum-of-diameters of ≥30% with HER3-DXd treatment (Figure 1). Among the 52 of 57 patients with prior treatment that included platinum-based chemotherapy, those with a history of brain metastases (25 of 52) had a confirmed ORR of 32% (95% CI, 15.0-53.5; 1 CR, 7 PR, 12 SD, 4 progressive disease [PD], 1 NE) compared with 41% (95% CI, 22.4-61.2; 11 PR, 7 SD, 4 PD, 5 NE) in patients without a history of brain metastases (27 of 52).
Treatment durations for each patient in the pooled HER3-DXd (5.6 mg/kg IV Q3W) population are shown with the times of first responses in Figure 2A. Two patients continued study treatment following radiographic disease progression.

At a median follow-up of 10.2 months, median PFS was 8.2 (95% CI, 4.4-8.3) months (Figure 2B; 16 of 57 patients were ongoing without events), and the median OS was not reached at the time of data cutoff (95% CI, 9.4-NE months; Figure 2C; 35 of 57 patients were ongoing without events).

Confirmed responses occurred at a similar frequency among the subgroups of patients who had received EGFR TKI and platinum-based chemotherapy prior to study entry (N=52; Supplementary Table S3 and Supplementary Figures S2A and S2B) and patients who had received both osimertinib and platinum-based chemotherapy prior to study entry (N=44; Table 3 and Supplementary Figures S2C and S2D). Sixteen patients in the dose escalation part had prior EGFR TKI (including osimertinib) but had not received prior platinum-based chemotherapy; in these patients, the confirmed ORR was 63% (95% CI, 35.4-84.8), and median PFS was 7.6 (95% CI, 5.4-13.7) months.

**Biomarker Analysis**

HER3 membrane expression was quantified using an immunohistochemistry (IHC)-based H-score (0-300 scale). Representative examples of IHC staining and associated H-scores are shown in Supplementary Figure S3A-D. The analysis of pretreatment biopsy tissue, which was available for 43 of 57 patients in the pooled HER3-DXd (5.6 mg/kg IV Q3W) population, demonstrated that tumor HER3 expression was observed in all patients; the median H-score was 180 (range, 2–280; Figure 3A). There appeared to be no correlation between HER3 membrane H-score in the tumor and the time between a patient’s last EGFR TKI dose and their analyzed tumor biopsy (Figure 3B). The confirmed best overall response (BOR) in patients according to tumor HER3 membrane expression level by H-score is shown in Figures 3C and 3D. Confirmed responses were seen across a wide range of baseline tumor HER3 membrane H-scores, but there was a trend toward enrichment of confirmed responses in patients with higher baseline H-scores.

*EGFR* activating mutations were detected in tumor tissue or ctDNA in blood (collected prior to treatment with HER3-DXd) from all patients in the pooled HER3-DXd (5.6 mg/kg IV Q3W)
population. Most patients had the common $EGFR$ activating mutations Ex19del or L858R, but the enrollment criteria also allowed the inclusion of patients with atypical $EGFR$ activating mutations (specifically G719X and L861Q, with others possible following discussion with the sponsor). Among the 7 of 57 patients with atypical $EGFR$ activating mutations (G719X, L861Q, and Ex19ins), the BORs were 1 CR and 3 PR (confirmed); 1 patient had SD and 2 were not evaluable for response. Genomic alterations known to be associated with $EGFR$ TKI resistance were identified in 77% of patients (44/57). Diverse known mechanisms of $EGFR$ TKI resistance were detected, including $EGFR$ C797S, $MET$ or $HER2$ amplification, and $BRAF$ fusion; furthermore, several patients had no known $EGFR$ TKI resistance mechanism (Supplementary Figure S4). HER3-DXd treatment resulted in antitumor activity across this spectrum of known and unknown $EGFR$ TKI resistance mechanisms (Figure 1). In the 23 of 57 patients with known $EGFR$-related resistance mechanisms (excluding T790M), the confirmed ORR was 35% (CR/PR, 8; SD, 7; PD, 5; NE, 3). In the 13 of 57 patients with known $EGFR$-independent resistance mechanisms, the confirmed ORR was 46% (CR/PR, 6; SD, 4; PD, 2; NE, 1). In the 21 of 57 patients with other/unknown resistance mechanisms, the confirmed ORR was 38% (CR/PR, 8; SD, 8; PD, 2; NE, 3).

