HER-3 as a New Target in NSCLC

Edgardo S. Santos, MD, FACP
Medical Oncology-Thoracic
Clinical Associate Professor
Charles E. Schmidt School of Medicine/Florida Atlantic University
Treasurer, FLASCO
President, FLASCO Foundation

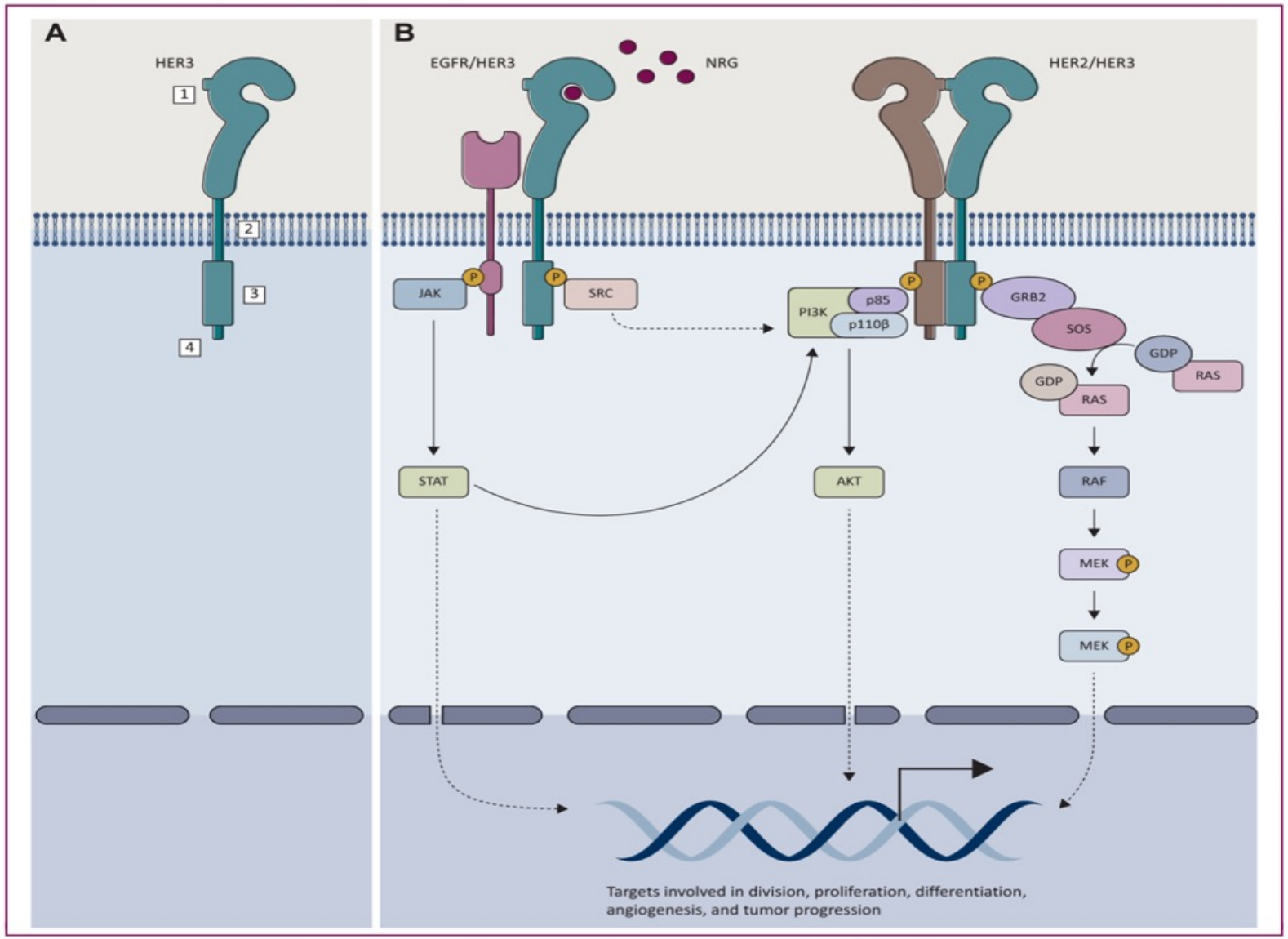
November 18, 2023

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

OLA
Oncology Latin American Association

Targeting HER-3 for Cancer Therapy-Background:

