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Targeting Resistance in EGFRm NSCLC with HER3-Directed ADCs in the Community Setting

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Learning Objectives

Upon completion of this activity, participants should be better able to:

- Evaluate the role of HER3 biology and the rationale for HER3-directed ADCs in the management of EGFRm NSCLC, including overcoming resistance mechanisms
- Integrate emerging evidence for HER3-directed ADCs in the team-based management of advanced EGFRm NSCLC following progression on EGFR-targeted therapies
- Develop best practice strategies in the multidisciplinary team-based surveillance and management of treatment-related adverse events
- Apply SDM when considering individualized treatment plans with patients/caregivers to optimize therapeutic selection and improve patient outcomes when using HER3-directed ADCs

Overcoming Resistance: HER3 in the Management of EGFRm NSCLC

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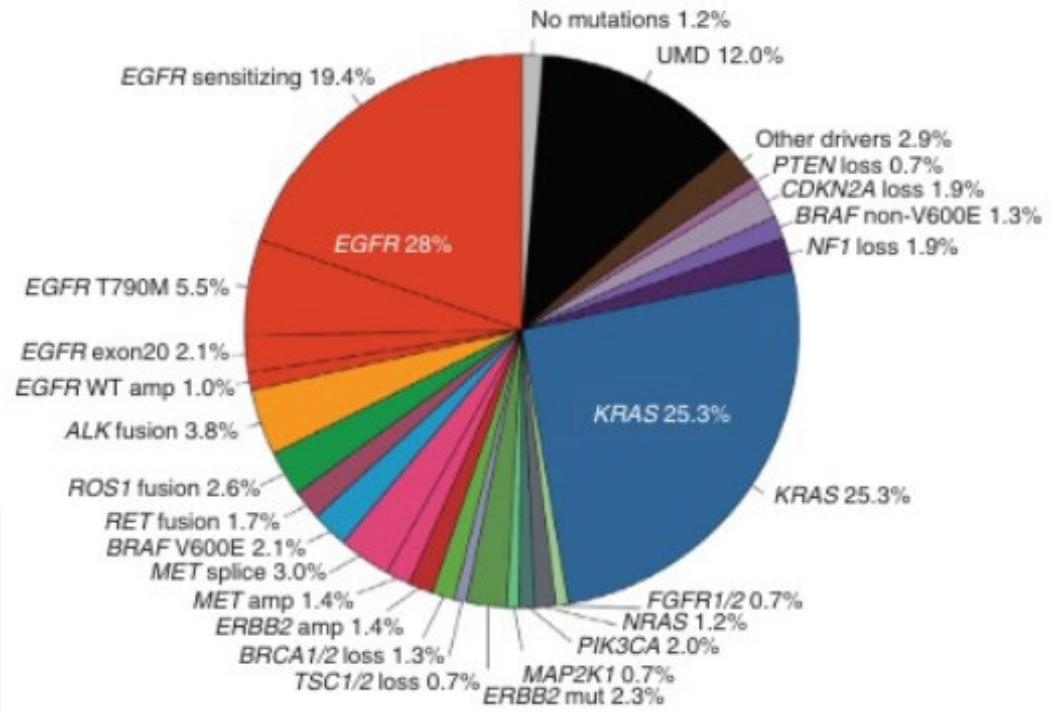
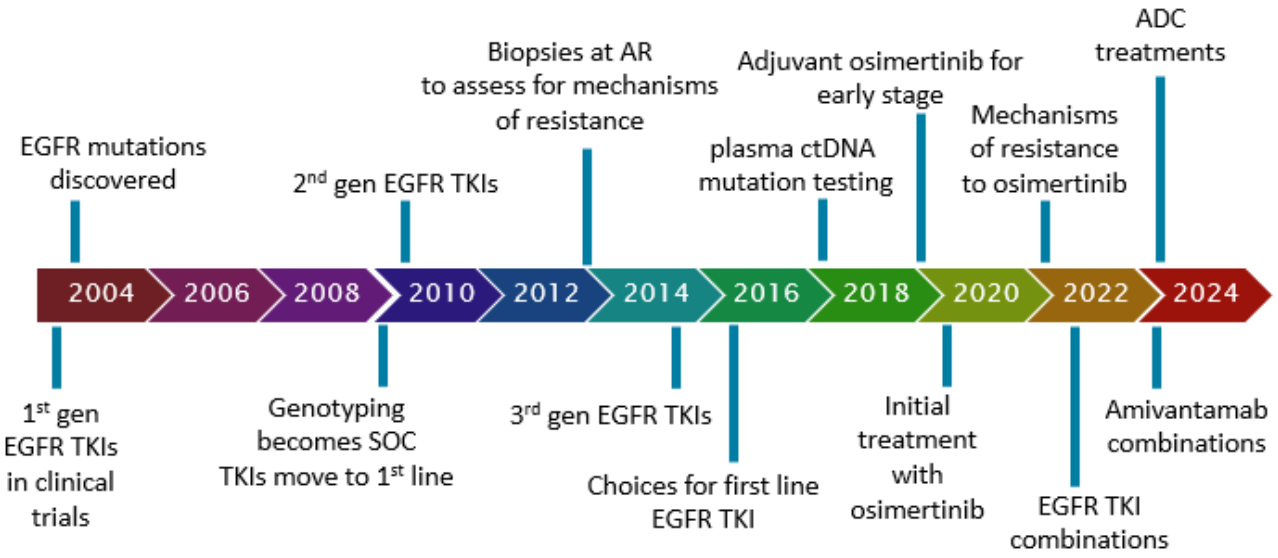
EGFR-Mutant Lung Cancer