The association between response to HER3-DXd and clearance of $EGFR$ activating mutations was evaluated using ctDNA obtained at baseline and during therapy. Early clearance of ctDNA was defined by undetectable Ex19del or L858R at Week 3 or Week 6 following detection of either mutation prior to treatment. Early clearance of ctDNA was evaluable in 40 of 57 patients from the pooled HER3-DXd (5.6 mg/kg IV Q3W) population. While the confirmed ORR was 43% (17/40) in these patients, the confirmed ORR was 68% (13/19) in patients with early clearance of ctDNA compared with 19% (4/21) in patients without early clearance. No patient with early clearance of ctDNA had a confirmed BOR of PD (Figure 4A). While median PFS in all 40 patients evaluable for early clearance of ctDNA was 8.2 (95% CI, 4.4-8.3) months, median PFS was longer in patients with early clearance of ctDNA vs those without (8.3 [95%CI, 5.4-NE] months vs 4.4 [95%CI, 1.4-8.3] months; HR, 0.33; 95% CI, 0.13-0.81; Figure 4B). In all patients in whom the allelic frequency of the $EGFR$ activating mutations Ex19del or L858R could be quantified in pretreatment ctDNA (where the minor variant frequency was >1%; 25 of 57 patients), reductions relative to baseline were observed (Figure 4C).
Pharmacokinetics

Patients in the dose escalation part received HER3-DXd infusions prepared from a frozen liquid formulation, while patients in the dose expansion part received HER3-DXd infusions prepared from a lyophilized powder formulation. Pharmacokinetic (PK) parameters for released MAAA-1181a (the HER3-DXd payload) and MAAA-1181a conjugated antibody for the patients in dose escalation and dose expansion Cohort 1 are summarized in Supplementary Table S6. The mean (SD) serum concentration-time profiles of the MAAA-1181a conjugated antibody (for 3.2, 4.8, 5.6, and 6.4 mg/kg doses) and released payload MAAA-1181a (5.6 mg/kg) are shown in Supplementary Figure S5A-B.

In the 3.2 mg/kg to 6.4 mg/kg dose range, the maximum serum concentration ($C_{max}$) of the MAAA-1181a conjugated antibody increased approximately dose proportionally, whereas the area under the concentration vs time curve (AUC) for the MAAA-1181a conjugated antibody increased slightly greater than dose proportionally (Supplementary Figure S6A-B).

Twenty-four patients from the dose escalation 5.6 mg/kg group (N=10; frozen liquid formulation) and dose expansion Cohort 1 (N=14; lyophilized powder formulation) were included in a PK comparability analysis. The geometric mean ratios (GMR) of lyophilized powder/frozen liquid for the PK parameters of $C_{max}$, $AUC_{last}$, and $AUC_{0-21d}$ at Cycle 1 were in the range of 93.4% to 96.4% for MAAA-1181a conjugated antibody (Supplementary Table S7), indicating that MAAA-1181a conjugated antibody exposure is similar for the lyophilized powder and frozen liquid formulations at 5.6 mg/kg IV Q3W and that no dose adjustment is warranted between frozen liquid and lyophilized powder formulations of HER3-DXd. The GMRs for the PK parameters of $C_{max}$, $AUC_{last}$, and $AUC_{0-21d}$ of the released payload MAAA-1181a are shown in Supplementary Table S7.
DISCUSSION

Treatment options remain limited for patients with EGFR-mutated NSCLC who develop resistance to EGFR TKI therapy. Although targeting specific resistance mechanisms has demonstrated clinical efficacy, these molecular alterations are diverse; development and deployment of specific therapeutic approaches against each resistance mechanism might be impractical. In addition, the majority of first line osimertinib-resistant lung cancers do not harbor an obvious, currently targetable genomic mechanism of resistance (11). In the current study, we explore a ubiquitous biological feature of EGFR-mutated lung cancers, the expression of HER3, and clinically evaluate the targeting of this tumor marker by HER3-DXd. In contrast to most previous studies in EGFR-mutated NSCLC that focused on targeting specific genomic alterations, HER3-DXd provides a newer investigational treatment strategy that might provide benefit to a broader patient population with HER3 protein expression. The findings of this study show that HER3-DXd provides a feasible therapeutic approach with clinically meaningful antitumor activity with an ORR of 39% and median PFS of 8.2 months.

The majority of patients with EGFR-mutated NSCLC have tumor that expresses membrane HER3 and, because of the breadth of its expression, HER3 is an attractive molecular target for therapeutic intervention (19). A previous strategy to block the ligand-binding site of HER3 with an unconjugated antibody (such as patritumab or seribantumab) in combination with erlotinib did not confer clinically meaningful efficacy in EGFR-mutated NSCLC (19,32,33). HER3-DXd has a mechanism of action that is distinct from monoclonal antibody therapies; as an ADC, it is designed to produce antitumor activity through targeted delivery of its cytotoxic payload. The mechanism of action of an ADC is complex, and multiple factors are relevant to its antitumor activity: target antigen expression on the cell surface, ADC internalization and trafficking to the lysosome, enzymatic cleavage of the ADC (in the case of HER3-DXd, by cathepsin L and B), and the cytotoxic activity of the delivered payload (in the case of HER3-DXd, a topoisomerase I inhibitor) (22,26).