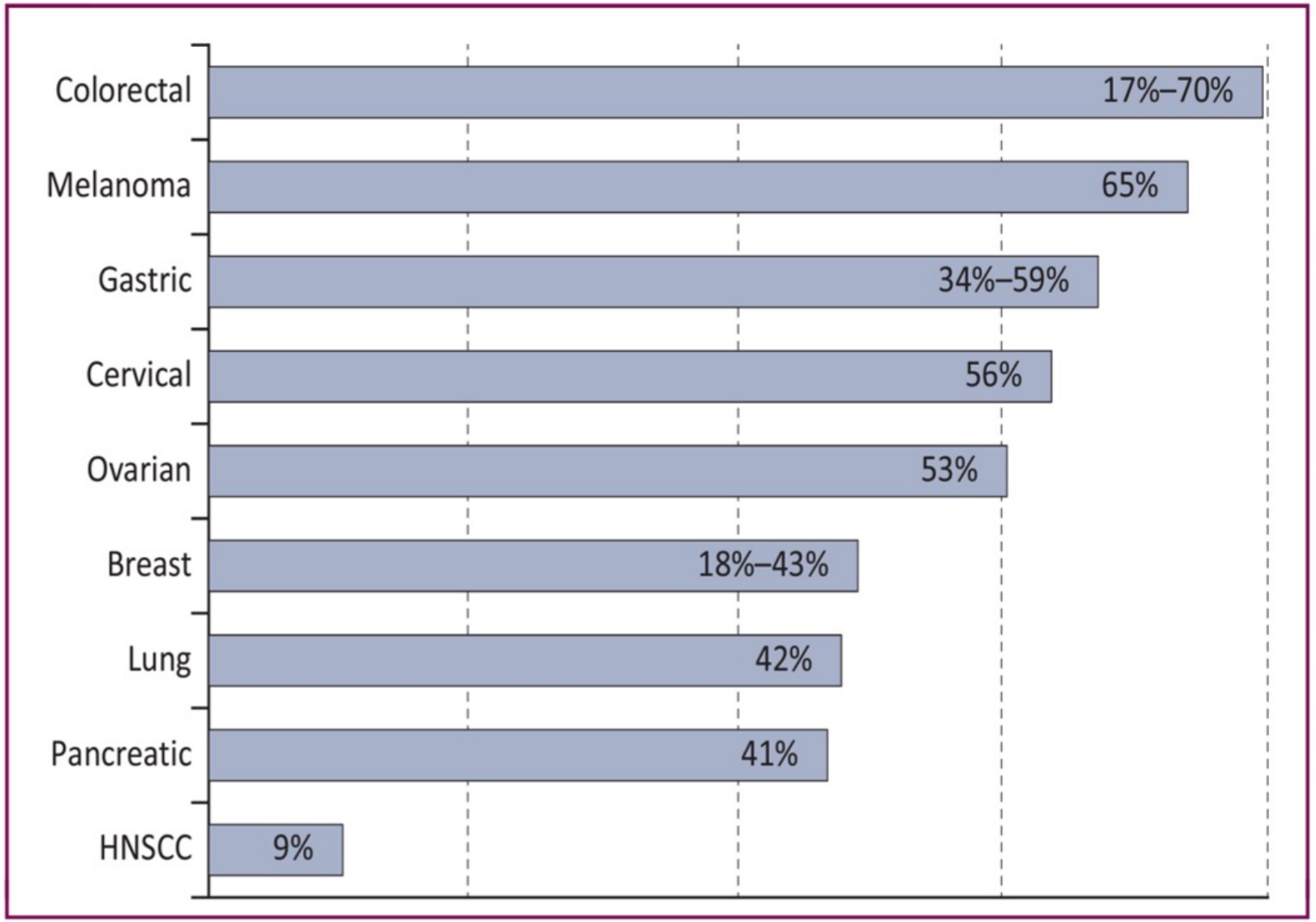
- HER-3 is a member of the human epidermal growth factor receptors family.
- Its main ligands are neuregulins 1 and 2.
- It has a poor tyrosine kinase activity; however, HER3 can heterodimerize with HER2 and/or EGFR, leading to a drastic enhancement of transphosphorylation and activation of downstream signaling pathways.
- The above promotes oncogenesis, metastatic dissemination, and drug resistance.



Uliano J et al. ESMO Open. 2023; Feb;8(1): 100790.

Targeting HER-3 for Cancer Therapy-Background:

- HER-3 is expressed across solid tumors and multiple efforts have been done to therapeutically target HER3 by blocking either the ligand binding domain or its dimerization with other receptors.



Uliano J et al. ESMO Open. 2023; Feb;8(1): 100790.

Targeting HER-3 for Cancer Therapy-Background:

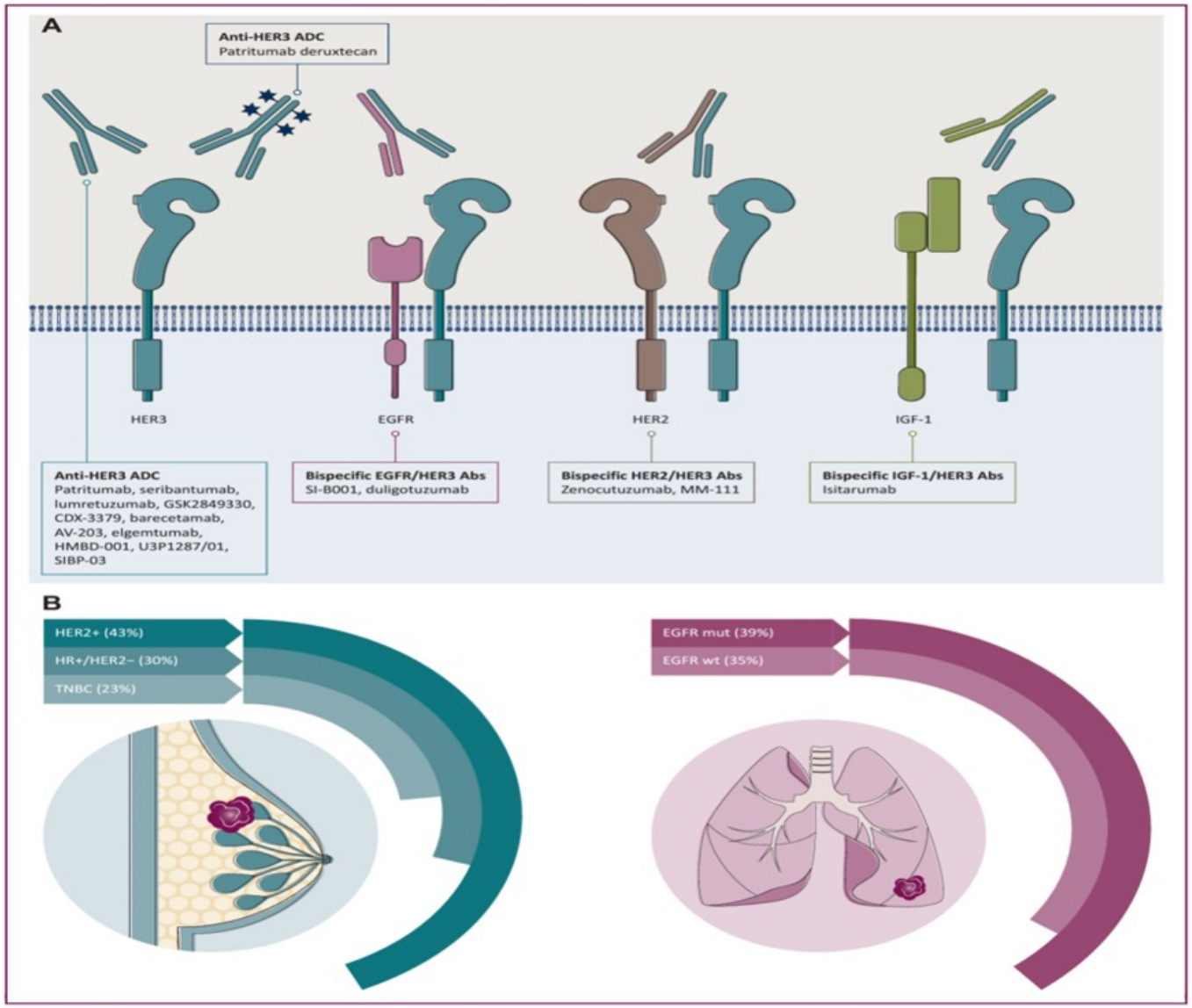
- Anti-HER-3 MoAbs or bispecific antibodies have led to unsatisfactory results across several tumor types.

