SUPPLEMENTAL MATERIALS

Contents

ADDITIONAL METHODS

Assessment of Intracranial Response

A specialist neuro-oncologist group a conducted blinded independent central review (CNS BICR) of the cranial imaging of 225 patients from HERTHENA-Lung01 treated with HER3-DXd 5.6 mg/kg IV Q3W. The assessment criteria are given in the table below.

	CNS RECIST (2 primary readers plus 1 adjudicator)
Lesion definition	
Target	Up to 5 lesions in CNS not previously irradiated or with progression following treatment Enhancing intraparenchymal brain metastases that can be measured in ≥1 dimension (LD in the plane of measurement is to be recorded) with a minimum size of 10 mm or 2× the slice thickness by MRI scan, whichever is larger
Nontarget	All others not selected as target
Response assessment	
Complete response	Disappearance of all target lesions (SOD % change from screening −100) and all nontarget lesions
Partial response	≥30% decrease in SOD of target lesions from baseline, taking as reference the screening SOD. Additionally, progression of target lesions must not be present
Stable disease	Neither sufficient shrinkage of target lesions to qualify for PR nor sufficient increase to qualify for PD, taking as reference the nadir SOD (or the screening SOD if the screening is the nadir value)
Progressive disease	Increase of 20% from nadir in target lesions, unequivocal progression in nontarget lesion, or unequivocal new lesion

BICR, blinded independent central review; CNS, central nervous system; IV, intravenous; LD, longest diameter; MRI, magnetic resonance imaging; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SOD, sum of diameters.

ADDITIONAL RESULTS

Analysis of the Potential Association Between Thrombocytopenia and Bleeding Events, and Neutropenia and Infection Events

In order to identify the patients who experienced grade ≥3 bleeding events due to grade ≥3 thrombocytopenia, the sponsor programmatically identified patients who experienced grade ≥3 bleeding events within ±14 days of a laboratory abnormality of grade ≥3 platelet count decreased event irrespective of the cause indicated by the investigator. Similarly, patients who experienced grade ≥3 infection within ±14 days of a grade ≥3 neutrophil count decreased event were identified.

Among the 4 patients who experienced grade ≥3 bleeding (gastrointestinal hemorrhage and hemothorax, each n=1) or grade ≥3 infection (sepsis and septic shock, each n=1) within the ±14-day range, only in 1 was a potential relationship with thrombocytopenia or neutropenia deemed possible:

Patient A: After thoracentesis for increased existing pleural effusion, the patient developed dyspnea and had low hemoglobin levels, which resulted in a diagnosis of hemothorax by the investigator. Platelet count was low at time of the event (20,000/uL [range, 150,000-400,000/uL]); however, the investigator considered the hemothorax unrelated to the study drug based on their clinical judgment.

Events in the other 3 patients were as follows:

- Patient B had a gastrointestinal hemorrhage. The source of bleeding was a septic mesenteric mass, per investigator. On the day of the event, the platelet count was within the normal range (165 G/L [range, 150-350 G/L]).
- Patient C developed sepsis due to *E faecalis* based on blood culture, per investigator. On the day of the event, the absolute neutrophil count was high ($9.2\times10^3/mm^3$ [range, $2\text{-}7\times10^3/mm^3$]).
- Patient D experienced septic shock due to acute onset of right inguinal painful swelling with cellulitis that deteriorated and spread to left inguinal region.

In all of these cases, the investigator did not consider the event to be study drug related.

SUPPLEMENTAL TABLES

Supplemental Table S1. Data From Previous Studies of Patients With *EGFR*-Mutated NSCLC

	REVEL[19,a] **(ramucirumab plus docetaxel arm) (N=628)**	**Yang *et al*[4] Retrospective data (N=60)**	**Patel *et al*[5] Real world data (N=273)**	**U102[7,23] HER3-DXd phase 1 (N=78)**
Patient population	NSCLC (2% with *EGFR*-activating mutations)	*EGFR*-mutated NSCLC previously treated with gefitinib and cytotoxic chemotherapy	*EGFR*-mutated NSCLC previously treated with osimertinib and PBC	*EGFR*-mutated NSCLC previously treated with third-generation EGFR TKI and PBC
Line of treatment	2L	3L	3L+	3L+
Therapy	Ramucirumab plus docetaxel	Various[b]	Various[c]	HER3-DXd
ORR (95% CI), %	22.9 (19.7-26.4)	PBC: 10.0 Other chemotherapy: 0	14.1 (3.7-33.1)[d]	41.0 (30.0-52.7)
PFS, median (95% CI), mo	4.5 (4.2-5.4)	PBC: 3.2 Other chemotherapy: 2.8	3.3 (2.8-4.4)	6.4 (4.4-10.8)
OS, median (95% CI), mo	10.5 (9.5-11.2)	PBC: 10.6 Other chemotherapy: 7.5	8.6 (7.4-9.8)	16.2 (11.2-21.9)

2L, second line; 3L, third line; 3L+, third line and later; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
[a] The primary endpoint in HERTHENA-Lung01 was based on the REVEL ramucirumab plus docetaxel arm (later studies have reported data for more similar patient populations).
[b] Erlotinib, PBC, other cytotoxic chemotherapies.
[c] Immunotherapy, alternate EGFR TKI therapy, PBC, or other cytotoxic chemotherapies as single-agent therapy or in combination.
[d] Estimated real-world confirmed ORR, (Patel JD, et al. IASLC 2023 WCLC. Abstract 2201).