Because of the antigen specificity of HER3-DXd, we explored the association of HER3 expression in pretreatment tumor tissues with clinical response. Although confirmed responses were observed across tumors with a broad range of HER3 membrane H-scores, there was a slight enrichment of confirmed responses in patients with higher HER3 membrane H-scores at baseline. An important area of future investigation is to understand the utility of alternative measures of HER3 expression, other biomarkers related to the expression of HER3
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dimerization partners, and the dynamics of HER3 expression to predict clinical benefit in patients treated with HER3-DXd. These characteristics will be further explored in this study (cohort 3; Supplementary Figure S1) and in additional clinical evaluations of HER3-DXd. In addition, analysis is ongoing into identifying markers beyond HER3 expression, including internalization, drug processing, and DNA damage repair, using patient samples from this study.

Beyond radiographic and clinical measures of antitumor activity, this study also demonstrated an increased response rate and prolonged PFS in the subset of patients who achieved early clearance of ctDNA; this has been observed previously for a broad range of therapies, including EGFR TKIs and immune checkpoint inhibitors (34-36). In this study, reduction of ctDNA for the EGFR activating mutations Ex19del or L858R was observed in all patients with quantifiable ctDNA levels at baseline, with maximum reductions occurring between Day 15 and Day 148. Although the analysis of ctDNA is an investigational approach to monitor tumor dynamics and response to therapy, the clinical utility of these data at the current time has not yet been determined.

The safety profile of HER3-DXd was manageable, with a low rate of discontinuation due to TEAEs (9% [7/81]). Dose reduction and dose delay were successfully used in individual circumstances to mitigate toxicity and to avoid permanent discontinuation of study treatment. The most common toxicities comprised those related to gastrointestinal toxicity or cytopenia, and the most common grade ≥3 TEAEs comprised cytopenia (most commonly thrombocytopenia and neutropenia). No single TEAE was identified as a major cause of treatment discontinuation. No patient discontinued study treatment due to thrombocytopenia; when it occurred, the onset of grade ≥3 thrombocytopenia was typically early during study treatment (median time to first onset, 8 days) and was transient (median duration, 8 days). Drug-related ILD is an identified risk with DXd-based ADCs (29) (T-DXd is approved in the United States with boxed warnings for ILD and embryofetal toxicity) and surveillance and early management are important in the treatment of patients with this class of therapy (Supplementary Table S5). However, in the present study of HER3-DXd, the frequency of adjudicated treatment-related ILD was low (5% [4/81]), analogous to the incidences reported in trials of EGFR TKIs for patients with NSCLC (ILD rate, 0-5.7% (37)). Overall, the safety profile of HER3-DXd in this study was similar to that observed for HER3-DXd in patients with metastatic breast cancer (38).
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The data presented in this report support further study of HER3-DXd in this setting, and a pivotal, phase 2, global study of HER3-DXd in patients with *EGFR*-mutated NSCLC after disease progression on EGFR TKI and platinum-based chemotherapy has been initiated (HERTHENA-Lung01; NCT04619004). A phase 1, dose escalation and dose expansion study has been initiated to evaluate HER3-DXd in combination with osimertinib (and also as monotherapy) in patients with *EGFR*-mutated NSCLC with tumor progression after treatment with osimertinib monotherapy and no platinum-based chemotherapy (NCT04676477). In addition, HER3-DXd is also being evaluated in HER3-expressing metastatic breast cancer (NCT02980341) and metastatic colorectal cancer (NCT04479436).
METHODS

Trial Design and Patients

This is a global, open-label, multiple-dose, 2-part, phase 1 study conducted at 22 sites in the United States, Japan, Asia, and Europe (Supplementary Figure S1). In the dose escalation part, HER3-DXd was assessed in patients with metastatic or unresectable EGFR-mutated NSCLC who had acquired resistance to EGFR TKI (per Jackman criteria (39)). In the dose expansion part, HER3-DXd is being assessed in 3 cohorts: Cohort 1: EGFR-mutated (G719X, Ex19del, L858R, or L861Q; other EGFR activating mutations may be eligible following discussion with the sponsor) adenocarcinoma NSCLC treated with ≥1 prior EGFR TKI and ≥1 prior platinum-based chemotherapy regimen; Cohort 2: squamous or nonsquamous NSCLC without EGFR activating mutations and with prior anti–PD-1/PD-L1 therapy (unless unable or unwilling); Cohort 3: EGFR-mutated (G719X, Ex19del, L858R, or L861Q; other EGFR activating mutations may be eligible following discussion with the sponsor) NSCLC, including any histology other than combined small and non-small cell with ≥1 prior EGFR TKI and ≥1 prior platinum-based chemotherapy regimen.