Table 1. HER3-targeted agents under clinical development

Drug type	Name of the compound	Mechanism of action	Phase of clinical development
Monoclonal antibodies	Patritumab (U3-1287)	HER3-directed MoAb	Phase III
	Seribantumab (MM-121)	HER3-directed MoAb	Phase II
	Lumretuzumab (RO5479599)	Immunoconjugate containing a glycoengineered, humanized HER3-directed MoAb; ADCC	Phase Ib/II
	GSK2849330	HER3-directed MoAb	Phase I
	CDX-3379	A human HER3-directed MoAb	Phase II
	Barecetamab (ISU104)	A fully human HER3-directed MoAb.	Phase I
	AV-203	A humanized HER3-directed MoAb.	Phase I
	Elgemtumab (LJM716)	HER3-directed MoAb	Phase I/II
	HMBD-001	Anti-HER3 MoAb	Phase I/II
	U3P1287/01 (AMG888)	Anti-HER3 MoAb	Phase I
	SIBP-03	HER3-directed recombinant humanized MoAb	Phase Ia
Bispecific antibodies	Zenocutuzumab (MCLA-128)	HER2/HER3-directed IgG bispecific antibody; ADCC	Phase II
	Sym013	An antibody mixture composed of six humanized IgG1 MoAbs EGFR, HER2, and HER3 directed	Phase I/II
	Isitarumab (MM-141)	HER3/IGF-1R-directed bispecific antibody	Phase II
	SI-B001	EGFR/HER3-directed bispecific IgG	Phase I
	MM-111	HER2/HER3 bispecific antibody	Phase I
	Duligotuzumab (MEHD7954A)	EGFR/HER3-directed bispecific antibody	Phase II
ADCs	Patritumab deruxtecan (U3 1402)	HER3-directed ADC, composed of patritumab, an HER3-directed MoAb, conjugated to the topoisomerase I inhibitor DX 8951	Phase I/II

Targeting HER-3 for Cancer Therapy-Background:

- The ADC Patritumab deruxtecan (a HER-3-directed delivery of cytotoxic payloads) has recently demonstrated encouraging activity in several tumor types.

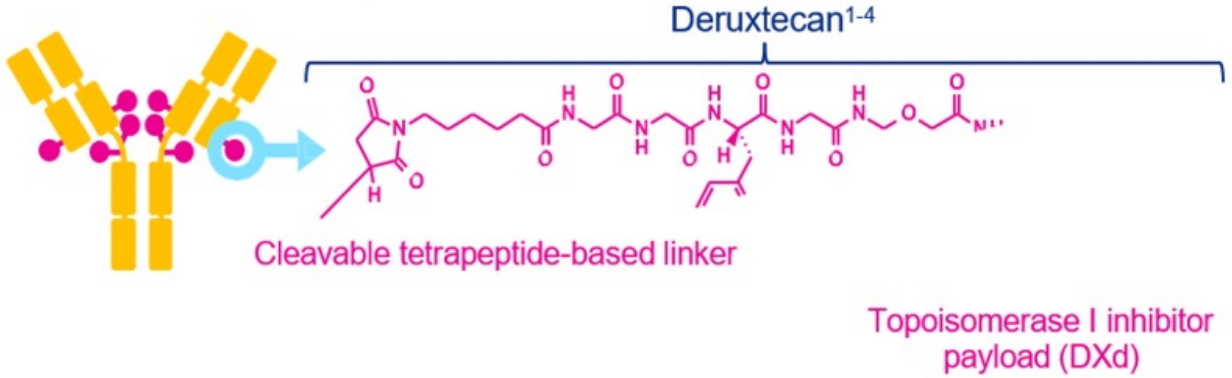


Uliano J et al. ESMO Open. 2023; Feb;8(1): 100790.

