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Patritumab Deruxtecan (HER3-DXd) in *EGFR*-Mutated NSCLC Following EGFR TKI and Platinum-Based Chemotherapy: HERTHENA-Lung01

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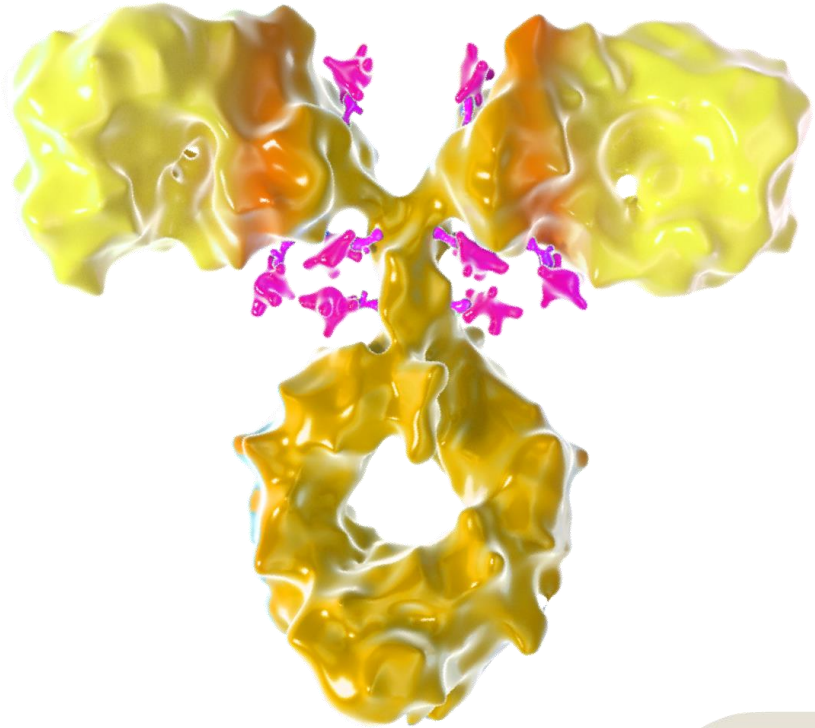
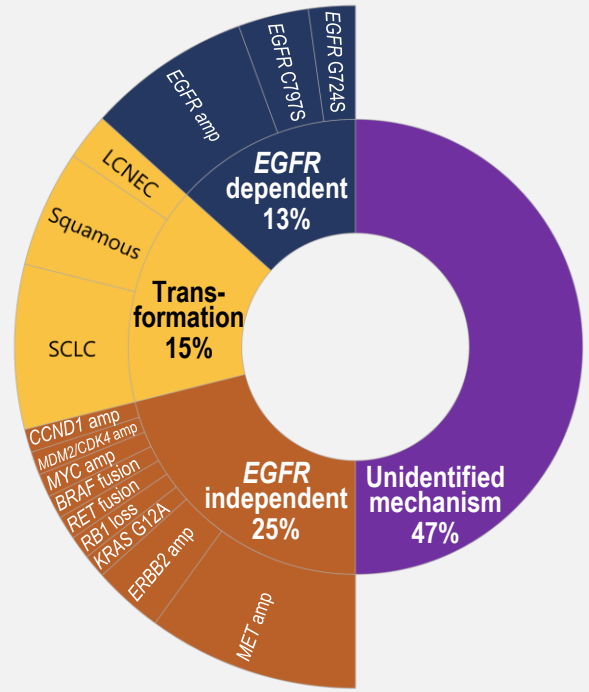


Efficacious and Tolerable New Therapies Are Needed for *EGFR*-Mutated NSCLC After Failure of an EGFR TKI and Platinum-Based Chemotherapy

- *EGFR*-activating mutations occur in 14% to 38% of patients with NSCLC[1,a]
  - Development of resistance to EGFR TKI therapy is typical[2]
  - Platinum-based chemotherapy is commonly administered after failure of EGFR TKI therapy[3]
- Salvage therapies after EGFR TKI therapy and platinum-based chemotherapy provide only a limited and transient clinical benefit[5,6]
  - Real-world PFS after progression with osimertinib and platinum-based chemotherapy: 3.3 (95% CI, 2.8-4.4) months[6]
  - Estimated real-world cORR: 14.1% (95% CI, 3.7%-33.1%)[7]
- CNS metastases are common in this population,[8] and therapies to ensure CNS control are needed

Mechanisms of Resistance to First-Line Osimertinib Are Diverse[4]



HERTHENA-Lung01 evaluated the efficacy and safety of patritumab deruxtecan (HER3-DXd) in patients with *EGFR*-mutated NSCLC after progression with EGFR TKI therapy and platinum-based chemotherapy