General eligibility criteria included age ≥18 years; ECOG performance status of 0 or 1; and adequate bone marrow, organ, and cardiac function. Patients with a history of or suspected ILD/pneumonitis were excluded, as were patients with any evidence of small cell histology or combined small cell and non–small cell histology. Stable brain metastases were allowed. Eligibility criteria for the dose escalation part included metastatic/unresectable, EGFR-mutated, EGFR TKI-resistant NSCLC after progression on osimertinib, or T790M negative after progression on erlotinib, gefitinib, or afatinib; and available pretreatment tumor tissue (after progression on EGFR TKIs) for retrospective analysis of HER3 expression. Eligibility criteria for the dose expansion part Cohort 1 included EGFR-mutated NSCLC adenocarcinoma; ≥1 prior EGFR TKI and ≥1 prior platinum-based chemotherapy regimen (patients with EGFR T790M following treatment with erlotinib, gefitinib, afatinib, or dacomitinib must have received and have progressed following treatment with osimertinib, unless unable or unwilling). Investigators obtained written informed consent from all patients prior to study participation. The study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation consolidated Guideline E6 for Good Clinical Practice, and applicable local regulatory requirements. The study was approved by the institutional review board or ethics committee for each site.
Procedures

Patients received HER3-DXd IV Q3W on day 1 of each cycle of a 21-day cycle. Patients in the dose escalation received 3.2 mg/kg to 6.4 mg/kg HER3-DXd IV Q3W, which was guided by a Bayesian logistic regression model following the Escalation with Overdose Control (EWOC) principle. In the dose expansion part, patients in Cohorts 1 and 2 received the RDE of 5.6 mg/kg HER3-DXd IV Q3W (40); patients in Cohort 3 were randomized 1:1 to receive the RDE (Cohort 3a), or an uptitration of HER3-DXd (Cohort 3b). Two formulations were dosed in this study: frozen liquid drug product and lyophilized drug product. The frozen liquid drug product (used in dose escalation) was 50 mg of HER3-DXd in a 2.5 mL solution (20 mg/mL) in a single-use vial. The lyophilized drug product (used in dose expansion Cohort 1) was 100 mg of HER3-DXd in lyophilized powder dosage form in a single-use vial to be reconstituted with 5 mL of water for injection to 20 mg/mL.

Analysis of Genomic Alterations and Exploratory Biomarkers

Patients provided archival tumor tissue or consented to a fresh tumor biopsy as a pretreatment sample. End-of-treatment biopsies were optional; on-study biopsies were optional for all cohorts except for cohort 3. Blood samples were analyzed for ctDNA to validate findings from tumor tissue samples as part of these exploratory analyses.

Analysis of genomic alterations was performed centrally using Oncomine™ Comprehensive Assay v3 (Thermo Fisher Scientific, CA, USA) from formalin-fixed, paraffin-embedded tumor tissue. If available, results from local testing were included in the list of detected genomic alterations. Any additional mutations detected using GuardantOMNI™ assays (Guardant Health, CA, USA) in ctDNA from blood collected prior to treatment with HER3-DXd were also included. For the ctDNA-based data, a minor allelic frequency of 0.1% was used as a threshold for detection of mutations.

Analyses of HER3 membrane H-score and clearance of ctDNA were performed for the patients in dose escalation and dose expansion Cohort 1 who received the HER3-DXd RDE (5.6 mg/kg IV Q3W).

HER3 membrane expression was assessed by IHC in pretreatment tumor samples. HER3 IHC was performed on formalin-fixed, paraffin-embedded (FFPE) tissue using the BenchMark ULTRA IHC/ISH system. Staining was conducted with an anti-HER3 recombinant rabbit
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Monoclonal antibody (clone SP438) after antigen retrieval in CC1 buffer followed by detection with OptiView DAB IHC Detection Kit (Ventana Medical Systems, Inc).

HER3 IHC staining of tumor cells was evaluated by determining the percentage of tumor cells with membrane and cytoplasmic staining at specific intensities as follows: 0 (absence of staining), 1+ (weak staining), 2+ (moderate intensity staining), and 3+ (strong staining). From these data, the H-scores (a weighted summed score) were calculated for each patient sample for both cytoplasmic and membrane components.