Supplemental Table S2. Demographics and Clinical Characteristics at Baseline for the Uptitration Arm

		Uptitration arm (n=50)
Age at informed consent	Median (range), years	60.5 (32-78)
	<65 years, n (%)	35 (70.0)
	≥65 years, n (%)	15 (30.0)
Sex, n (%)	Male	21 (42.0)
	Female	29 (58.0)
Race, n (%)	American Indian or Alaskan Native	0
	Asian	31 (62.0)
	Black or African American	1 (2.0)
	Native Hawaiian or Other Pacific Islander	0
	White	15 (30.0)
	Other	3 (6.0)
Smoking history, n (%)	Never	30 (60.0)
	Ever	20 (40.0)
EGFR-activating mutations, n (%)	Ex19del (not L858R)	32 (64.0)
	L858R (not Ex19del)	18 (36.0)
	Ex19del and L858R	0
Histology, n (%)	Adenocarcinoma	50 (100)
	Squamous	0
	Other	0
Tumor stage at study entry, n (%)	IVA	19 (38.0)
	IVB	31 (62.0)
ECOG performance status, n (%)	0	16 (32.0)
	1	34 (68.0)
	2	0
History of brain metastases, n (%)	Yes	29 (58.0)
	No	21 (42.0)
Baseline metastatic lesion location by BICR, n (%)	Adrenal	2 (4.0)
	Bone	17 (34.0)
	Brain	18 (36.0)
	Liver	10 (20.0)
Baseline SOD by BICR	Median (range), mm	63.5 (11-191)
Time since initial NSCLC diagnosis	Median (range), months	46.1 (11.0-190.1)

Prior PBC, n (%)		50 (100)
Prior EGFR TKI, n (%)	Any EGFR TKI	50 (100)
	3G EGFR TKI[a]	44 (88.0)
	Only 3G EGFR TKI	13 (26.0)
	3G and other EGFR TKI	31 (62.0)
	No 3G EGFR TKI	6 (12.0)
Prior immunotherapy, n (%)[b]	Any immunotherapy	19 (38.0)
	Immunotherapy in last regimen	6 (12.0)
No. of prior lines of systemic therapy in the locally advanced or metastatic setting	Median (range)	3 (2-11)
	1, n (%)	0
	2, n (%)	13 (26.0)
	≥3, n (%)	37 (74.0)

3G, third generation; BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PBC, platinum-based chemotherapy; SOD, sum of diameters; TKI, tyrosine kinase inhibitor.

[a] Patients with prior third-generation EGFR TKI therapy had received osimertinib (n=42) and lazertinib (n=3; 1 patient also received osimertinib).

[b] Patients with prior immunotherapies had received pembrolizumab (n=9), atezolizumab (n=5), nivolumab (n=5), durvalumab (n=1), and zimberelimab (n=1).

Supplemental Table S3. Antitumor Activity in the Uptitration Arm and the Fixed-Dose Arm at Primary Data Cutoff (Responses by BICR per RECIST)

	Uptitration arm (n=50)	5.6 mg/kg (n=225)
Confirmed ORR (95% CI), %	16.0 (7.2-29.1)	28.4 (22.6-34.8)
Complete response, n (%)	1 (2.0)	1 (0.4)
Partial response, n (%)	7 (14.0)	63 (28.0)
Stable disease/non-CR/non-PD, n (%)	30 (60.0)	102 (45.3)
Progressive disease, n (%)	10 (20.0)	43 (19.1)
Not evaluable, n (%)	2 (4.0)	16 (7.1)
Disease control rate (95% CI), %	76.0 (61.8-86.9)	73.8 (67.5-79.4)
Duration of response, median (95% CI), mo	7.1 (2.8-15.2)	6.0 (4.4-7.2)
Patients with DOR ≥6 mo, %	50.0	43.8
Progression-free survival, median (95% CI), mo	6.7 (4.2-8.8)	5.5 (5.1-5.9)
Overall survival, median (95% CI), mo	14.0 (9.4-16.6)	11.8 (11.2-12.6)

BICR, blinded independent central review; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.
Primary data cutoff, November 21, 2022.
Median duration of follow-up, 13.1 (range, 9.0-21.60 months).

Supplemental Table S4. Safety Summary

	Safety population	Uptitration arm
	HER3-DXd 5.6 mg/kg (n=225)	**HER3-DXd 3.2→4.8→6.4 mg/kg (n=50)**
Any TEAE, n (%)	224 (99.6)	50 (100)
CTCAE grade ≥3	146 (64.9)	31 (62.0)
CTCAE grade ≥4	65 (28.9)	7 (14.0)
Serious TEAE	90 (40.0)	16 (32.0)
Associated with death	24 (10.7)[a]	5 (10.0)[b]
Associated with treatment discontinuation	16 (7.1)[c]	5 (10.0)[d]
Associated with dose interruption	91 (40.4)	22 (44.0)
Associated with dose reduction	48 (21.3)	14 (28.0)
Study drug–related TEAE, n (%)	215 (95.6)	43 (86.0)
CTCAE grade ≥3	102 (45.3)	19 (38.0)
CTCAE grade ≥4	40 (17.8)	2 (4.0)
Serious TEAE	34 (15.1)	4 (8.0)
Associated with death	4 (1.8)[e]	0
Grade ≥3 TEAEs occurring in ≥5% of patients, n (%)		
Thrombocytopenia (grouped PT)[f]	47 (20.9)	4 (8.0)
Neutropenia (grouped PT)[g]	43 (19.1)	10 (20.0)
Anemia (grouped PT)[h]	32 (14.2)	3 (6.0)
Leukopenia (grouped PT)[i]	22 (9.8)	1 (2.0)
Fatigue	13 (5.8)	2 (4.0)
All-grade TEAEs occurring in ≥5% of patients, n (%)		
Nausea	148 (65.8)	32 (64.0)
Thrombocytopenia (grouped PT)	98 (43.6)	17 (34.0)
Decreased appetite	95 (42.2)	21 (42.0)
Neutropenia (grouped PT)	80 (35.6)	19 (38.0)
Constipation	77 (34.2)	16 (32.0)
Anemia (grouped PT)	75 (33.3)	15 (30.0)
Fatigue	70 (31.1)	12 (24.0)
Diarrhea	62 (27.6)	12 (24.0)