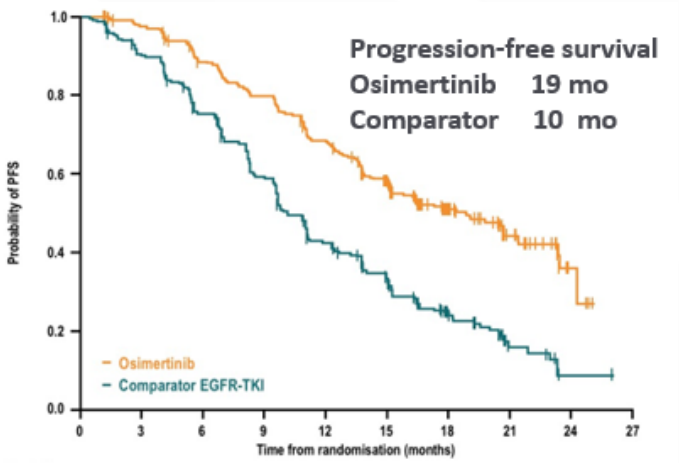




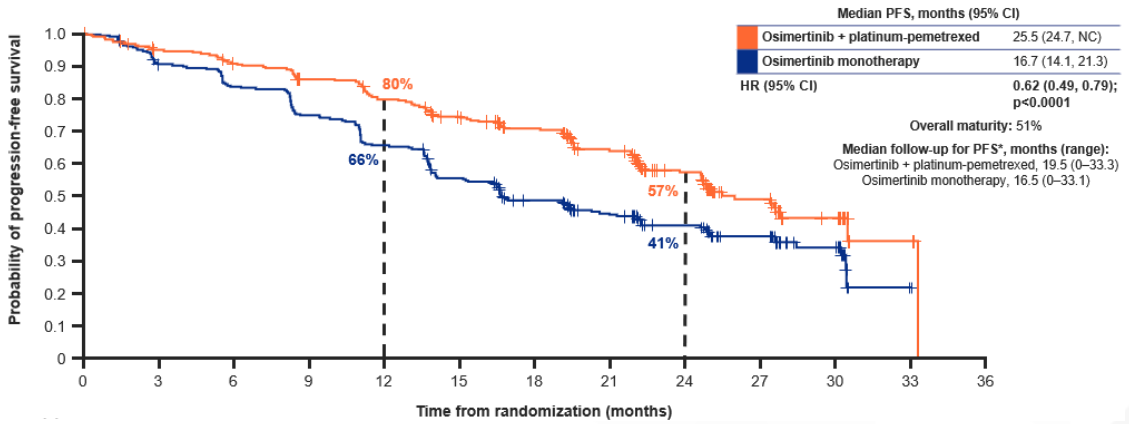
ADC, antibody-drug conjugate; EGFR, epidermal growth factor receptor; SOC, standard of care; TKI, tyrosine kinase inhibitor.
Jordan EJ, et al. *Cancer Discov.* 2017;7(6):596-609.