Assessment of EGFR-mutated (Ex19del and L858R) ctDNA by GeneStrat (Biodesix) was conducted from C1D1 to C5D1 for every cycle, at C7D1 and C9D1, and then on day 1 of every third cycle through end of treatment. Early clearance of ctDNA was defined as nondetectable plasma of both EGFR Ex19del and EGFR L858R at Week 3 or Week 6, where at least 1 of either EGFR Ex19del or EGFR L858R was detectable at baseline.

Pharmacokinetic Assay and Analysis

The PK assay methods for measuring MAAA-1181a conjugated antibody and the released payload MAAA-1181a were developed and validated at PPD Laboratories (Richmond, VA). The method for measuring MAAA-1181a conjugated antibody is an ELISA in human serum with a quantitation range of 100 to 4000 ng/mL. The method for measuring the released payload MAAA-1181a is a liquid chromatography-mass spectrometry assay in human serum with a quantitation range of 10 to 2000 pg/mL. Samples with analyte concentrations above the respective assay’s upper limit of quantitation are diluted into each assay’s quantitation range and analyzed.

Noncompartmental analysis was conducted using Phoenix™ WinNonlin® (Version 8.1, Certara, L.P., Princeton, NJ). The power model to assess dose proportionality has the following form: \( Y = a \cdot (\text{dose})^b \). “\( Y \)” is the PK parameter, and “\( a \)” and “\( b \)” are the coefficient and exponent of the power equation, respectively. Following logarithmic transformation, the power model can be analyzed using linear regression.

Objectives and Endpoints

For the dose escalation part, the primary objective in dose escalation was to assess the safety and tolerability of HER3-DXd and determine the RDE. Primary endpoints included AEs, serious
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AEs (SAE), and other safety assessments. Secondary objectives in the dose escalation part were to investigate the antitumor activity of HER3-DXd, as well as to characterize the PK of MAAA-1181a conjugated antibody and released MAAA-1181a. Secondary endpoints included confirmed responses by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, ORR, disease control rate (DCR), DOR, time to response (TTR), PFS, OS, and serum concentration and PK parameters of MAAA-1181a conjugated antibody and released MAAA-1181a. Exploratory objectives included identification of biomarkers that correlate with HER3-DXd activity. Exploratory endpoints included correlation of biomarkers with clinical activity of HER3-DXd.

For the dose expansion part, the primary objective was to assess the antitumor activity of HER3-DXd. Primary endpoints included confirmed ORR by BICR per RECIST 1.1. Secondary endpoints included ORR by investigator per RECIST 1.1, DCR, DOR, TTR, PFS by BICR and by investigator per RECIST 1.1, and OS. Secondary objectives in dose expansion were to assess safety and tolerability of HER3-DXd, as well as characterize the PK of MAAA-1181a conjugated antibody and released MAAA-1181a. Secondary endpoints included SAEs, TEAEs, physical examination findings, vital signs, ophthalmologic findings, standard clinical laboratory parameters, electrocardiogram parameters, echocardiogram/multigated acquisition scan findings, and serum concentration and PK parameters of MAAA-1181a conjugated antibody and released MAAA-1181a. Exploratory objectives included the identification of biomarkers that correlate with HER3-DXd activity. Exploratory endpoints included correlation of biomarkers (eg, ctDNA, HER3 IHC) with clinical activity of HER3-DXd.

**Statistical Analysis**

Descriptive statistics were provided for selected demographic, efficacy, safety, and PK data from both dose escalation and dose expansion parts. Assessments of change from baseline to posttreatment included only patients with both baseline and posttreatment measurements. Safety analyses were performed based on the safety analysis set, which included all patients who were enrolled in the dose escalation part and dose expansion part Cohort 1 and received at least 1 dose of HER3-DXd (N=81). Efficacy analyses were performed based on the efficacy analysis set, which is identical to the safety analysis set. PK analyses were performed based on the PK analysis set, which included all patients in the safety analysis set who had at least 1 PK sample with measurable concentration of MAAA-1181a conjugated antibody or MAAA-1181a.
ORR and DCR and their 2-sided 95% exact confidence interval (using the Clopper-Pearson method) were provided. Distribution of the time-to-event endpoints was estimated using the Kaplan-Meier method. TEAEs were defined as AEs starting or worsening during the on-treatment period (from the start date of study treatment to 47 days after the end date of study treatment). SAEs starting or worsening after 47 days, if reported as related to the study treatment, were also defined as TEAEs.