Vomiting	61 (27.1)	11 (22.0)
Leukopenia (grouped PT)	59 (26.2)	10 (20.0)
Alopecia	57 (25.3)	13 (26.0)
Dyspnea	42 (18.7)	2 (4.0)
Asthenia	42 (18.7)	7 (14.0)
Aspartate aminotransferase increased	38 (16.9)	9 (18.0)
Hypokalemia	38 (16.9)	6 (12.0)
Cough	37 (16.4)	5 (10.0)
Abdominal pain (grouped PT)[j]	36 (16.0)	8 (16.0)
Headache	27 (12.0)	9 (18.0)
Stomatitis (grouped PT)[k]	27 (12.0)	7 (14.0)
Alanine aminotransferase increased	26 (11.6)	9 (18.0)
Pyrexia	25 (11.1)	7 (14.0)
Weight decreased	23 (10.2)	9 (18.0)
Epistaxis	22 (9.8)	1 (2.0)
COVID-19	22 (9.8)	3 (6.0)
Back pain	21 (9.3)	7 (14.0)
Blood alkaline phosphatase increased	21 (9.3)	1 (2.0)
Arthralgia	20 (8.9)	4 (8.0)
Edema peripheral	20 (8.9)	3 (6.0)
Hypoalbuminemia	20 (8.9)	1 (2.0)
Insomnia	17 (7.6)	5 (10.0)
Malaise	16 (7.1)	6 (12.0)
Hyperglycemia	16 (7.1)	2 (4.0)
Hyponatremia	15 (6.7)	2 (4.0)
Pneumonia	15 (6.7)	3 (6.0)
Dysgeusia	14 (6.2)	1 (2.0)
Dyspepsia	14 (6.2)	2 (4.0)
Pneumonitis	14 (6.2)	1 (2.0)
Blood lactate dehydrogenase increased	13 (5.8)	1 (2.0)
Dizziness	13 (5.8)	4 (8.0)
Pruritus	13 (5.8)	1 (2.0)
Blood creatinine increased	12 (5.3)	3 (6.0)

Pleural effusion	12 (5.3)	2 (4.0)
Treatment duration, median (range), months	5.5 (0.7-18.2)	5.3 (0.7-17.9)
Dose intensity, median (range), mg/kg/cycle	5.5 (3.2-6.0)	4.5 (3.0-6.0)
Relative dose intensity, median (range), %	97.7 (57.1-107.8)	95.4 (51.2-104.4)

CTCAE, Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; PT, preferred term; TEAE, treatment-emergent adverse event.
Primary data cutoff, November 21, 2022.
[a] Disease progression (n=11); pneumonia (n=3); NSCLC (n=2); acute respiratory distress syndrome, dyspnea, gastrointestinal perforation, hypercapnia, cholestatic jaundice, pneumonitis, respiratory failure, sepsis (n=1 each).
[b] Disease progression (n=4), respiratory failure (n=1).
[c] Pneumonitis (n=4); bilirubin increased (n=2); dyspnea (n=2); anemia, asthenia, duodenal perforation, fatigue, cholestatic jaundice, portal hypertension, urosepsis, white blood cell count decreased (n=1 each).
[d] Cognitive disorder, interstitial lung disease, malaise, pneumonitis, weight decreased (n=1 each).
[e] Pneumonitis, pneumonia, gastrointestinal perforation, respiratory failure (n=1 each).
[f] Platelet count decreased, thrombocytopenia.
[g] Neutropenia, neutrophil count decreased.
[h] Anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[i] Leukopenia, white blood cell count decreased.
[j] Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper.
[k] Stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering.

Supplemental Table S5. Antitumor Activity by Baseline EGFR TKI Resistance–Associated Genomic Alterations (Efficacy Population [n=225][a])

	Type of EGFR TKI resistance mechanism			
	***EGFR*-dependent (only) n=34**	***EGFR*-independent (only) n=81**	**Both *EGFR*-dependent and -independent n=32**	**None identified n=77**
Confirmed ORR (95% CI), %	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)
Disease control rate (95% CI), %	73.5 (55.6-87.1)	76.5 (65.8-85.2)	68.8 (50.0-83.9)	72.7 (61.4-82.3)
Duration of response, median (95% CI), mo	8.3 (4.1-NE)	7.1 (4.2-13.6)	4.2 (2.9-6.9)	6.0 (4.4-14.1)
Patients with duration of response ≥6 mo, n/N (%)	7/11 (63.6)	10/22 (45.5)	3/12 (25.0)	8/21 (38.1)
Progression-free survival, median (95% CI), mo	5.5 (3.0-9.6)	5.4 (4.2-7.5)	4.7 (2.7-5.6)	5.6 (4.4-8.3)
Overall survival, median (95% CI), mo	14.3 (6.8-NE)	11.6 (10.3-14.6)	9.5 (4.5-11.8)	13.1 (11.6-13.9)

EGFR, epidermal growth factor receptor; NE, not evaluable; ORR, objective response rate; TKI, tyrosine kinase inhibitor.
Snapshot data cutoff, May 18, 2023.
[a] 224 patients had available baseline data for genomic alterations.