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



Properties of this ADC:

- ✓ Payload mechanism of action: topoisomerase I inhibitor1-4,a
- ✓ High potency of payload1-4,a
- ✓ High drug to antibody ratio ~81,2,a
- ✓ Payload with short systemic half-life2,3,a,b
- ✓ Stable linker-payload
- ✓ Tumor-selective cleavable linker1-5,a
- ✓ Bystander antitumor effect2,6,a

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.

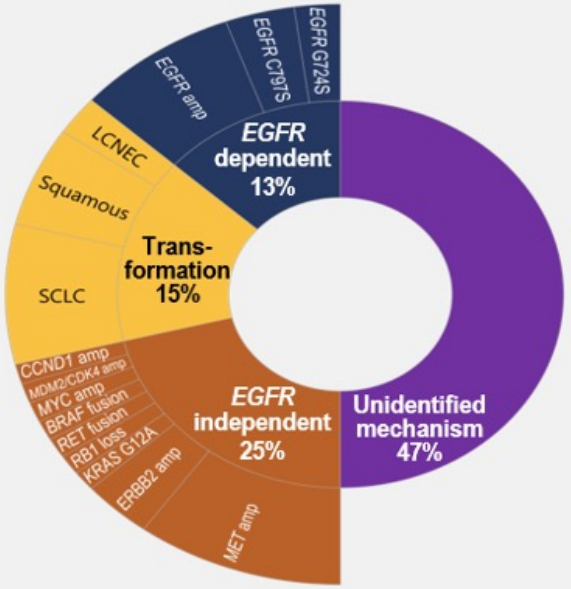
1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050.
5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388.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

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.

Helena A. Yu. IASLC World Conference on Lung Cancer; Sept 9-12, 2023, Singapore.

HERTHENA-Lung01

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

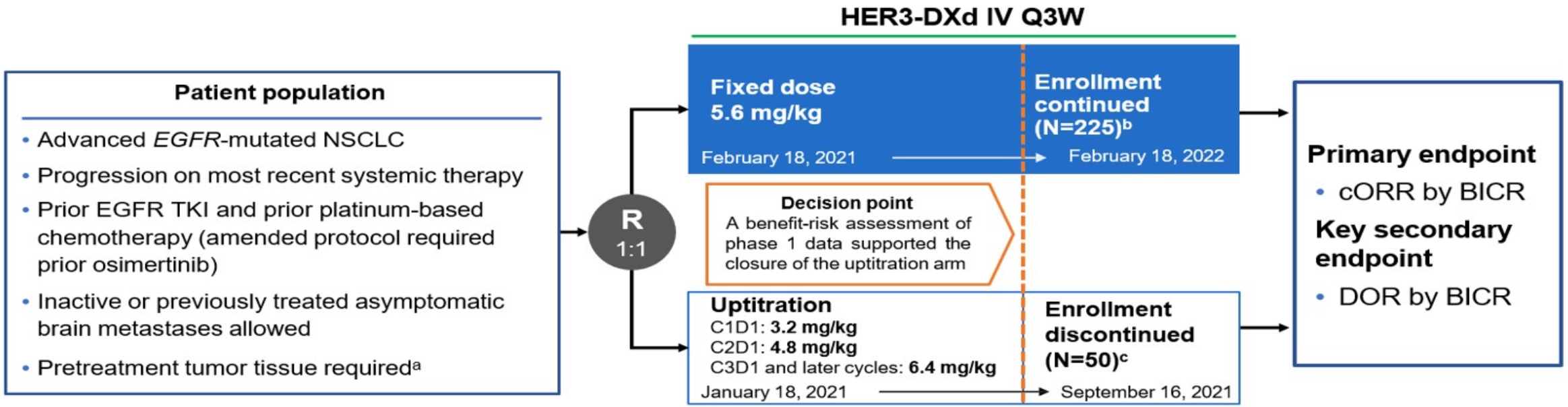
- A phase 1 study of HER3-DXd for advanced NSCLC demonstrated efficacy in patients with *EGFR*-activating mutations and diverse mechanisms of resistance to EGFR TKIs (including *EGFR*-dependent and -independent mechanisms)
  - The study showed that HER3-DXd 5.6 mg/kg administered intravenously every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

HERTHENA-Lung01

Patritumab Deruxtecan
HERTHENA-Lung01

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.

Helena A. Yu. IASLC World Conference on Lung Cancer; Sept 9-12, 2023, Singapore.

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.