ACKNOWLEDGMENTS

We thank the patients, their families, and their caregivers for their participation. We also thank Masayuki Kanai, Maha Karnoub, Kei Enomoto, Ru Chen, Pang-Dian Fan, Minseok Lee, Ling He, and Pomy Shrestha for their valuable contributions.

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REFERENCES


### Table 1. Demographics, Baseline Characteristics, and Prior Therapies

<table>
<thead>
<tr>
<th></th>
<th>Dose escalation</th>
<th>Dose expansion</th>
<th>Pooled RDE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.2 mg/kg (N=4)</td>
<td>4.8 mg/kg (N=15)</td>
<td>5.6 mg/kg (N=12)</td>
<td>6.4 mg/kg (N=5)</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>59.5 (51-67)</td>
<td>56.0 (44-76)</td>
<td>63.0 (50-77)</td>
<td>68.0 (60-80)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>3 (75)</td>
<td>10 (67)</td>
<td>8 (67)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Time since first NSCLC diagnosis, median (range), months</td>
<td>32 (19.8-60.4)</td>
<td>50 (15.9-121.9)</td>
<td>31 (11.1-72.2)</td>
<td>37 (12.7-50.8)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>0</td>
<td>2 (50)</td>
<td>7 (47)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>History of CNS metastases, n (%)</td>
<td>4 (100)</td>
<td>8 (53)</td>
<td>6 (50)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>No. of prior lines of systemic therapy in the locally advanced or metastatic setting, median (range)</td>
<td>4 (2-5)</td>
<td>4 (2-5)</td>
<td>2.5 (1-9)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Prior EGFR TKI therapy, n (%)</td>
<td>4 (100)</td>
<td>15 (100)</td>
<td>12 (100)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Prior osimertinib, n (%)</td>
<td>3 (75)</td>
<td>15 (100)</td>
<td>12 (100)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Prior PBC, n (%)</td>
<td>2 (50)</td>
<td>9 (60)</td>
<td>7 (58)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Prior PBC and osimertinib</td>
<td>1 (25)</td>
<td>9 (60)</td>
<td>7 (58)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Prior immunotherapy, n (%)</td>
<td>2 (50)</td>
<td>3 (20)</td>
<td>2 (17)</td>
<td>0</td>
</tr>
</tbody>
</table>

PBC, platinum-based chemotherapy.

*a* Pooled patients who received the HER3-DXd RDE, including 12 patients in the 5.6 mg/kg group in the dose escalation part and 45 patients in the dose expansion part.

*b* n=43.

*c* n=55.

*d* n=79.

*e* By BICR per RECIST 1.1.

*f* Patients with multiple EGFR activating mutations are listed in more than 1 row.

*g* No patients received prior treatment with a topoisomerase I inhibitor.

*h* EGFR TKI therapies included afatinib, dacomitinib, erlotinib, gefitinib, olmutinib, and osimertinib.

*i* Prior immunotherapies included atezolizumab, ipilimumab, nivolumab, and pembrolizumab.
**Table 2. Adverse Events Summary**

<table>
<thead>
<tr>
<th>TEAEs, n (%)</th>
<th>Pooled RDE 5.6 mg/kg (N=57)</th>
<th>All patients 3.2/4.8/5.6/6.4 mg/kg (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>57 (100)</td>
<td>81 (100)</td>
</tr>
<tr>
<td>Grade ≥3 TEAEs</td>
<td>42 (74)</td>
<td>52 (64)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>25 (44)</td>
<td>32 (40)</td>
</tr>
<tr>
<td>TEAEs associated with treatment discontinuation</td>
<td>6 (11)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 (9)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>TEAEs associated with dose reduction</td>
<td>12 (21)</td>
<td>18 (22)</td>
</tr>
<tr>
<td>TEAEs associated with dose interruption</td>
<td>21 (37)</td>
<td>30 (37)</td>
</tr>
<tr>
<td>TEAEs associated with death</td>
<td>4 (7)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (6)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Treatment-related TEAEs</td>
<td>55 (96)</td>
<td>78 (96)</td>
</tr>
<tr>
<td>Grade ≥3 treatment-related TEAEs</td>
<td>31 (54)</td>
<td>38 (47)</td>
</tr>
<tr>
<td>Treatment-related TEAEs associated with death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious treatment-related TEAEs</td>
<td>12 (21)</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Grade ≥3 TEAEs occurring in ≥5% of patients, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased/thrombocytopenia</td>
<td>17 (30)</td>
<td>21 (26)</td>
</tr>
<tr>
<td>Neutrophil count decreased/neutropenia</td>
<td>11 (19)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (14)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Anemia/hemoglobin decreased</td>
<td>5 (9)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (9)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5 (9)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>4 (7)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>White blood cell count decreased/leukopenia</td>
<td>4 (7)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (5)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Lymphocyte count decreased/lymphopenia</td>
<td>3 (5)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Adjudicated ILD, n (%)</td>
<td>5 (9)&lt;sup&gt;∗&lt;/sup&gt;</td>
<td>5 (6)&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adjudicated treatment-related ILD, n (%)</td>
<td>4 (7)&lt;sup&gt;∗&lt;/sup&gt;</td>
<td>4 (5)&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Fatigue (2 patients); decreased appetite, interstitial lung disease, neutrophil count decreased, pneumonitis, and upper respiratory tract infection (1 patient each).

