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

Helena A. Yu,[1] Yasushi Goto,[2] Hidetoshi Hayashi,[3] Enriqueta Felip,[4] James Chih-Hsin Yang,[5] Martin Reck,[6] Kiyotaka Yoh,[7] Se-Hoon Lee,[8] Luis Paz-Ares,[9] Benjamin Besse,[10] Paolo Bironzo,[11] Dong-Wan Kim,[12] Melissa L. Johnson,[13] Yi-Long Wu,[14] Qian Dong,[15] Pang-Dian Fan,[15] Pomy Shrestha,[15] David W. Sternberg,[15] Dalila Sellami,[15] Pasi A. Jänne[16]

[1]Department of Medicine, Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Kindai University, Osaka, Japan; [4]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]National Taiwan University Hospital, Taipei City, Taiwan; [6]Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, LungenClinic Grosshansdorf, Grosshansdorf, Germany; [7]National Cancer Center Hospital East, Kashiwa, Japan; [8]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine and Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, Republic of Korea; [9]Hospital Universitario 12 de Octubre, Spanish National Cancer Research Center, Universidad Complutense and CIBERONC, Madrid, Spain; [10]Université Paris-Saclay, Gustave Roussy, Villejuif, France; [11]Department of Oncology, University of Torino, Torino, Italy; [12]Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Hospital, Seoul, Republic of Korea; [13]Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN, USA; [14]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Southern Medical University, Guangzhou, China; [15]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [16]Dana-Farber Cancer Institute, Boston, MA, USA

PURPOSE

- 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

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
  - TEAEs 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 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)

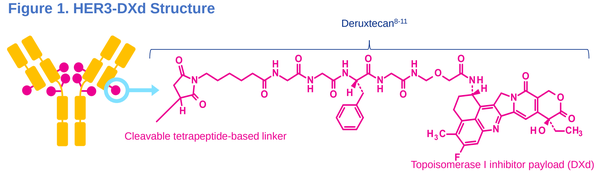
Quick Response (QR) link to the simultaneous publication in the *Journal of Clinical Oncology* (Yu HA, et al. *J Clin Oncol.* Published online September 10, 2023)

Previously presented at IASLC 2023 World Conference on Lung Cancer.

BACKGROUND

- 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 (adenocarcinoma)[1]
  - 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[4,5]
  - Real-world PFS after progression with osimertinib and platinum-based chemotherapy: 3.3 (95% CI, 2.8-4.4) months[5]
  - Estimated real-world cORR: 14.1% (95% CI, 3.7%-33.1%)[6]
- CNS metastases are common in this population,[7] and therapies to ensure CNS control are needed
- HER3-DXd is an ADC composed of 3 parts: a fully human anti-HER3 IgG1 mAb (patritumab), a topoisomerase I inhibitor payload (DXd), and a tumor selective, tetrapeptide-based cleavable linker that covalently bonds the other 2 components[8-12] (**Figure 1**)

Figure 1. HER3-DXd Structure

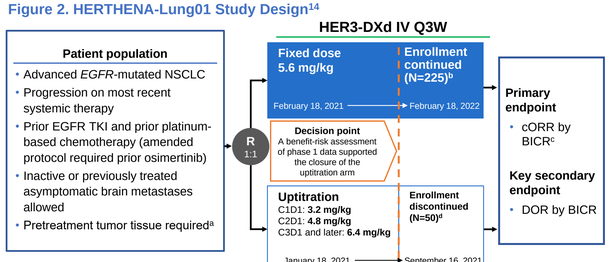


- A phase 1 study of HER3-DXd for advanced NSCLC demonstrated efficacy in patients with *EGFR*-activating mutations and diverse mechanisms of resistance to EGFR TKIs (including *EGFR*-dependent and -independent mechanisms)[13]
  - The study showed that HER3-DXd 5.6 mg/kg administered intravenously every 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

METHODS

- HERTHENA-Lung01 is an ongoing phase 2 trial in patients with advanced *EGFR*-mutated NSCLC who had prior treatment with EGFR TKI therapy and platinum-based chemotherapy (**Figure 2**)
  - Patients with inactive or previously treated asymptomatic brain metastases were allowed
- 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

Figure 2. HERTHENA-Lung01 Study Design[14]



Primary data cutoff: 21 Nov 2022.[e]
Snapshot data cutoff: 18 May 2023 (additional 6 months of follow-up).
Data are presented for the 5.6-mg/kg fixed-dose arm.
[a] Inclusion not based on detection of HER3 expression. [b] 226 patients were enrolled; 225 received ≥1 dose. [c] Complete or partial response confirmed ≥4 weeks after initial response (RECIST version 1.1). [d] 51 patients were enrolled; 50 received ≥1 dose. [e] 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.