1L Treatments for EGFR-Mutant Advanced Lung Cancer

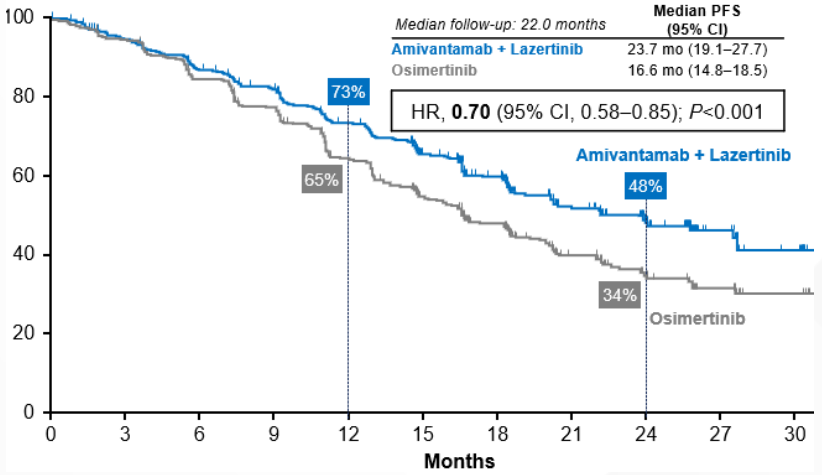
Osimertinib



Osimertinib + chemotherapy



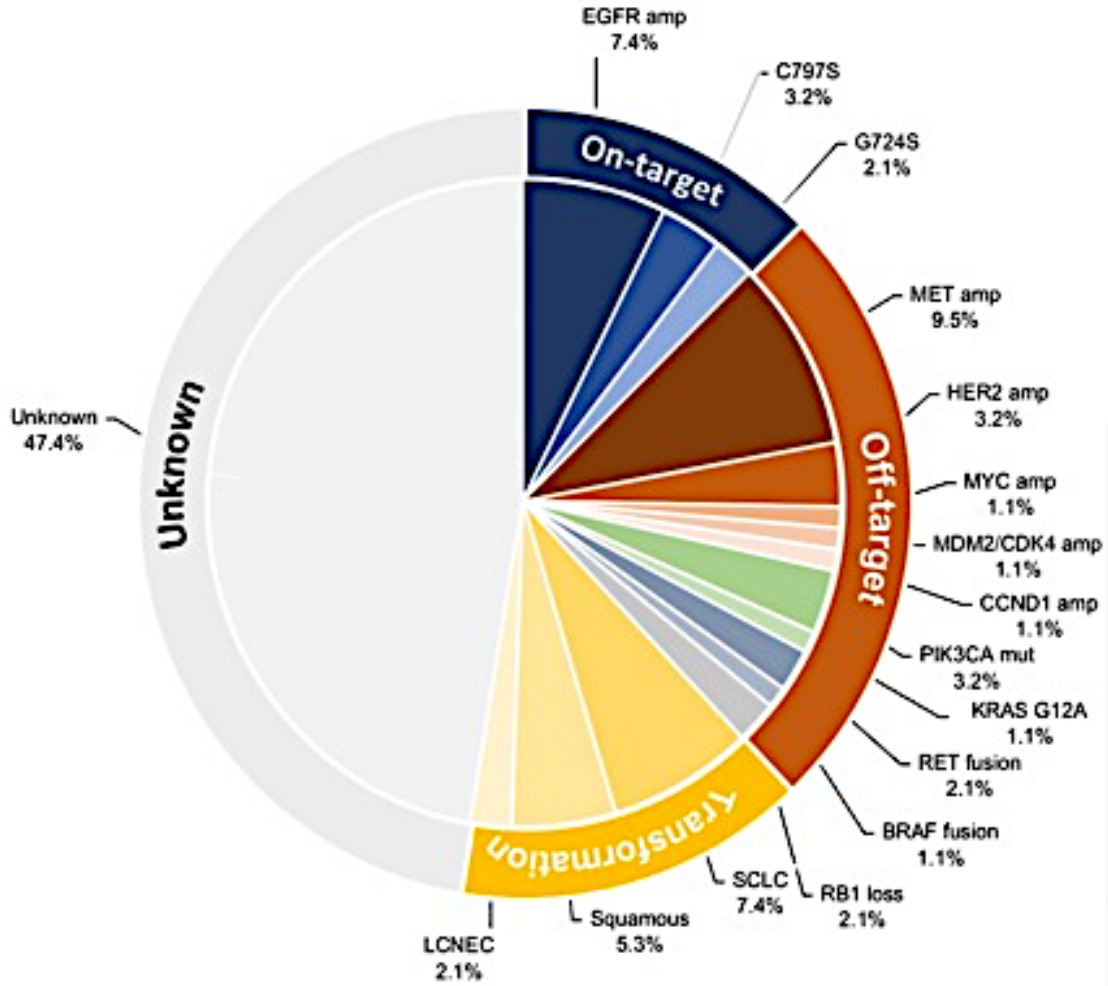
Amivantamab + Lazertinib*



*Currently not an approved first-line combination.
EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival.
Soria J-C, et al; for the FLAURA Investigators. *N Engl J Med*. 2018;378:113-125.
Ramalingam SS, et al. ESMO 2019. Abstract 567.