<sup>b</sup> Fatigue (2 patients); nausea, decreased appetite, interstitial lung disease, neutrophil count decreased, pneumonitis, and upper respiratory tract infection (1 patient each).

<sup>c</sup> TEAEs associated with death were respiratory failure (2 patients) and disease progression and shock (1 patient each).
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d TEAEs associated with death were respiratory failure and disease progression (2 patients each) and shock (1 patient).
e Two grade 1, one grade 2, one grade 3, and one grade 5.
f Two grade 1, one grade 2, and one grade 3.
## Table 3. Responses by BICR per RECIST 1.1

<table>
<thead>
<tr>
<th></th>
<th>Pooled RDE (5.6 mg/kg)</th>
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<tbody>
<tr>
<td></td>
<td>All pooled (N=57)</td>
</tr>
<tr>
<td><strong>Confirmed ORR, % (n) [95% CI]</strong></td>
<td>39 (22) [26.0-52.4]</td>
</tr>
<tr>
<td><strong>BOR, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>CR, 1 (2)</td>
<td></td>
</tr>
<tr>
<td>PR, 21 (37)</td>
<td></td>
</tr>
<tr>
<td>SD, 19 (33)</td>
<td></td>
</tr>
<tr>
<td>PD, 9 (16)</td>
<td></td>
</tr>
<tr>
<td>NE, 7 (12)</td>
<td></td>
</tr>
<tr>
<td><strong>DCR, a % (n) [95% CI]</strong></td>
<td>72 (41) [58.5-83.0]</td>
</tr>
<tr>
<td><strong>TTR, median (range), months</strong></td>
<td>2.6 (1.2-5.4)</td>
</tr>
<tr>
<td><strong>Duration of response, median (95% CI), months</strong></td>
<td>6.9 (3.1-NE)</td>
</tr>
<tr>
<td><strong>Progression-free survival, median (95% CI), months</strong></td>
<td>8.2 (4.4-8.3)</td>
</tr>
<tr>
<td><strong>Overall survival, median (95% CI), months</strong></td>
<td>NE (9.4-NE)</td>
</tr>
</tbody>
</table>

**PBC, platinum-based chemotherapy.**

a DCR = rate of confirmed BOR of CR, PR, or SD.
Table Legends

**Table 1.** Demographics, Baseline Characteristics, and Prior Therapies

*Footnotes:*
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- c n=55.
- d n=79.
- e By BICR per RECIST 1.1.
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- g No patients received prior treatment with a topoisomerase I inhibitor.
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*Footnotes:*
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- b Fatigue (2 patients); nausea, decreased appetite, interstitial lung disease, neutrophil count decreased, pneumonitis, and upper respiratory tract infection (1 patient each).
- c TEAEs associated with death were respiratory failure (2 patients) and disease progression and shock (1 patient each).
- d TEAEs associated with death were respiratory failure and disease progression (2 patients each) and shock (1 patient).
- e Two grade 1, one grade 2, one grade 3, and one grade 5.
- f Two grade 1, one grade 2, and one grade 3.

**Table 3.** Responses by BICR per RECIST 1.1

*Footnotes:*
- PBC, platinum-based chemotherapy.
- a DCR = rate of confirmed BOR of CR, PR, or SD.
Figure Legends

Figure 1. Best percentage change in the tumor sum-of-diameters from baseline for the pooled HER3-DXd (5.6 mg/kg IV Q3W) population. Tumor genomic alterations prior to treatment with HER3-DXd are provided for each patient. Six patients could not be evaluated for BOR due to lack of adequate postbaseline tumor assessment and are not shown; 1 patient had a BOR of NE due to achieving SD too early (<5 weeks) and is shown with hatched markings.