Supplemental Table S6. Summary of Interstitial Lung Disease Adjudication

	CTCAE grade by adjudication committee/investigator, n (%)					
	1	**2**	**3**	**4**	**5**	**All grade**
HER3-DXd 5.6 mg/kg, safety population (n=225)						
Patients with potential ILD events (investigator-reported grade)	8 (3.6)	2 (0.9)	3 (1.3)	3 (1.3)	3 (1.3)	19 (8.4)
Not adjudicated as of reporting	0	0	0	0	0	0
Adjudicated as not ILD (investigator-reported grade)	2 (0.9)	0	0	2 (0.9)	3 (1.3)	7 (3.1)
Adjudicated as ILD (committee-adjudicated grade)[a]	1 (0.4)	8 (3.6)	2 (0.9)	0	1 (0.4)[b]	12 (5.3)
Adjudicated as drug-related ILD	1 (0.4)	8 (3.6)	2 (0.9)	0	1 (0.4)	12 (5.3)
Adjudicated as not drug-related ILD	0	0	0	0	0	0
HER3-DXd 3.2→4.8→6.4 mg/kg, uptitration arm (n=50)						
Patients with potential ILD events (investigator-reported grade)	0	1 (2.0)	1 (2.0)	0	1 (2.0)	3 (6.0)
Not adjudicated as of reporting	0	0	0	0	0	0
Adjudicated as not ILD (investigator-reported grade)	0	0	0	0	1 (2.0)	1 (2.0)
Adjudicated as ILD (committee-adjudicated grade)[c]	0	2 (4.0)	0	0	0	2 (4.0)
Adjudicated as drug-related ILD	0	2 (4.0)	0	0	0	2 (4.0)
Adjudicated as not drug-related ILD	0	0	0	0	0	0

CTCAE, Common Terminology Criteria for Adverse Events; IgA, immunoglobulin A; ILD, interstitial lung disease; PBC, platinum-based chemotherapy; PD-L1, programmed cell death 1 ligand 1.
Primary data cutoff, November 21, 2022.
[a] Median time to onset of adjudicated ILD (all drug related) was 53 (range, 9-230) days.
[b] The patient died on day 166. Grade 4 pneumonitis had developed on day 146, after cycle 7, and the patient was treated with steroids (methylprednisolone), antibiotics (azithromycin, piperacillin-tazobactam), oxycodone, morphine, and furosemide. Prior to study entry, the patient had 4 lines of treatment: 1) erlotinib, 2) osimertinib, 3) carboplatin and paclitaxel, and 4) anti–PD-L1 + PBC (the anti–PD-L1, atezolizumab, ended on day −76). The patient was a 60-year-old, White, female, former smoker (10 pack years), with a history of grade 1 IgA nephropathy.
[c] Median time to onset of adjudicated ILD (both drug related) was 205 (range, 162-248) days.

Supplemental Table S7. Adverse Events by Prior Immunotherapy (Safety Population [n=225])

	HER3-DXd 5.6 mg/kg by prior immunotherapy		
	None (n=135)	**Earlier prior regimen (n=38)**	**Last prior regimen (n=52)**
Any TEAE, n (%)	134 (99.3)	38 (100)	52 (100)
CTCAE grade ≥3	87 (64.4)	25 (65.8)	34 (65.4)
CTCAE grade ≥4	37 (27.4)	12 (31.6)	16 (30.8)
Serious TEAE	49 (36.3)	19 (50.0)	22 (42.3)
Associated with death	13 (9.6)	5 (13.2)	6 (11.5)
Associated with treatment discontinuation	9 (6.7)	3 (7.9)	4 (7.7)
Associated with dose interruption	58 (43.0)	15 (39.5)	18 (34.6)
Associated with dose reduction	28 (20.7)	8 (21.1)	12 (23.1)
Study drug–related TEAE, n (%)	130 (96.3)	35 (92.1)	50 (96.2)
CTCAE grade ≥3	58 (43.0)	19 (50.0)	25 (48.1)
CTCAE grade ≥4	23 (17.0)	7 (18.4)	10 (19.2)
Serious TEAE	15 (11.1)	9 (23.7)	10 (19.2)
Associated with death	2 (1.5)	1 (2.6)	1 (1.9)

CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
Primary data cutoff, November 21, 2022.