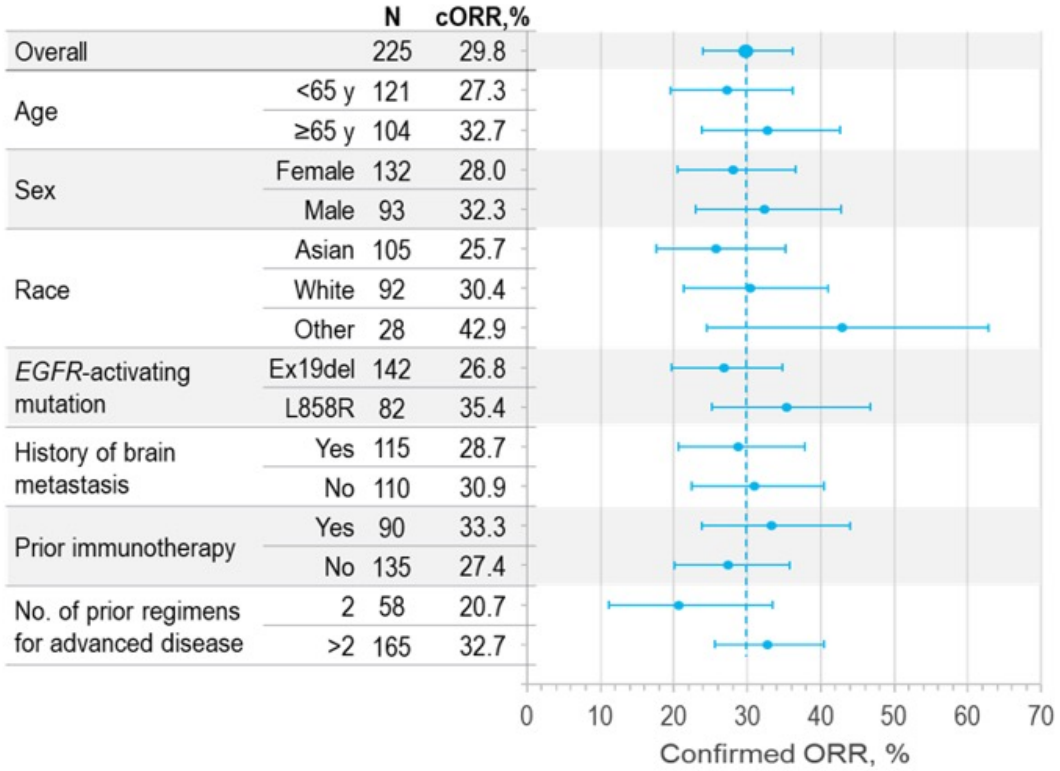
Patritumab Deruxtecan
HERTHENA-Lung01

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



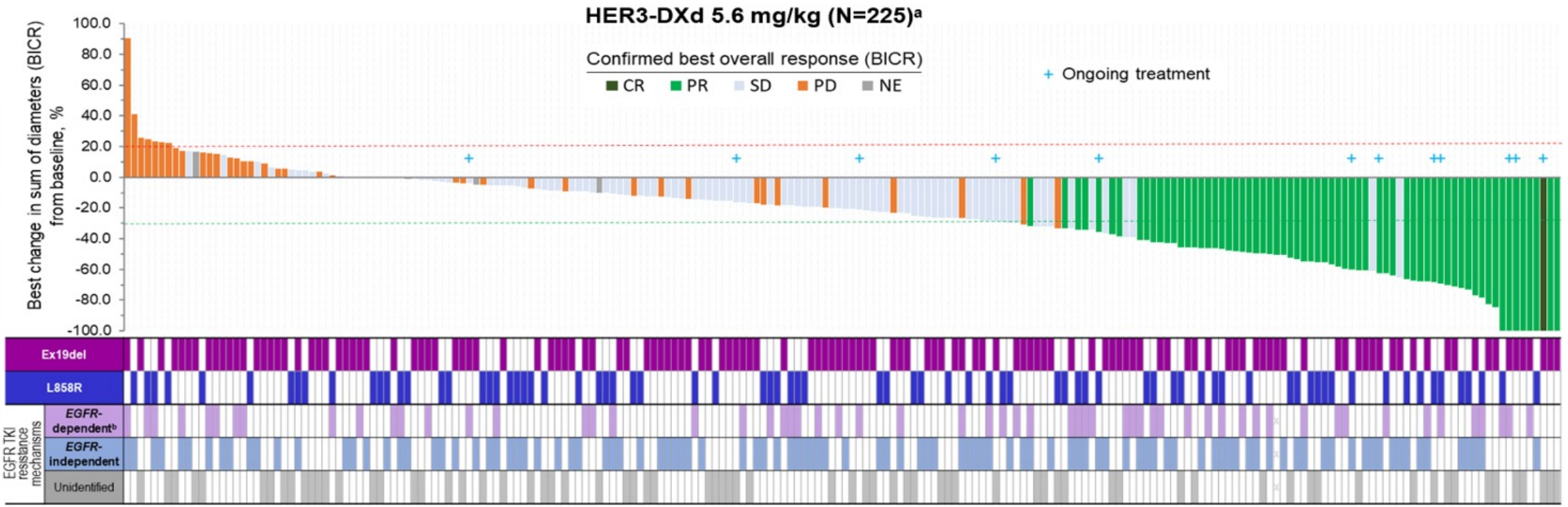
3G, third generation; BICR, blinded independent central review; cORR, confirmed objective response rate (CR or PR confirmed ≥4 weeks after initial response [RECIST v1.1]); CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; OS, overall survival; PBC, platinum-based 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]).

Helena A. Yu. IASLC World Conference on Lung Cancer; Sept 9-12, 2023, Singapore.

HERTHENA-Lung01

Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance

Patritumab Deruxtecan
HERTHENA-Lung01



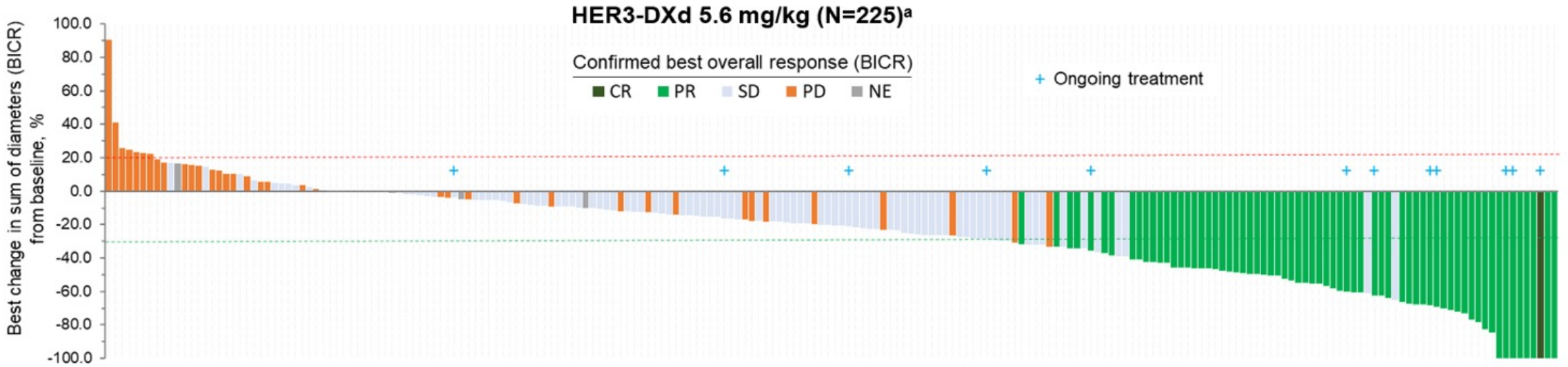
Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