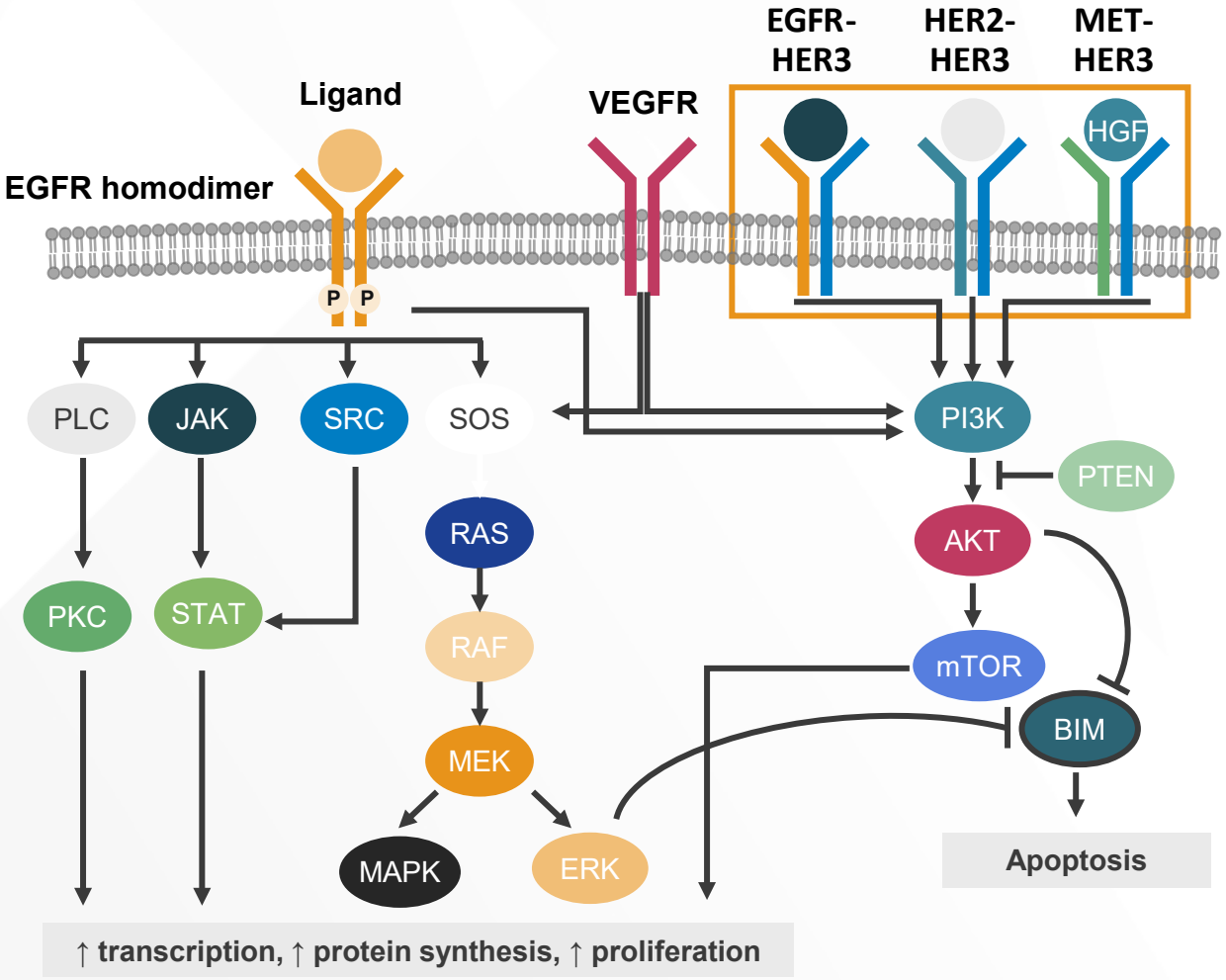
Mechanisms of Resistance to Osimertinib

- Mechanisms of resistance to first-line osimertinib are diverseand no one mechanism is dominant **so upfront combinations to prevent resistance not appropriate without a biomarker**
- With development of better EGFR inhibitors, there is more off target resistance seen
- High incidence of lineage plasticity including both small cell and squamous transformation
- Frequent acquired gene alterations such as gene fusions which are rare de novo
- There will be a role for non-biomarker selected therapies that focus on enhanced EGFR on-target inhibition or address general tumor biology