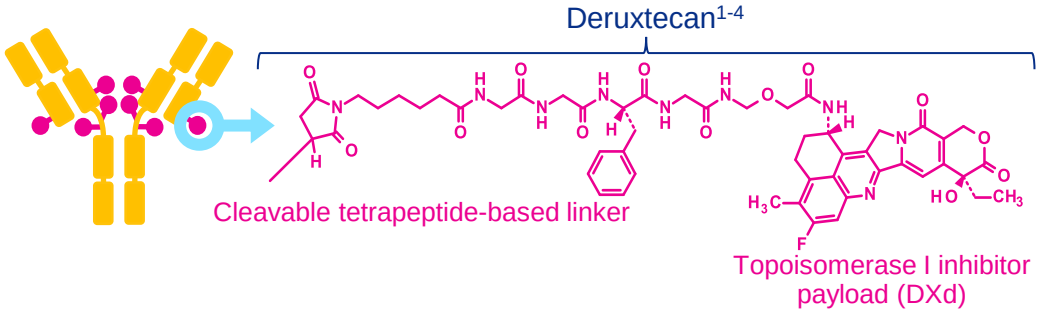
CNS, central nervous system; cORR, confirmed objective response rate; LCNEC, large cell neuroendocrine carcinoma; PFS, progression-free survival; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor.
[a] Data for patients with adenocarcinoma.

1. Zhang Y-L, et al. *Oncotarget.* 2016;7(48):78985-78993. 2. Schoenfeld AJ, Yu HA. *J Thorac Oncol*. 2020;15(1):18-21. 3. Han B, et al. *Onco Targets Ther.* 2018;11:2121-2129. 4. Choudhury NJ, et al. *J Thorac Oncol.* 2023;18(4):463-475. 5. Yang C-J, et al. *BMC Pharmacol Toxicol.* 2017;18(1):82. 6. Patel JD, et al. AACR 2023. Poster 6754. 7. Patel JD, et al. IASLC 2023 WCLC. Abstract 2201. 8. Gillespie CS, et al. *J Thorac Oncol*. Epub, June 29, 2023.

Patritumab Deruxtecan (HER3-DXd)

HER3-DXd is an ADC composed of 3 parts[1-4]:

- A fully human anti-HER3 IgG1 mAb (patritumab)
- A topoisomerase I inhibitor payload (DXd)
- A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



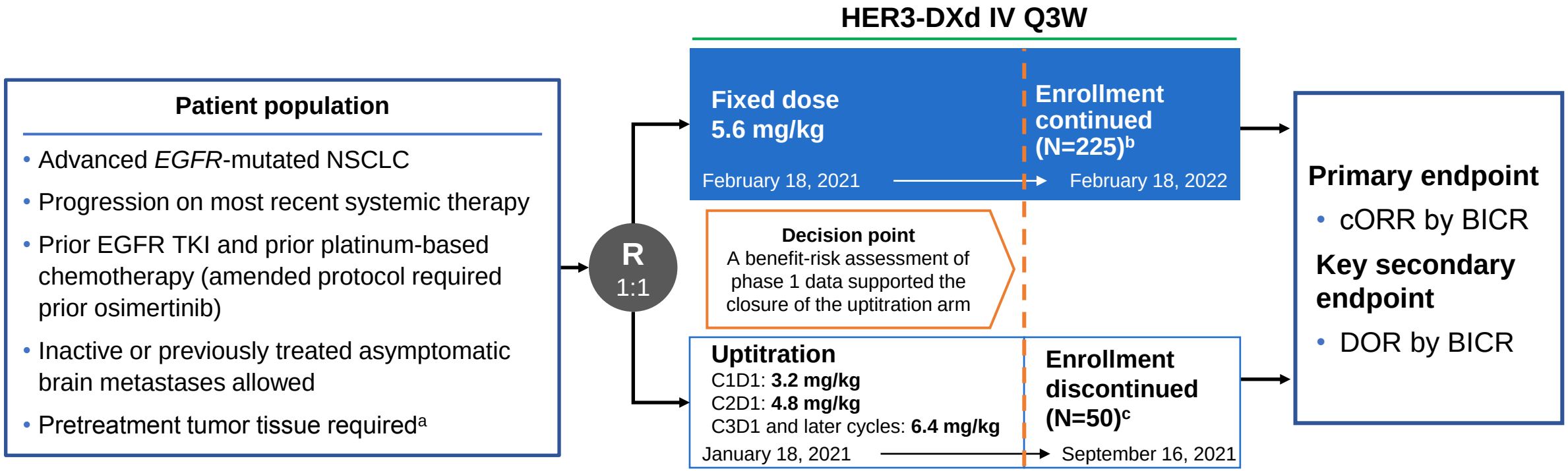
Payload mechanism of action: topoisomerase I inhibitor[1-4,a]
High potency of payload[1-4,a]
High drug to antibody ratio ≈8[1,2,a]
Payload with short systemic half-life[2,3,a,b]
Stable linker-payload[2-4,a]
Tumor-selective cleavable linker[1-5,a]
Bystander antitumor effect[2,6,a]