RESULTS

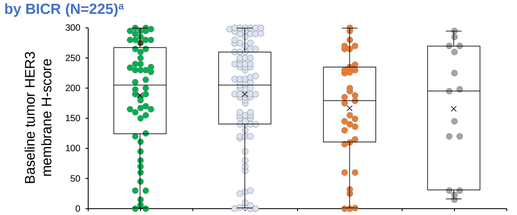
- As of the 18 May 2023 snapshot data cutoff, 225 patients had been treated with HER3-DXd. Patients in HERTHENA-Lung01 were heavily pretreated and had adverse prognostic characteristics (**Table**)
- Clinically meaningful efficacy was similar in the overall population and across baseline patient and disease characteristics (**Figure 3**)
- Efficacy was seen across a broad range of pretreatment tumor HER3 membrane expression levels (**Figure 4**), and tumor reduction occurred across diverse mechanisms of EGFR TKI resistance (**Figure 5**)
- Intracranial efficacy was observed in patients with brain metastases at baseline and no prior radiotherapy to the brain (**Figure 6**)

Table. 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)

[a] These patients had ECOG performance status of 0 or 1 at screening. [b] One patient had Ex19del and L858R mutations. [c] Two patients had 1 prior line of therapy.

Figure 4. Association of Baseline Tumor HER3 Membrane H-Score With Confirmed BOR by BICR (N=225)[a]



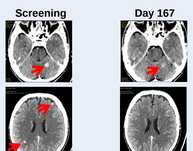
Confirmed BOR (BICR)	CR/PR	SD	PD	NE
Biomarker-evaluable patients, n/n	54/67	89/99	35/43	15/16
H-score, median (range)	205 (0-300)	205 (0-300)	179 (0-300)	195 (15-295)

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

Figure 6. Intracranial Response by CNS BICR per CNS RECIST and Example Scans

	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)

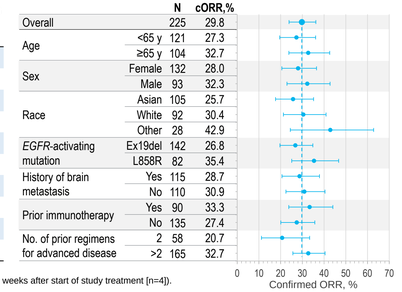
Partial CNS Response in a Patient With a Measurable CNS BICR Target Lesion



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

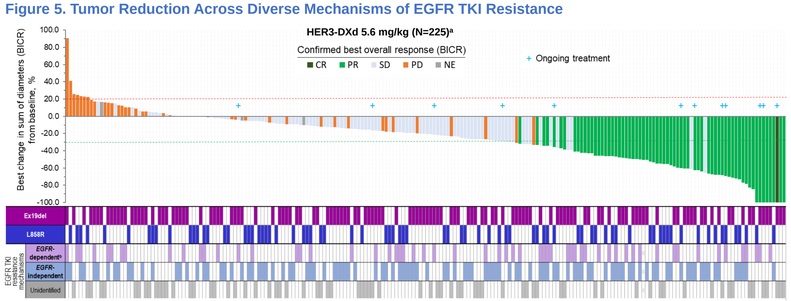
Figure 3. Overall Confirmed Responses and Survival and Confirmed Responses in Different Subgroups

	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)**
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.
[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]).

Figure 5. Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance

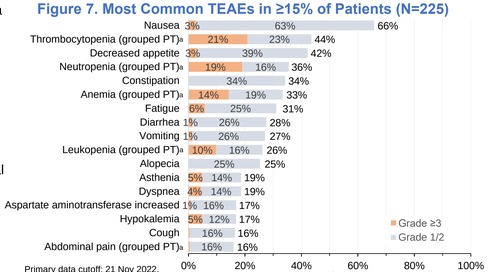


Type of EGFR TKI resistance mechanism	*EGFR*-dependent only (n=34)	*EGFR*-independent only (n=81)	Both *EGFR*-dependent and -independent (n=32)	None identified (n=77)
Confirmed ORR (95% CI), %	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)

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

- HER3-DXd 5.6 mg/kg IV Q3W demonstrated a manageable and tolerable safety profile (**Figure 7**)
  - TEAEs led to treatment discontinuation in 16 patients (7.1%)
  - 24 patients (10.7%) died due to TEAEs, and 4 deaths (1.8%) were considered treatment related
  - 12 ILD events (5.3%) were adjudicated as treatment related by an independent central review committee (1 grade 1, 8 grade 2, 2 grade 3, 1 grade 5)
- Any hematologic toxicities typically occurred early in treatment, were transient, and were not associated with clinical sequelae

Figure 7. Most Common TEAEs in ≥15% of Patients (N=225)



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

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ABBREVIATIONS

1L, first line; 3G, third generation; ADC, antibody-drug conjugate; BICR, blinded independent central review; BOR, best overall response; C, cycle; CNS, central nervous system; cORR, confirmed objective response rate; CR, complete response; D, day; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; IgG1, immunoglobulin G1; ILD, interstitial lung disease; IV, intravenous; mAb, monoclonal antibody; NE, not evaluable; NSCLC, non-small cell lung cancer; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; PT, preferred term; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

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