EGFR, epidermal growth factor receptor.
Jordan EJ, et al. *Cancer Discov.* 2017;7(6):596-609.

HER3 in NSCLC



- HER3 is a member of the ErbB/HER protein kinase family[1,2]
- HER family members heterodimerize with HER3
- Downstream signaling leads to cell proliferation, cancer cell survival
- HER3 expression can mediate resistance to targeted therapy[2]

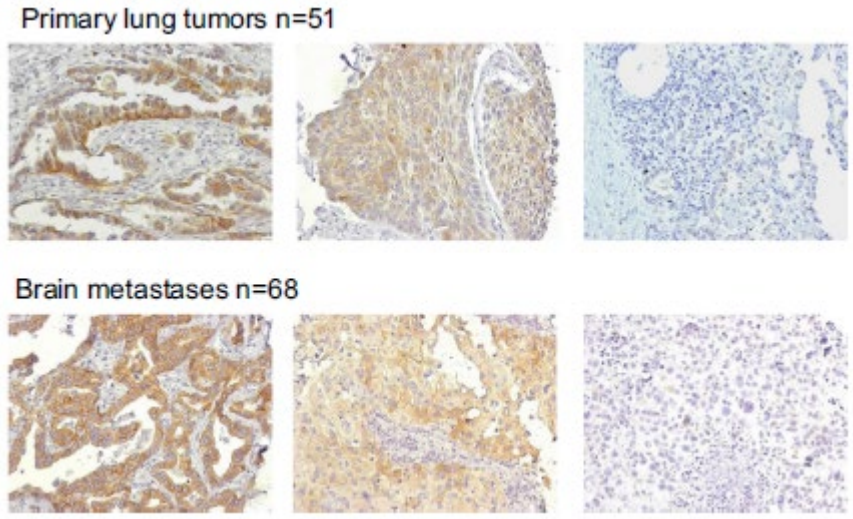
EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3.

Dokala A, Thakur SS. *Oncogene.* 2017;36(17):2337-2344.
Lyu H, et al. *Acta Pharm Sin B.* 2018;8(4):503-510.