- A phase 1 study of HER3-DXd for advanced NSCLC demonstrated efficacy in patients with *EGFR*-activating mutations and diverse mechanisms of resistance to EGFR TKIs (including *EGFR*-dependent and -independent mechanisms)[7]
  - The study showed that HER3-DXd 5.6 mg/kg administered intravenously every 3 weeks was associated with a tolerable and manageable safety profile
- Promising data from the phase 1 trial led to initiation of the phase 2 HERTHENA-Lung01 trial of HER3-DXd in patients with *EGFR*-mutated NSCLC who were treated previously with EGFR TKI and platinum-based chemotherapy

ADC, antibody-drug conjugate; HER, human epidermal growth factor receptor; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
[a] The clinical relevance of these features is under investigation. [b] Based on animal data.

1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046. 7. Jänne PA et al. *Cancer Discov.* 2022;12(1):74-89.

HERTHENA-Lung01 Study Design[1]



Primary data cutoff, 21 Nov 2022[d]
Snapshot data cutoff, 18 May 2023 (additional 6 months follow-up)
Data are presented for the 5.6-mg/kg fixed-dose arm

- Efficacy from snapshot data cutoff—median study follow-up, 18.9 (range, 14.9-27.5) months
- Safety from primary data cutoff—median treatment duration, 5.5 (range, 0.7-18.2) months

BICR, blinded independent central review; C, cycle; cORR, confirmed objective response rate (complete or partial response confirmed ≥4 weeks after initial response [RECIST version 1.1]); D, day; DOR, duration of response; HER, human epidermal growth factor receptor; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.
[a] Inclusion not based on detection of HER3 expression. [b] 226 patients were enrolled; 225 received ≥1 dose. [c] 51 patients were enrolled; 50 received ≥1 dose. [d] Data cutoff for the primary analysis occurred when all enrolled patients had either ≥9 months of follow-up or had discontinued from the study earlier.
1. Yu HA, et al. *Future Oncol*. 2023;19:1319-1329.

Patients Were Heavily Pretreated and Had Adverse Prognostic Characteristics

Baseline characteristics		HER3-DXd 5.6 mg/kg (N=225)
Age, median (range), years		64 (37-82)
Female, n (%)		132 (59)
Asian, n (%)		105 (47)
Time since initial NSCLC diagnosis, median (range), months		41.0 (9.1-224.7)
ECOG performance status, n (%)	0/1	73 (32)/149 (66)
	2[a]	3 (1)
Sum of target lesion diameters at baseline (BICR), median (range), mm		68 (11-248)
History of CNS metastasis, n (%)		115 (51)
Brain metastasis at baseline (BICR), n (%)		72 (32)
Liver metastasis at baseline (BICR), n (%)		75 (33)
EGFR-activating mutations, n (%)[b]	Ex19del	142 (63)
	L858R	82 (36)
No. of prior lines of systemic therapy (locally advanced/metastatic)	Median (range)	3 (1-11)[c]
	2 prior lines, n (%)	58 (26)
	>2 prior lines, n (%)	165 (73)
Prior cancer regimens, n (%)	Prior EGFR TKI therapy	225 (100)
	Prior third-generation EGFR TKI	209 (93)
	Prior platinum-based chemotherapy	225 (100)
	Prior immunotherapy	90 (40)