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.

Helena A. Yu. IASLC World Conference on Lung Cancer; Sept 9-12, 2023, Singapore.

Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance

Patritumab Deruxtecan
HERTHENA-Lung01



	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.

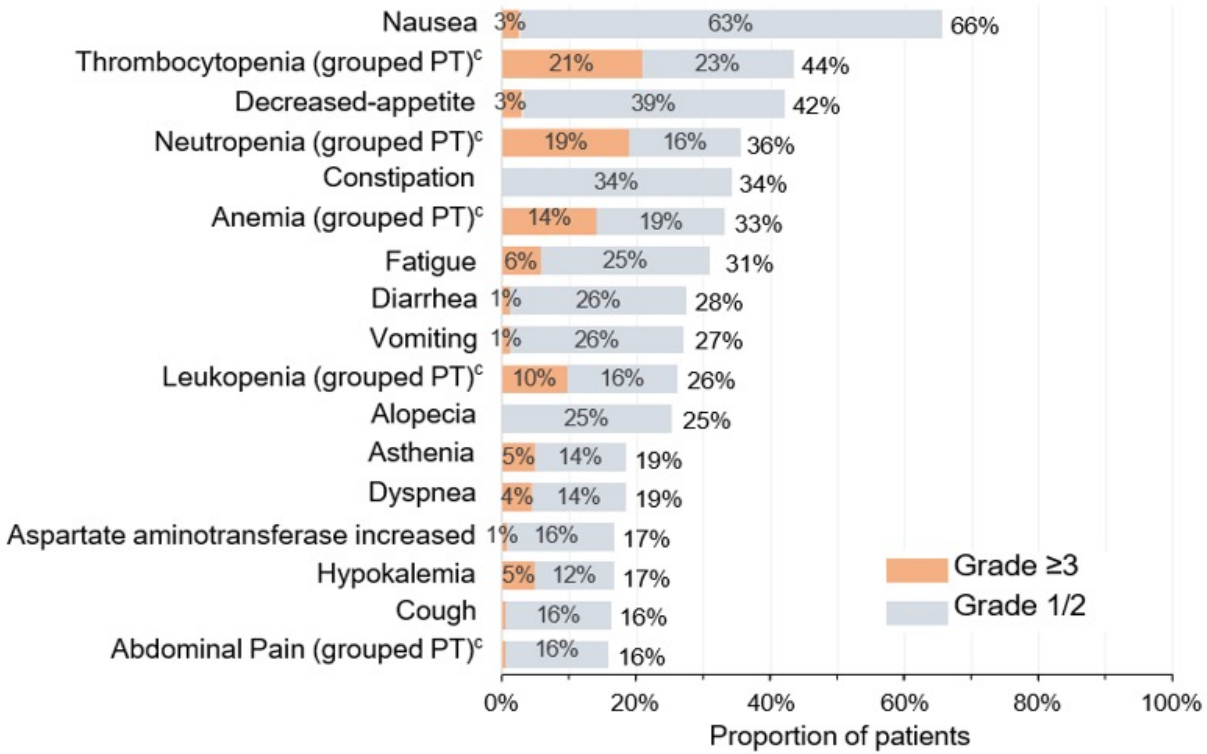
Patritumab Deruxtecan
HERTHENA-Lung01

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)