Footnotes:

a Genomic analysis was performed centrally using Oncomine™ Comprehensive Assay v3 (Thermo Fisher Scientific, CA, USA). Results from local testing are included, if available, together with any additional mutations detected using GuardantOMNI™ assay of ctDNA in blood collected prior to treatment with HER3-DXd. For ctDNA analysis, a minor allelic frequency of ≥0.1% was used as a threshold for detection of mutations.

b Patient had multiple tumor mutations comprising CDKN2A A143V; PIK3CA E542K, E545K, E726K; ERBB2 K200N; and ERBB3 Q847*, Q849*.

Figure 2. Tumor response as assessed by BICR in patients treated with HER3-DXd at 5.6 mg/kg (N=57). (A) Swimmer plot showing treatment duration, first occurrence of confirmed tumor response, and progression. Prior treatment and history of CNS metastases are indicated for each patient. (B) Kaplan-Meier plot of progression-free survival probability. (C) Kaplan-Meier plot of overall survival probability.

Footnotes:

a Markers show the time of the initial response for confirmed responses. Two patients continued treatment after progression. In 1 case (top of swimmer plot), the patient had an equivocal (small) lesion and continued on treatment, but the lesion was later assessed as unequivocal—the swimmer plot is marked PD at the date of the lesion’s first appearance. In the other case, treatment continued because PD was determined by BICR but not by the local investigator (the study treatment discontinuation criteria were based on local tumor assessment).

Figure 3. Pretreatment HER3 membrane expression and association with BOR. BOR was assessed by BICR in patients treated with HER3-DXd at 5.6 mg/kg (43 of 57 patients evaluable for HER3 membrane expression). (A) Distribution of pretreatment HER3 membrane H-score (0-300). (B) Pretreatment HER3 membrane H-score and association with time since last treatment with EGFR TKI. (C, D) Pretreatment HER3 membrane H-score and confirmed BOR.
**Figure 4. Analyses of ctDNA changes.** (A) Proportions of confirmed BOR (BICR per RECIST 1.1) by early clearance of ctDNA\(^a\). (B) Kaplan-Meier plots showing PFS by early clearance of ctDNA\(^a\). (C) Waterfall plot showing maximum change relative to baseline in the minor variant frequency of *EGFR* activating mutations in ctDNA and confirmed BOR by BICR (25 of 57 patients were evaluable\(^b\)).

**Footnotes:**

- cBOR, confirmed BOR; MVF, minor variant frequency.
- Early clearance of ctDNA was defined as nondetectable plasma of both *EGFR* Ex19del and *EGFR* L858R at Week 3 or Week 6, where ≥1 allele comprising *EGFR* Ex19del or *EGFR* L858R was detectable at baseline. Serial ctDNA samples were collected from 45 of 57 patients, but 5 did not have evaluable ctDNA data for either Week 3 or 6. In the 17 patients not evaluable for early clearance of ctDNA, responses were: CR/PR, 29%; SD, 24%; PD, 17%; NE, 35%.
- Fewer patients (25 of 57) were evaluable for relative change in ctDNA than for early clearance of ctDNA (40 of 57), as the former required ctDNA levels to be above the limit of quantification (MVF >1%); the latter required levels to be above the limit of detection, which was lower (MVF >0.02%).
- Patients without GeneStrat data at C1D1 were analyzed if they had GuardantOMNI™ data at C1D1 when the MVF was >1%; this is because GeneStrat and GuardantOMNI™ data were concordant, except for the low MVF range (<1%).
Figure 2

(A) Treatment duration and assessments/events.

- History of CNS metastases
- Prior platinum-based chemotherapy
- Prior osimertinib

(B) Patients treated with HER3-DXd 5.6 m/kg (N=57)
Median (95% CI) PFS: 8.2 (4.4-8.3) months

(C) Patients treated with HER3-DXd 5.6 m/kg (N=57)
Median (95% CI) OS: NE (9.4-NE ) months
Figure 3

A

B

C

D

Pretreatment HER3 membrane H-score

Median H-score: 180
(range, 2-280)

Days between last EGFR TKI dose and biopsy

Same
day

0 50 100 150 200 250 300

100 150 200 250 300

10 100 1000

Patients ordered by pretreatment HER3 membrane H score

Confirmed BOR

CR

PR

SD

PD

NE

0 50 100 150 200 250 300

Pretreatment HER3 membrane H-score

Confirmed BOR (BICR)

CP/PR

SD

PD

NE

Biomarker-evaluable patients, n

Confirmed BOR (BICR)

CP/PR

SD

PD

NE

(92-268)

(4-280)

(2-251)

(36-215)
Figure 4

A. Proportion of patients with clearance of ctDNA and no clearance of ctDNA.

B. Progression-free survival probability with median PFS (95% CI) for clearance and no clearance.

C. Maximum relative change in MVF from baseline.
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