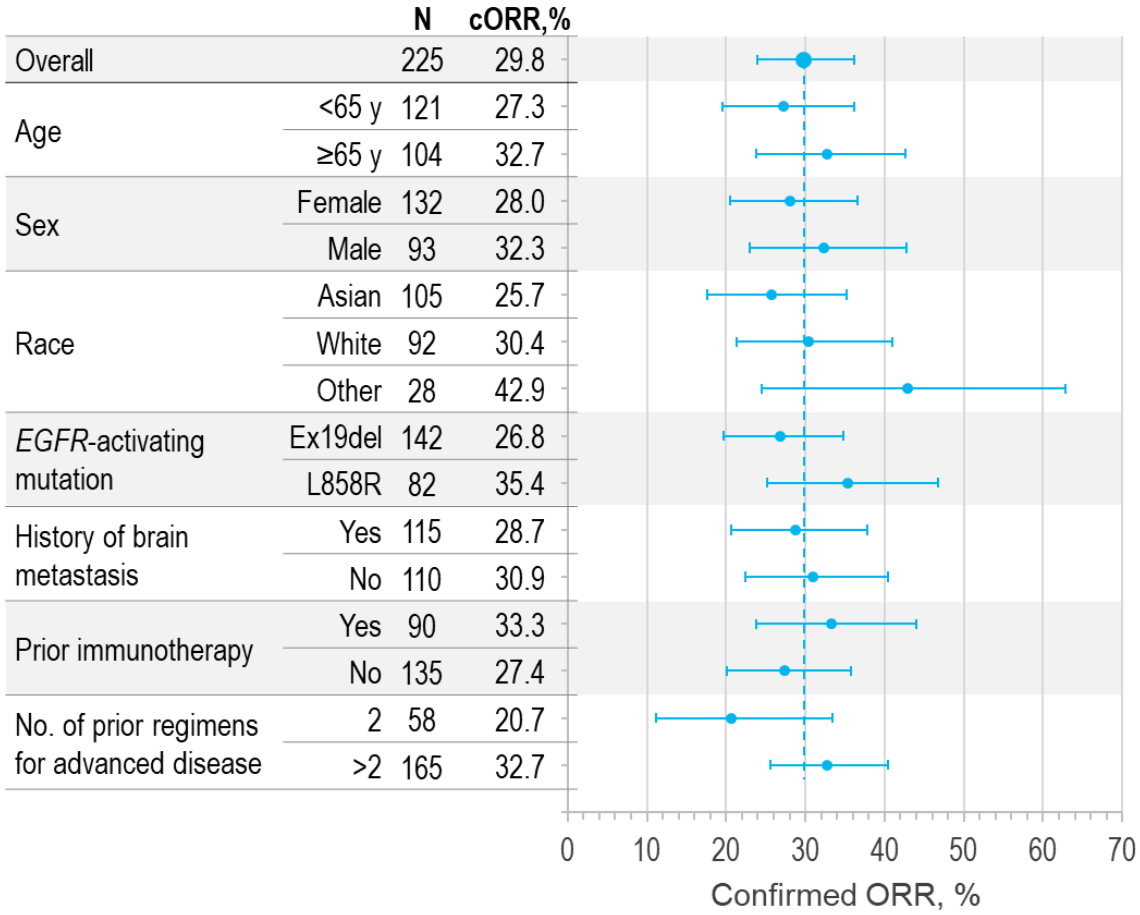
BICR, blinded independent central review; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.
[a] These patients had ECOG performance status of 0 or 1 at screening. [b] One patient had Ex19del and L858R mutations. [c] 2 patients had 1 prior line of therapy.

Clinically Meaningful Efficacy Was Observed in the Overall Population and Across Subgroups

Confirmed responses and survival		Prior EGFR TKI (any) and PBC (N=225)	Subset with prior 3G EGFR TKI and PBC (n=209)
cORR (95% CI), %		**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)

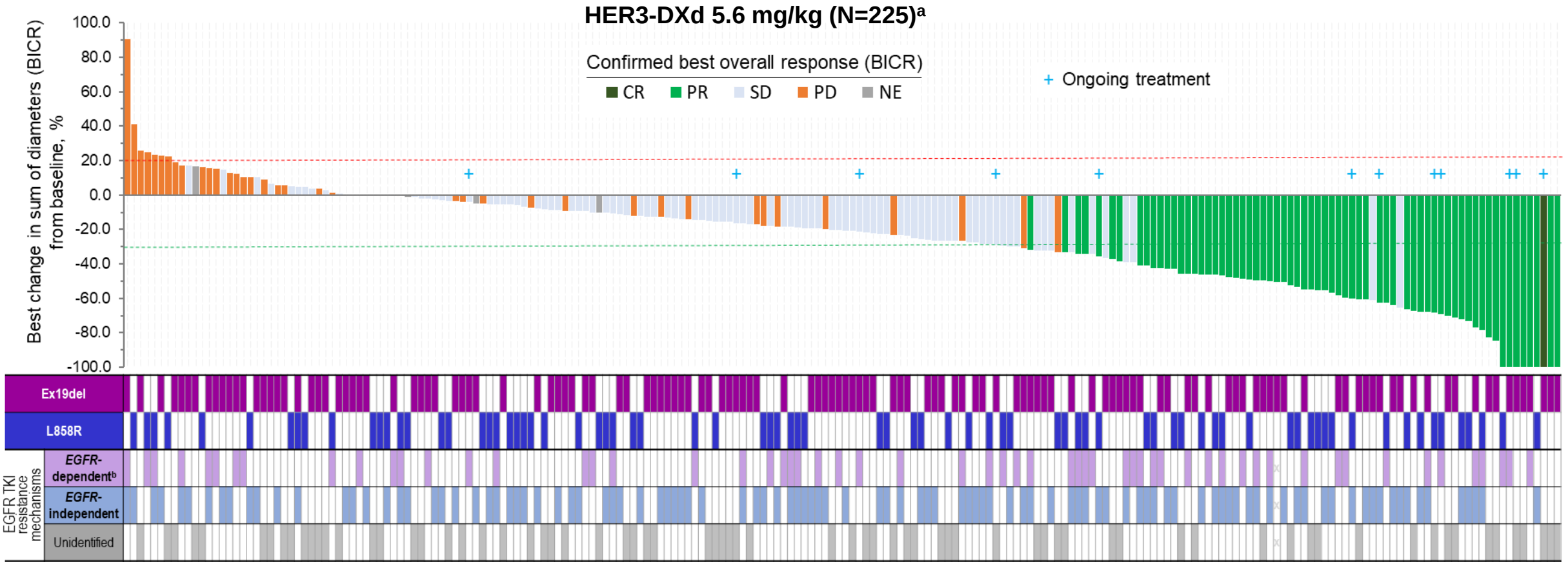
Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