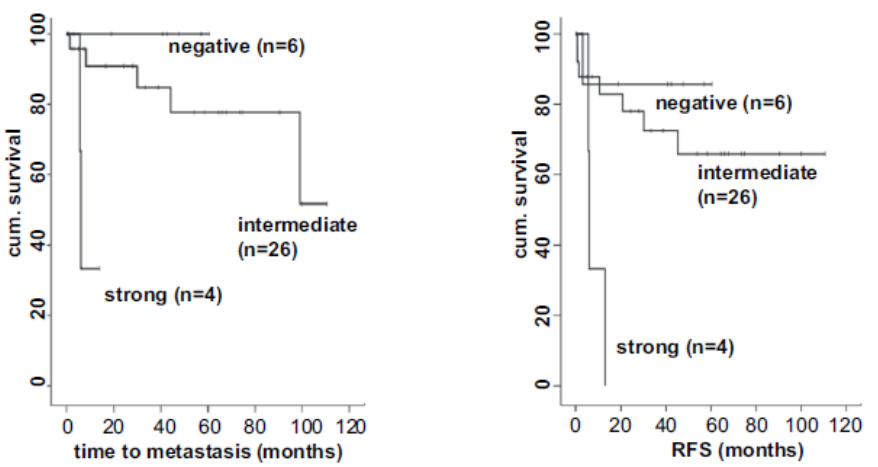
HER3 Expression in NSCLC

- HER3 mutations and genomic alterations are uncommon in NSCLC
- HER3 expression typically determined by IHC and quantified using H-score
- HER3 expression by IHC seen in 83% of NSCLCs
- High levels of expression are associated with progression and metastases
- Currently, HER3 testing is not recommended

HER3 Protein IHC in NSCLC



HER3 Expression and Risk of Progression and Relapse



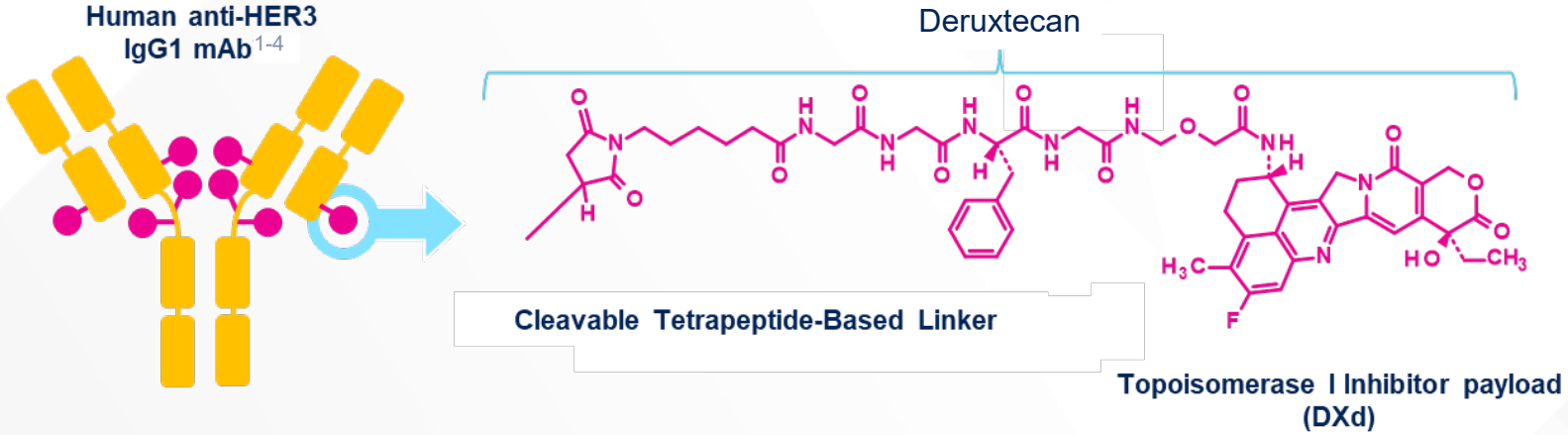
HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

Sithanandam G, Anderson LM. *Cancer Gene Ther.* 2008;15(7):413-448.
Scharpenseel H, et al. *Sci Rep.* 2019;9:7406.
Kumagai X, et al. *Thorac Cancer.* 2018;9(4):423-430.