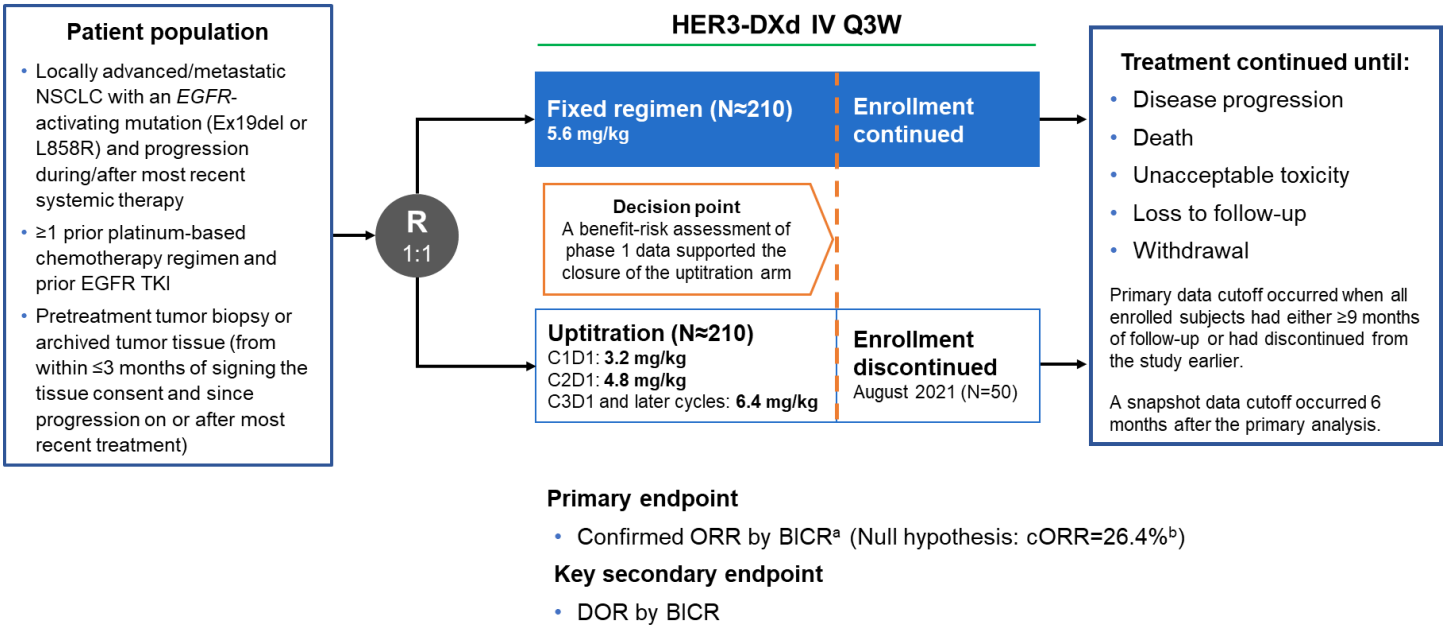
Supplemental Table S8. Interstitial Lung Disease by Prior Immunotherapy (Safety Population [n=225])

	CTCAE grade by adjudication committee/investigator, n (%)					
	1	**2**	**3**	**4**	**5**	**All grade**
No prior immunotherapy (n=135)						
Patients with potential ILD events (investigator-reported grade)	4 (3.0)	1 (0.7)	2 (1.5)	1 (0.7)	1 (0.7)	9 (6.7)
Not adjudicated as of reporting	0	0	0	0	0	0
Adjudicated as not ILD (investigator-reported grade)	2 (1.5)	0	0	1 (0.7)	1 (0.7)	4 (3.0)
Adjudicated as ILD (committee-adjudicated grade)	0	3 (2.2)	1 (0.7)	0	1 (0.7)	5 (3.7)
Adjudicated as drug-related ILD	0	3 (2.2)	1 (0.7)	0	1 (0.7)	5 (3.7)
Adjudicated as not drug-related ILD	0	0	0	0	0	0
Immunotherapy as earlier prior regimen (n=38)						
Patients with potential ILD events (investigator-reported grade)	2 (5.3)	1 (2.6)	0	1 (2.6)	1 (2.6)	5 (13.2)
Not adjudicated as of reporting	0	0	0	0	0	0
Adjudicated as not ILD (investigator-reported grade)	0	0	0	1 (2.6)	1 (2.6)	2 (5.3)
Adjudicated as ILD (committee-adjudicated grade)	0	3 (7.9)	0	0	0	3 (7.9)
Adjudicated as drug-related ILD	0	3 (7.9)	0	0	0	3 (7.9)
Adjudicated as not drug-related ILD	0	0	0	0	0	0
Immunotherapy as last prior regimen (n=52)						
Patients with potential ILD events (investigator-reported grade)	2 (3.8)	0	1 (1.9)	1 (1.9)	1 (1.9)	5 (9.6)
Not adjudicated as of reporting	0	0	0	0	0	0
Adjudicated as not ILD (investigator-reported grade)	0	0	0	0	1 (1.9)	1 (1.9)
Adjudicated as ILD (committee-adjudicated grade)	1 (1.9)	2 (3.8)	1 (1.9)	0	0	4 (7.7)
Adjudicated as drug-related ILD	1 (1.9)	2 (3.8)	1 (1.9)	0	0	4 (7.7)
Adjudicated as not drug-related ILD	0	0	0	0	0	0

CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease.
Primary data cutoff, November 21, 2022.