cORR by Patient and Disease Characteristics at Study Entry



3G, third generation; BICR, blinded independent central review; cORR, confirmed objective response rate (CR or PR confirmed ≥4 weeks after initial response [RECIST v1.1]); CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] Includes non-CR/non-PD. [b] No adequate postbaseline tumor assessment (n=12); SD too early (SD <5 weeks after start of study treatment [n=4]).

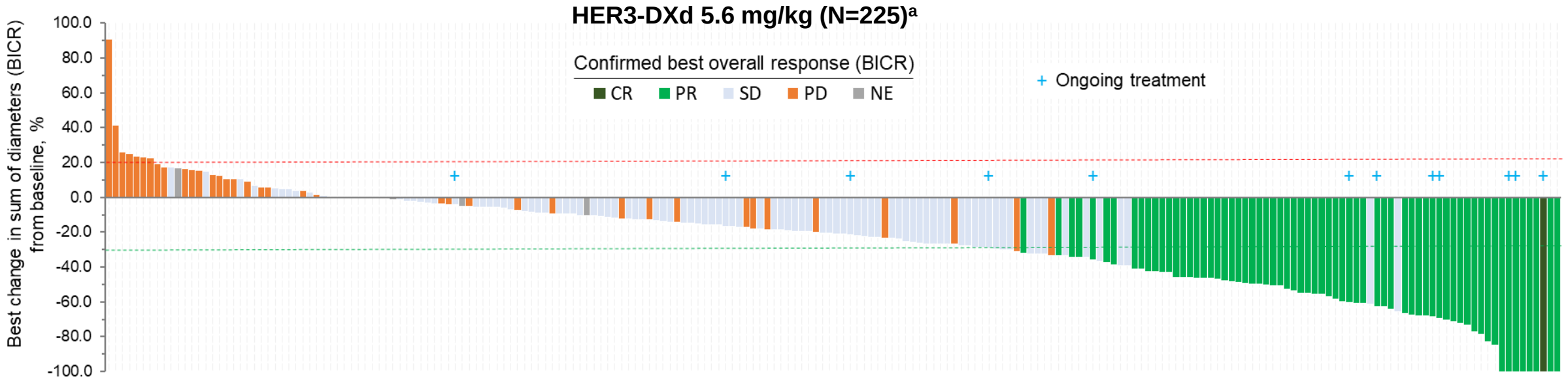
Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance



Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

BICR, blinded independent central review; CR, complete response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] 210 patients had evaluable target lesion measurements at both baseline and post baseline and are included. [b] T790M was not included as an *EGFR*-dependent mechanism of EGFR TKI resistance.

Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance



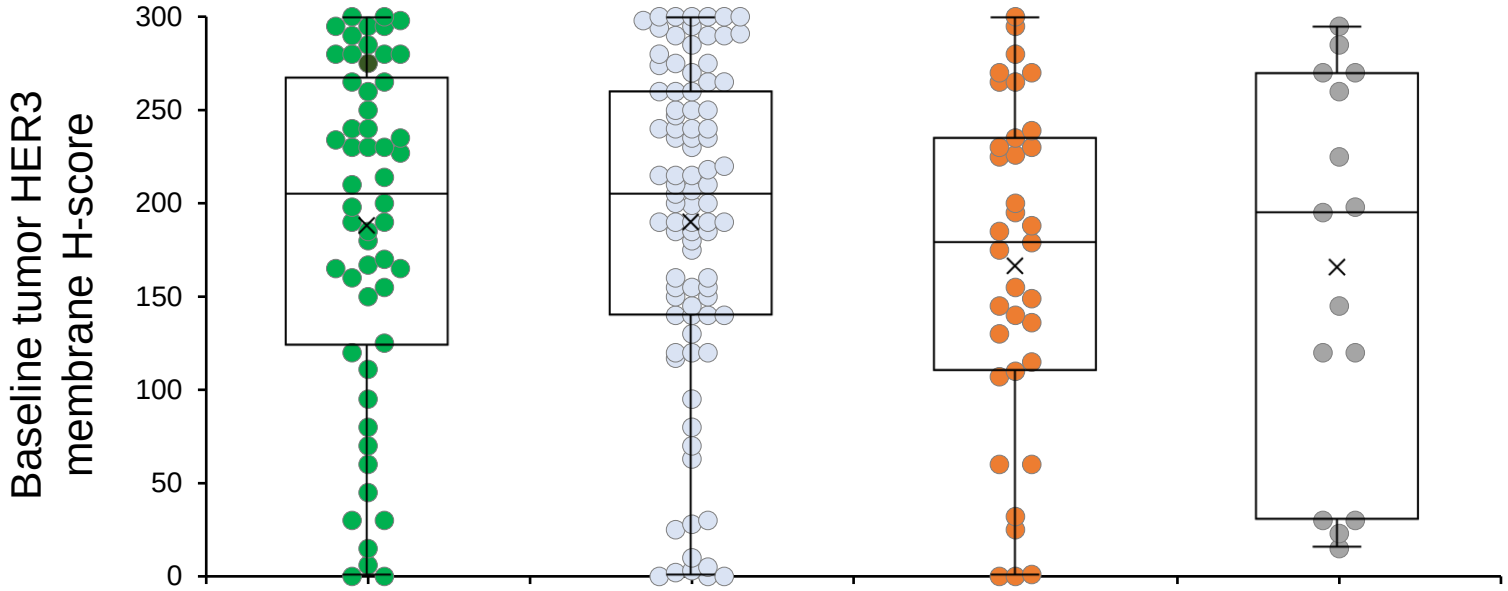
	Type of EGFR TKI resistance mechanism			
	EGFR-dependent, only (n=34)	*EGFR*-independent, only (n=81)	Both *EGFR*-dependent and -independent (n=32)	None identified (n=77)
Confirmed ORR (95% CI), %	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

BICR, blinded independent central review; CR, complete response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] 210 patients had evaluable target lesion measurements at both baseline and post baseline and are included.

Efficacy Observed Across a Broad Range of Pretreatment Tumor HER3 Membrane Expression Levels

Association of Baseline Tumor HER3 Membrane H-Score With Confirmed BOR by BICR Following Treatment With HER3-DXd 5.6 mg/kg (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	205	205	179	195
(range)	(0-300)	(0-300)	(0-300)	(15-295)

Response data are for the snapshot data cutoff, 18 May 2023.
Medians are indicated by horizontal lines; means are indicated by X.

BICR, blinded independent central review; BOR, best overall response; CR, complete response; HER, human epidermal growth factor receptor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a] 193 patients had tumor tissue 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.

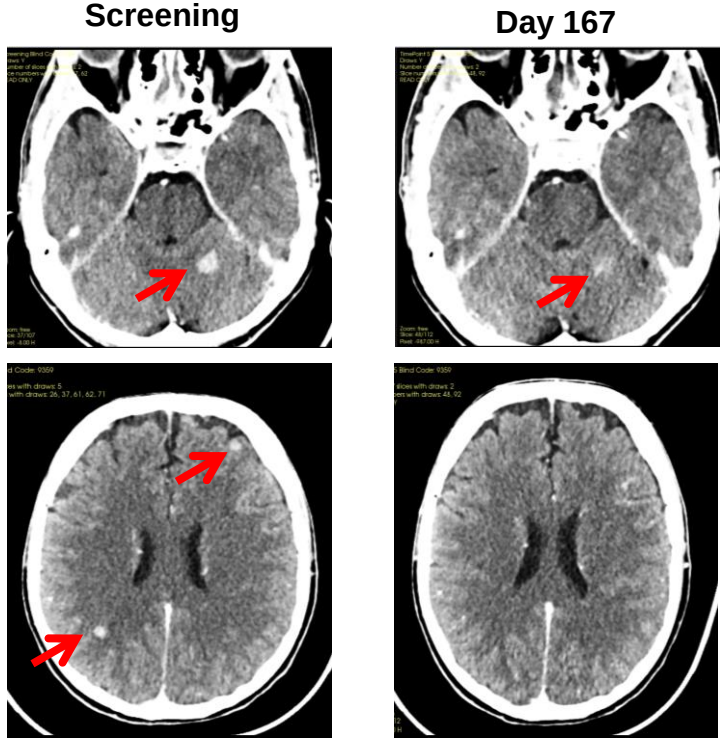
Intracranial Responses (by CNS BICR) Observed With HER3-DXd

Intracranial Efficacy of HER3-DXd in Patients With Brain Metastases at Baseline

Intracranial response by CNS BICR per CNS RECIST	Patients with brain metastasis at baseline and no prior radiotherapy (N=30)[a]
Confirmed ORR (95% CI), %	33.3 (17.3-52.8)
CR, n (%)	9 (30.0)[b]
PR, n (%)	1 (3.3)
SD, n (%)[c]	13 (43.3)
PD, n (%)	4 (13.3)
NE, n (%)	3 (10.0)
DCR (95% CI), %	76.7 (57.7-90.1)
DOR, median (95% CI), mo	8.4 (5.8-9.2)