ADC Clinical Trials and Emerging Evidence Supporting Various HER3-Directed ADCs & Other Emerging Classes

Patritumab Deruxtecan

- HER3-DXd is an ADC composed of 3 parts[1-4]:
  - A fully human anti-HER3 IgG1 mAb (patritumab)
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



7 Key Attributes of HER3-DXd

- 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]

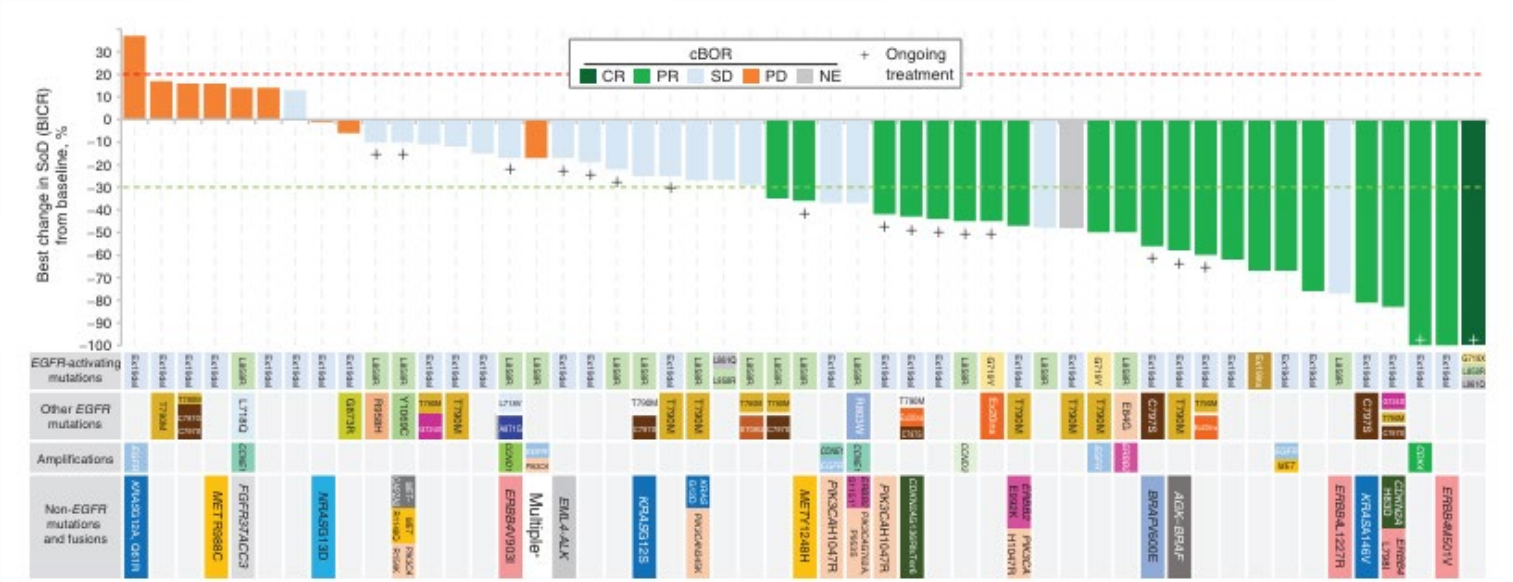
[a]The clinical relevance of these features is under investigation. [b]Based on animal data.

ADC, antibody-drug conjugate; HER3-DXd, patritumab deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
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.