SUPPLEMENTAL FIGURES

Supplemental Figure S1. Study Design



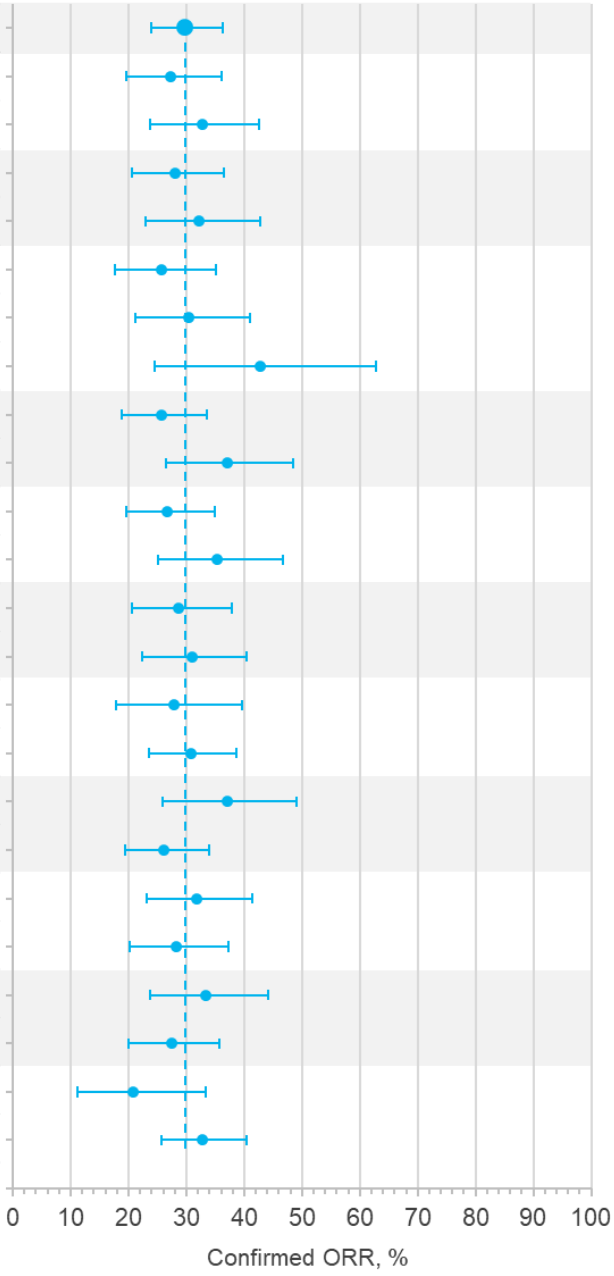
BICR, blinded independent central review; C, cycle; cORR, confirmed objective response rate; D, day; DOR, duration of response; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; Q3W, every 3 weeks; R, randomization; TKI, tyrosine kinase inhibitor.

[a] Complete response or partial response confirmed ≥4 weeks after the initial response.

[b] This was the upper bound of the exact 95% CI of the objective response rate (23%) observed in the ramucirumab plus docetaxel arm from the REVEL trial in patients with stage IV NSCLC whose disease had progressed on platinum-based chemotherapy.

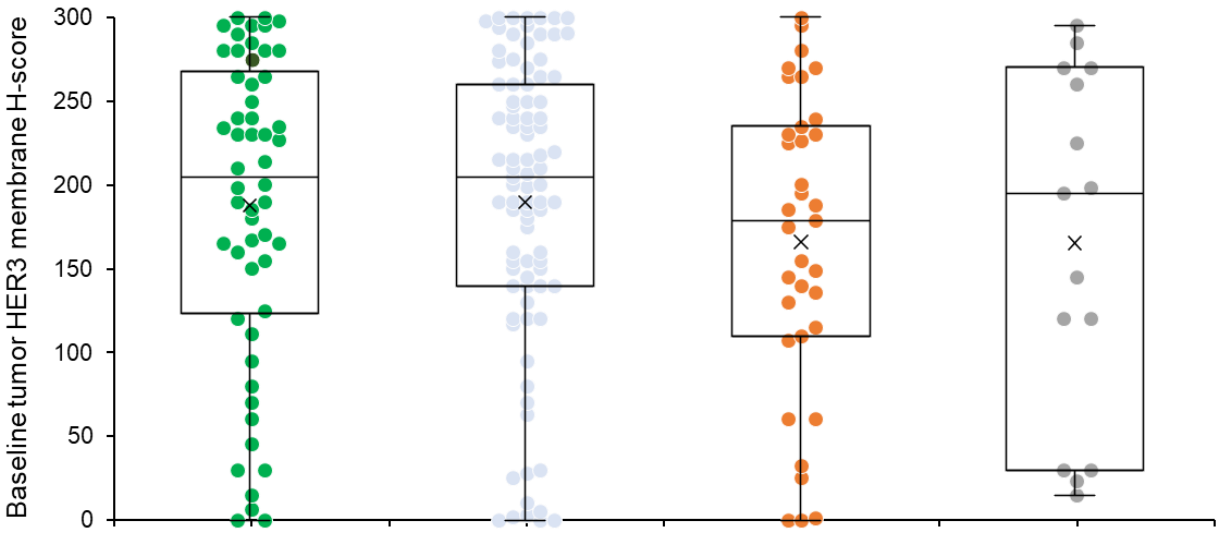
Supplemental Figure S2. Forest Plot of Confirmed Objective Response Rate by Baseline Subgroups

		N	CR/PR	cORR (95% CI), %
Overall		225	67	29.8 (23.9-36.2)
Age	<65 y	121	33	27.3 (19.6-36.1)
	≥65 y	104	34	32.7 (23.8-42.6)
Sex	Female	132	37	28.0 (20.6-36.5)
	Male	93	30	32.3 (22.9-42.7)
Race	Asian	105	27	25.7 (17.7-35.2)
	White	92	28	30.4 (21.3-40.9)
	Other	28	12	42.9 (24.5-62.8)
Smoking status	Never	144	37	25.7 (18.8-33.6)
	Ever	81	30	37.0 (26.6-48.5)
EGFR-activating mutation[a]	Ex19del	142	38	26.8 (19.7-34.8)
	L858R	82	29	35.4 (25.1-46.7)
History of brain metastasis	Yes	115	33	28.7 (20.6-37.9)
	No	110	34	30.9 (22.4-40.4)
Brain metastasis at baseline by BICR	Yes	72	20	27.8 (17.9-39.6)
	No	153	47	30.7 (23.5-38.7)
ECOG performance status[b]	0	73	27	37.0 (26.0-49.1)
	1	149	39	26.2 (19.3-34.0)
Baseline SoD of target lesions by BICR[c]	<median	107	34	31.8 (23.1-41.5)
	≥median	117	33	28.2 (20.3-37.3)
Prior immunotherapy	Yes	90	30	33.3 (23.7-44.1)
	No	135	37	27.4 (20.1-35.7)
No. of prior regimens for advanced disease[d]	2	58	12	20.7 (11.2-33.4)
	>2	165	54	32.7 (25.6-40.5)