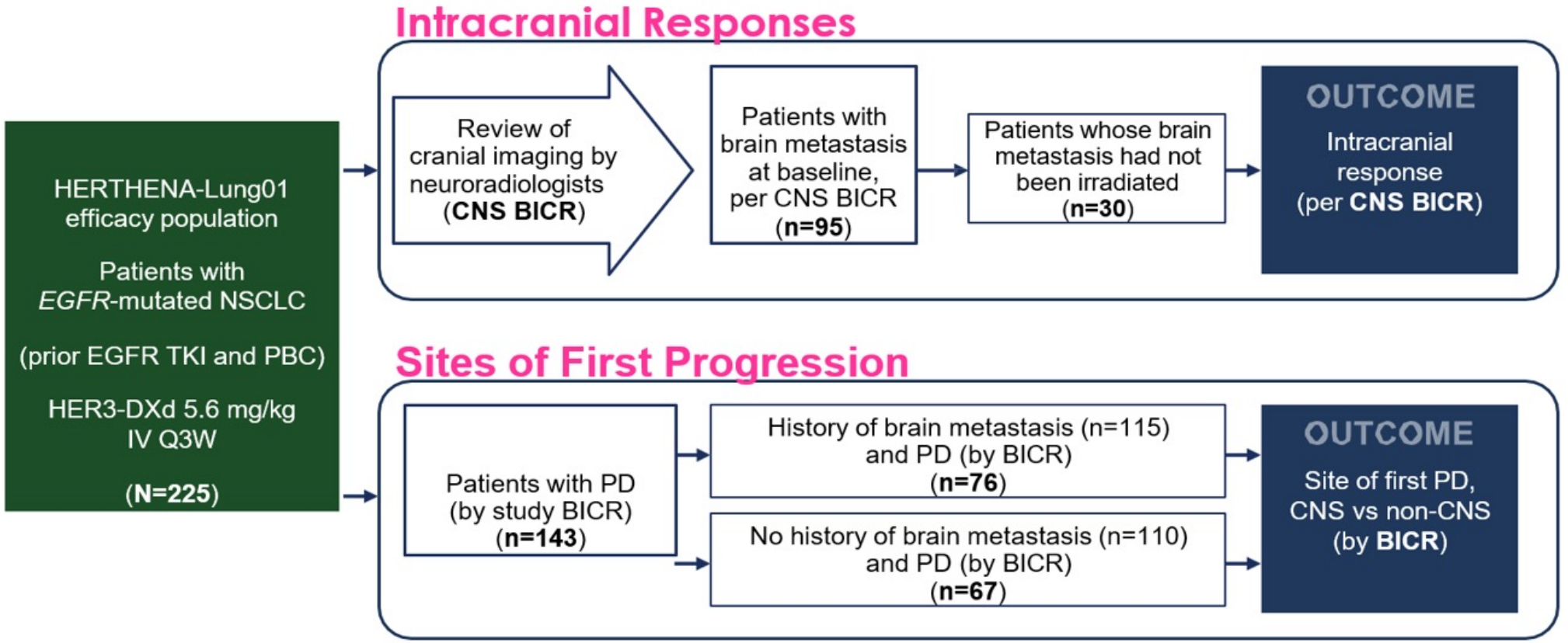
Any hematologic toxicities typically occurred early in treatment, were transient, and were not associated with clinical sequelae

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.

HERTHENA-Lung01

Patritumab Deruxtecan
HERTHENA-Lung01

Additional Analyses of HERTHENA-Lung01



BICR, blinded independent central review; CNS, central nervous system; IV, intravenous; NSCLC, non–small cell lung cancer; PBC, platinum-based chemotherapy; PD, progressive disease; RT, radiotherapy; Q3W, every 3 weeks; TKI, tyrosine kinase inhibitor.

Melissa L. Johnson, Sarah Cannon Research Institute, USA

Patritumab Deruxtecan
HERTHENA-Lung01

HER3-DXd Demonstrated Clinically Meaningful Intracranial Responses in Patients With no Prior Radiotherapy

Responses by CNS BICR[a]	All patients with baseline BM by CNS BICR (n=95)	Patients whose baseline BM had not been irradiated (n=30)[b]
CNS cORR, n (%) [95% CI]	19 (20.0) [12.5, 29.5]	10 (33.3) [17.3-52.8]
CR, n (%)	15 (15.8)	9 (30.0)[c]
PR, n (%)	4 (4.2)	1 (3.3)
SD/non-CR/non-PD, n (%)	57 (60.0)	13 (43.3)
PD, n (%)	13 (13.7)	4 (13.3)
NE, n (%)	6 (6.3)	3 (10.0)
CNS DCR (95% CI), %	80.0 (70.5, 87.5)	76.7 (57.7-90.1)
CNS DOR, median (95% CI), mo	9.2 (8.1-11.1)	8.4 (5.8-9.2)

Snapshot data cutoff, 18 May 2023.

Median study follow-up, 18.9 (range, 14.9-27.5) months.

BICR, blinded independent central review; BM, brain metastasis; CNS, central nervous system; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate (CR + PR + SD/non-CR/non-PD); DOR, duration of response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Responses assessed by a panel of neuroradiologists according to CNS RECIST criteria. [b] 7 patients had measurable target lesions; 23 had only nontarget lesions. [c] 8 patients had only nontarget lesions.

Melissa L. Johnson, Sarah Cannon Research Institute, USA

Patritumab Deruxtecan
HERTHENA-Lung01

The Rate of Intracranial Progression in Patients With no History of Brain Metastasis was Low

	History of brain metastasis		
Site of first PD (by BICR)[a]	Yes (n=115)	No (n=110)	All patients (N=225)
All sites, n (%)	76 (66)	67 (61)	143 (64)
Non-CNS, n (%)	63 (55)	65 (59)	128 (57)
CNS, n (%)	24 (21)	3 (3)	27 (12)
CNS and non-CNS, n (%)	11 (10)	1 (1)	12 (5)