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

Partial CNS Response in a Patient With a Measurable CNS BICR Target Lesion



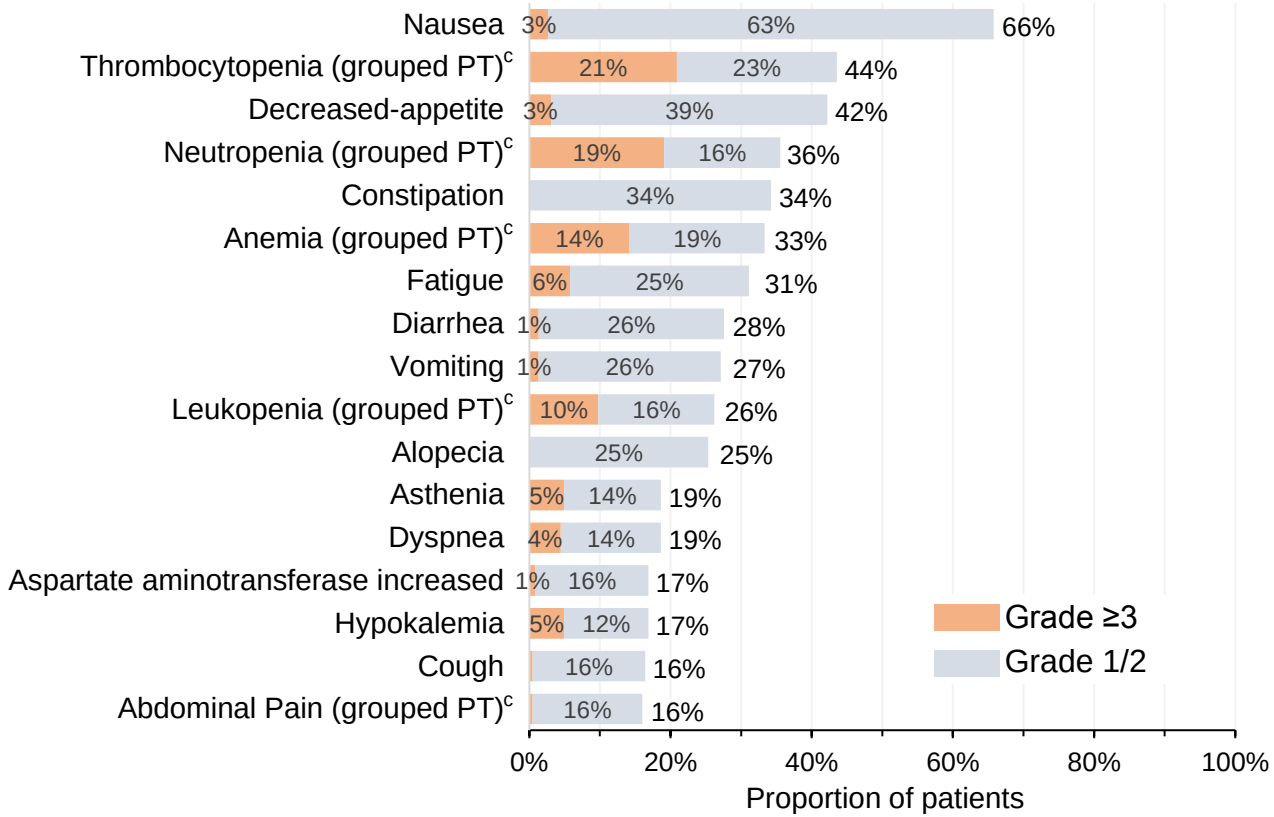
BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DCR, disease control rate (CR+PR+SD); DOR, duration of response; MRI, magnetic resonance imaging; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] 7 patients had measurable target lesions; 23 patients had only nontarget lesions. [b] 8 patients had only nontarget lesions. [c] Includes non-CR/non-PD.

The Safety Profile of HER3-DXd Was Manageable and Tolerable

Safety summary	HER3-DXd 5.6 mg/kg (N=225)
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation[a]	16 (7.1)
Associated with treatment dose reduction	48 (21.3)
Associated with treatment dose interruption	91 (40.4)
Grade ≥3 TEAE, n (%)	146 (64.9)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[b]	4 (1.8)
Grade ≥3	102 (45.3)
Serious TEAE	34 (15.1)
Adjudicated interstitial lung disease, n (%) [All were adjudicated as treatment-related]	12 (5.3)
Grade 1	1 (0.4)
Grade 2	8 (3.6)
Grade 3	2 (0.9)
Grade 4	0
Grade 5	1 (0.4)

Primary data cutoff, 21 Nov 2022.
Median treatment duration: 5.5 (range, 0.7-18.2) months.