BICR, blinded independent central review; cORR, confirmed objective response rate; CR, compete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PR, partial response; SOD, sum of diameters.
Snapshot data cutoff, May 18, 2023.
[a] Does not include 1 patient who had a tumor with both Ex19del and L858R (n=224).
[b] The subgroup of 3 patients with ECOG performance status of 3 was too small to report (n=222).
[c] 224 patients had evaluable target lesion measurements at baseline.
[d] Does not include 2 patients who had 1 prior line for advanced disease (n=223).

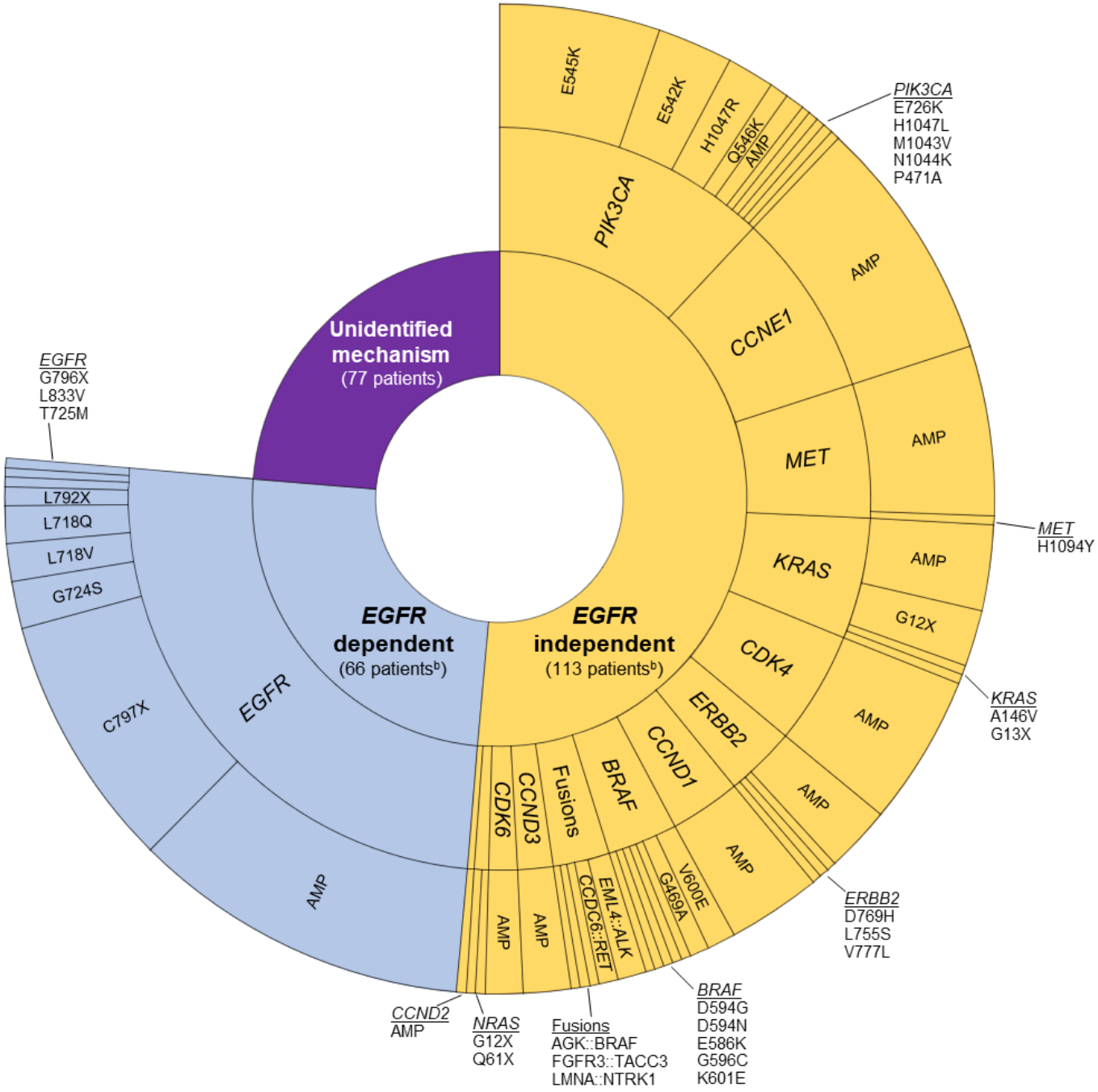
Supplemental Figure S3. Association of Baseline HER3 Membrane H-Score (in Patients With Evaluable Tumor Samples) With Confirmed Best Response by BICR (n=225)[a]



Confirmed BOR (BICR)	CR/PR	SD	PD	NE
Biomarker-evaluable patients, n/n	54/67	89/99	35/43	15/16
H-score, median (range)	205 (0-300)	205 (0-300)	179 (0-300)	195 (15-295)

BICR, blinded independent central review; BOR, best overall response; CR, compete response; HER3, human epidermal growth factor receptor 3; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
Medians are indicated by horizontal lines; means are indicated by X.
[a] 193 baseline samples were evaluable for H-score. Baseline was the sample on or before the first dose date and not earlier than 90 days before the first dose date. Highest HER3 membrane H-score value was used if multiple records were available. Response data are for the snapshot data cutoff, May 18, 2023.