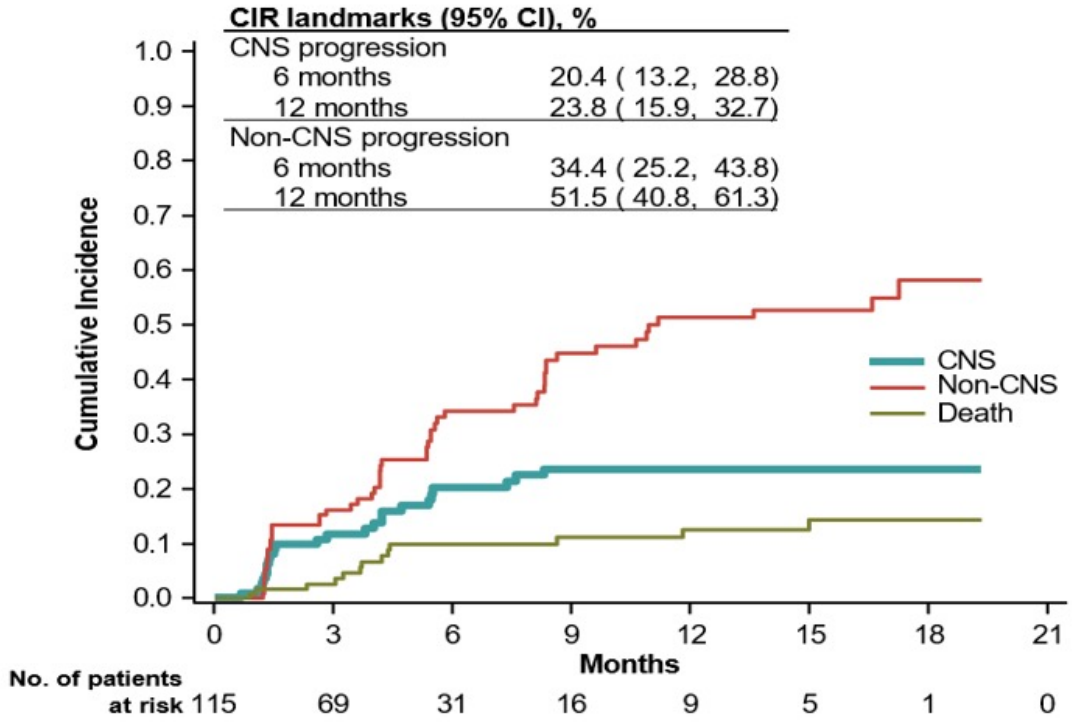
- 21% of patients with a history of brain metastasis had progression in the brain at first PD
- 3% of patients without a history of brain metastasis had progression in the brain at first PD

BICR, blinded independent central review; CNS, central nervous system; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Per RECIST version 1.1.

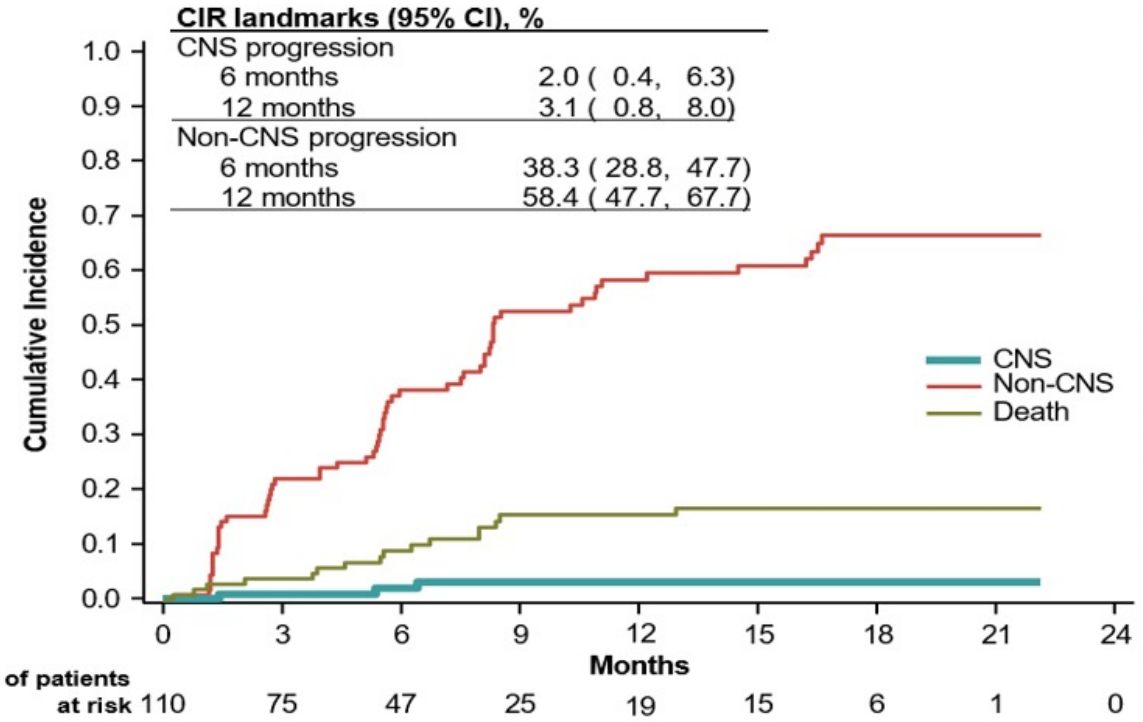
2023 ESMO Congress. Melissa L. Johnson, Sarah Cannon Research Institute, USA.

Cumulative Incidence Rates of CNS Progression, Non-CNS Progression, and Death

With History of Brain Metastasis (n=115)



With No History of Brain Metastasis (n=110)



CIR, cumulative incidence rate; CNS, central nervous system.

Conclusions on HER3-DXd

- 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.
- 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 showed clinically meaningful intracranial antitumor activity in patients with untreated brain metastases
  - Intracranial cORR, 33.3%
  - Intracranial DCR, 76.7%
- The IC antitumor activity provides support for the promising efficacy and disease control of HER3-DXd in the CNS
  - The rate at which the CNS was the first site of progression in patients with and without a history of brain metastasis was 21% and 3%, respectively.
  - Comparative efficacy in the CNS will be further evaluated in the randomized controlled trial HERTHENA-Lung02 (NCT05338970)

Conclusions on HER3-DXd

- 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)

- Ongoing clinical studies of HER3-DXd in patients with CNS metastasis:
  - ✓ PARAMETer (NCT05620914), a window-of-opportunity study evaluating the CNS penetration and pharmacodynamic activity of HER3-DXd in patients with CNS metastasis
  - ✓ TUXEDO-3 (NCT05865990), a phase 2 trial of HER3-DXd in patients with brain metastasis secondary to multiple solid tumor types