Most Common TEAEs Occurring in ≥15% of Patients (N=225)



Any hematologic toxicities typically occurred early in treatment, were transient, and were not associated with clinical sequelae

GI, gastrointestinal; TEAE, treatment-emergent adverse event.
[a] TEAEs leading to discontinuation included pneumonitis (n=4), blood bilirubin increased (n=2), dyspnea (n=2), and cholestatic jaundice, anemia, fatigue, portal hypertension, duodenal perforation, urosepsis, asthenia, and white blood count decreased (n=1 each). [b] TEAEs associated with death that were considered related to study drug included pneumonitis, respiratory failure, GI perforation, and pneumonia (no neutropenia) in 1 patient each. [c] Grouped terms.

Conclusions

- HER3-DXd provided clinically meaningful and durable efficacy (cORR, 29.8%) in patients with advanced *EGFR*-mutated NSCLC that progressed following EGFR TKI and platinum-based chemotherapy; efficacy was observed across diverse mechanisms of EGFR TKI resistance and across a broad range of pretreatment tumor HER3 membrane expression
- HER3-DXd showed clinically meaningful intracranial antitumor activity in patients with untreated brain metastases
  - Intracranial cORR, 33.3%
  - Intracranial DCR, 76.7%
- The safety profile of HER3-DXd in this population of heavily pretreated patients was manageable and tolerable and was consistent with previous reports
  - TEAE associated with treatment discontinuation, 7.1%
  - Adjudicated treatment-related ILD, 5.3%
- HER3-DXd has emerged as a promising therapy for patients with *EGFR*-mutated NSCLC after the failure of EGFR TKI and platinum-based chemotherapy, for whom available treatment options provide only limited efficacy

Ongoing Lung Cancer Trials

- A phase 3 trial of HER3-DXd vs platinum-based chemotherapy in *EGFR*-mutated NSCLC after progression on third-generation EGFR TKI therapy (HERTHENA-Lung02; NCT05338970)
- A phase 1 trial of HER3-DXd in combination with osimertinib in *EGFR*-mutated NSCLC after progression on 1L osimertinib or in previously untreated patients (NCT04676477)

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HERTHENA-Lung01, a Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in Epidermal Growth Factor Receptor–Mutated Non–Small-Cell Lung Cancer After Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Platinum-Based Chemotherapy

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ABSTRACT

PURPOSE Patritumab deruxtecan, or HER3-DXd, is an antibody-drug conjugate consisting of a fully human monoclonal antibody to human epidermal growth factor receptor 3 (HER3) attached to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker. We assessed the efficacy and safety of HER3-DXd in patients with epidermal growth factor receptor (*EGFR*)–mutated non–small-cell lung cancer (NSCLC).

METHODS This phase II study (ClinicalTrials.gov identifier: NCT04619004) was designed to evaluate HER3-DXd in patients with advanced *EGFR*-mutated NSCLC previously treated with EGFR tyrosine kinase inhibitor (TKI) therapy and platinum-based chemotherapy (PBC). Patients received HER3-DXd 5.6 mg/kg intravenously once every 3 weeks or an uptitration regimen (3.2 → 4.8 → 6.4 mg/kg). The primary end point was confirmed objective response rate (ORR; RECIST 1.1) by blinded independent central review (BICR), with a null hypothesis of 26.4% on the basis of historical data.

RESULTS Enrollment into the uptitration arm closed early on the basis of a prespecified benefit-risk assessment of data from the phase I U31402-A-U102 trial. In total, 225 patients received HER3-DXd 5.6 mg/kg once every 3 weeks. As of May 18, 2023, median study duration was 18.9 (range, 14.9-27.5) months. Confirmed ORR by BICR was 29.8% (95% CI, 23.9 to 36.2); median duration of response, 6.4 months; median progression-free survival, 5.5 months; and median overall survival, 11.9 months. The subgroup of patients with previous osimertinib and PBC had similar outcomes. Efficacy was observed across a broad range of pretreatment tumor HER3 membrane expression levels and across diverse mechanisms of EGFR TKI resistance. In patients with nonirradiated brain metastases at baseline (n = 30), the confirmed CNS ORR by BICR per CNS RECIST was 33.3% (95% CI, 17.3 to 52.8). The safety profile (National Cancer Institute Common Terminology Criteria for Adverse Events v5.0) was manageable and tolerable, consistent with previous observations.

CONCLUSION After tumor progression with EGFR TKI therapy and PBC in patients with *EGFR*-mutated NSCLC, HER3-DXd once every 3 weeks demonstrated clinically meaningful efficacy with durable responses, including in CNS metastases. A phase III trial in *EGFR*-mutated NSCLC after progression on an EGFR TKI is ongoing (HERTHENA-Lung02; ClinicalTrials.gov identifier: NCT05338970).

ACCOMPANYING CONTENT

Data Supplement

Protocol

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