Supplemental Figure S4. EGFR TKI resistance–associated genomic alterations (efficacy population [n=225][a])



EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.
[a] Genomic alterations known to be associated with EGFR TKI resistance were detected in the tumors of 147 of 224 patients in the efficacy population with available baseline data.
[b] 32 patients had tumors with both *EGFR*-dependent and *EGFR*-independent mechanisms of EGFR TKI resistance.

REFERENCES

1. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Non-Small Cell Lung Cancer, Version 3.2023. 2023
2. Han B, Yang L, Wang X, et al: Efficacy of pemetrexed-based regimens in advanced non-small cell lung cancer patients with activating epidermal growth factor receptor mutations after tyrosine kinase inhibitor failure: a systematic review. Onco Targets Ther 11:2121-2129, 2018
3. Hayashi H, Sugawara S, Fukuda Y, et al: A Randomized Phase II Study Comparing Nivolumab with Carboplatin-Pemetrexed for EGFR-Mutated NSCLC with Resistance to EGFR Tyrosine Kinase Inhibitors (WJOG8515L). Clin Cancer Res 28:893-902, 2022
4. Yang CJ, Hung JY, Tsai MJ, et al: The salvage therapy in lung adenocarcinoma initially harbored susceptible EGFR mutation and acquired resistance occurred to the first-line gefitinib and second-line cytotoxic chemotherapy. BMC Pharmacol Toxicol 18:21, 2017
5. Patel JD, Meng J, Phani S, et al: AACR 2023 Abstract 6754: Clinical characteristics, real-world treatment patterns, and clinical outcomes among patients with previously treated metastatic or unresectable EGFR-mutated non-small cell lung cancer in the United States. Cancer Research 83:6754, 2023
6. Scharpenseel H, Hanssen A, Loges S, et al: EGFR and HER3 expression in circulating tumor cells and tumor tissue from non-small cell lung cancer patients. Sci Rep 9:7406, 2019
7. Jänne PA, Baik C, Su WC, et al: Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor-Resistant, EGFR-Mutated Non-Small Cell Lung Cancer. Cancer Discov 12:74-89, 2022
8. Yonesaka K, Tanizaki J, Maenishi O, et al: HER3 Augmentation via Blockade of EGFR/AKT Signaling Enhances Anticancer Activity of HER3-Targeting Patritumab Deruxtecan in EGFR-Mutated Non-Small Cell Lung Cancer. Clin Cancer Res 28:390-403, 2022
9. Mishra R, Patel H, Alanazi S, et al: HER3 signaling and targeted therapy in cancer. Oncol Rev 12:355, 2018
10. Engelman JA, Zejnullahu K, Mitsudomi T, et al: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 316:1039-43, 2007
11. Li Q, Zhang R, Yan H, et al: Prognostic significance of HER3 in patients with malignant solid tumors. Oncotarget 8:67140-67151, 2017
12. Hashimoto Y, Koyama K, Kamai Y, et al: A Novel HER3-Targeting Antibody-Drug Conjugate, U3-1402, Exhibits Potent Therapeutic Efficacy through the Delivery of Cytotoxic Payload by Efficient Internalization. Clin Cancer Res 25:7151-7161, 2019
13. Koganemaru S, Kuboki Y, Koga Y, et al: U3-1402, a Novel HER3-Targeting Antibody-Drug Conjugate, for the Treatment of Colorectal Cancer. Mol Cancer Ther 18:2043-2050, 2019
14. Nakada T, Sugihara K, Jikoh T, et al: The latest research and development into the antibody-drug conjugate, [fam-] trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. Chem Pharm Bull (Tokyo) 67:173-185, 2019

15. Ogitani Y, Aida T, Hagihara K, et al: DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. Clin Cancer Res 22:5097-5108, 2016
16. Ueno S, Hirotani K, Abraham R, et al: U3-1402a, a novel HER3-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a potent tumor efficacy. Cancer Res 77:3092, 2017
17. Yonesaka K, Takegawa N, Watanabe S, et al: An HER3-targeting antibody-drug conjugate incorporating a DNA topoisomerase I inhibitor U3-1402 conquers EGFR tyrosine kinase inhibitor-resistant NSCLC. Oncogene 38:1398-1409, 2019
18. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009
19. Garon EB, Ciuleanu T-E, Arrieta O, et al: Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. The Lancet 384:665-673, 2014
20. Ge M, Zhuang Y, Zhou X, et al: High probability and frequency of EGFR mutations in non-small cell lung cancer with brain metastases. J Neurooncol 135:413-418, 2017
21. Jerusalem G, Park YH, Yamashita T, et al: Trastuzumab Deruxtecan in HER2-Positive Metastatic Breast Cancer Patients with Brain Metastases: A DESTINY-Breast01 Subgroup Analysis. Cancer Discov 12:2754-2762, 2022
22. Lin NU, Lee EQ, Aoyama H, et al: Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 16:e270-8, 2015
23. Hayashi H, Yu HA, Baik C, et al: First report of cohort 3 and extended follow-up data from the U31402-A-U102 study of HER3-DXd in EGFR-mutated NSCLC. Presented at the JSMO, 2023, Abstract e70378
24. Komatsu N, Sato S, Muramatsu S, et al: Abstract 3996: The impact of HER3 dynamics on the efficacy of HER3-DXd, a novel HER3 directed antibody-drug conjugate. Cancer Research 83:3996-3996, 2023
25. Ramalingam SS, Cheng Y, Zhou C, et al: Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study. Ann Oncol 29:viii740, 2018