Phase 1: Patritumab Deruxtecan

Characteristics	Pooled RDE (5.6 mg/kg) All pooled (*n* = 57)	Pooled RDE (5.6 mg/kg) Prior PBC and osimertinib (*n* = 44)
Confirmed ORR, % (*n*) [95% CI]	39 (22) [26.0-52.4]	39 (17) [24.4-54.5]
BOR, *n* (%)		
CR	1 (2)	1 (2)
PR	21 (37)	16 (36)
SD	19 (33)	13 (30)
PD	9 (16)	8 (18)
NE	7 (12)	6 (14)
DCR,[a] % (*n*) [95% CI]	72 (41) [58.5-83.0]	68 (30) [52.4-81.4]
TTR, median (range), months	2.6 (1.2-5.4)	2.7 (1.2-5.4)
Duration of response, median (95% CI), months	6.9 (3.1-NE)	7.0 (3.1-NE)
Progression-free survival, median (95% CI), months	8.2 (4.4-8.3)	8.2 (4.0-NE)
Overall survival, median (95% CI), months	NE (9.4-NE)	NE (8.2-NE)

Abbreviation: PBC, platinum-based chemotherapy.
[a]DCR = rate of confirmed BOR of CR, PR, or SD.

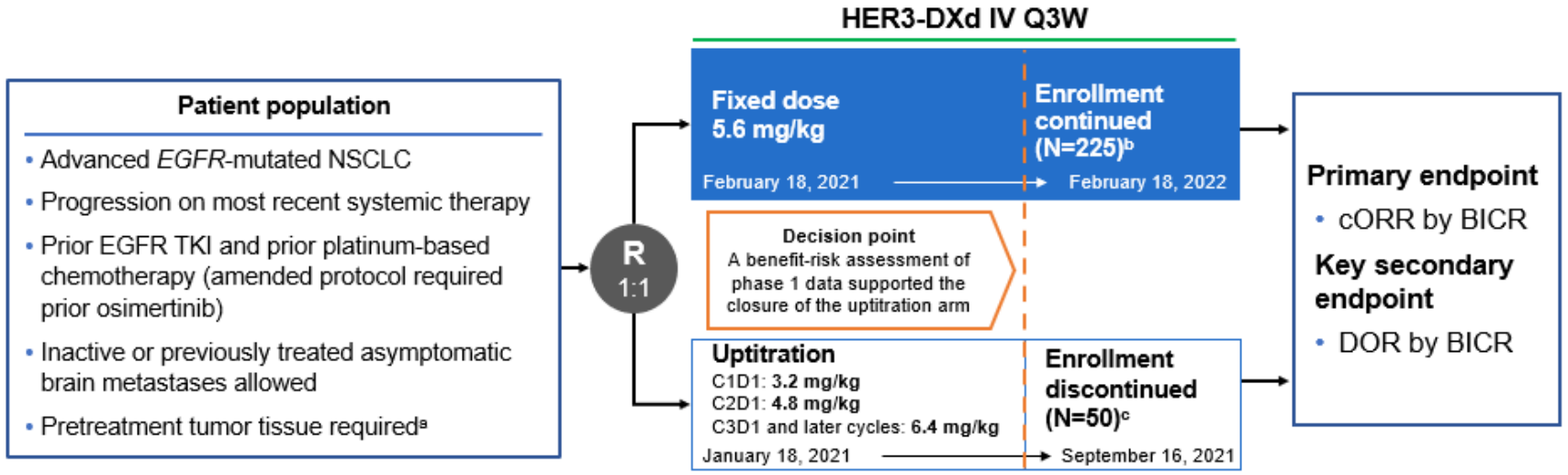


Patients with locally advanced or metastatic *EGFR*-mutated NSCLC with prior EGFR TKI therapy

BOR, best observed response; CR, complete response; DCR, disease control rate; EGFR, epidermal growth factor receptor; NE, not established; NSCLC, non-small cell lung cancer; ORR, objective response rate; PBC, platinum-based chemotherapy; PD, progressive disease; PR, partial response; RDE, recommended dose for expansion; SD, stable disease; TTR, time to relapse.

Jänne PA, et al. *Cancer Discov*. 2022;12(7):74-89.

HERTHENA-Lung 01 Phase 2



[a]Provided as either: Pretreatment tumor biopsy from at least 1 lesion not previously irradiated and amenable to core biopsy; or archival tumor tissue collected from a biopsy performed within 3 months prior to signing of the tissue consent and since progression while on or after treatment with the most recent cancer therapy regimen

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)
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)
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)

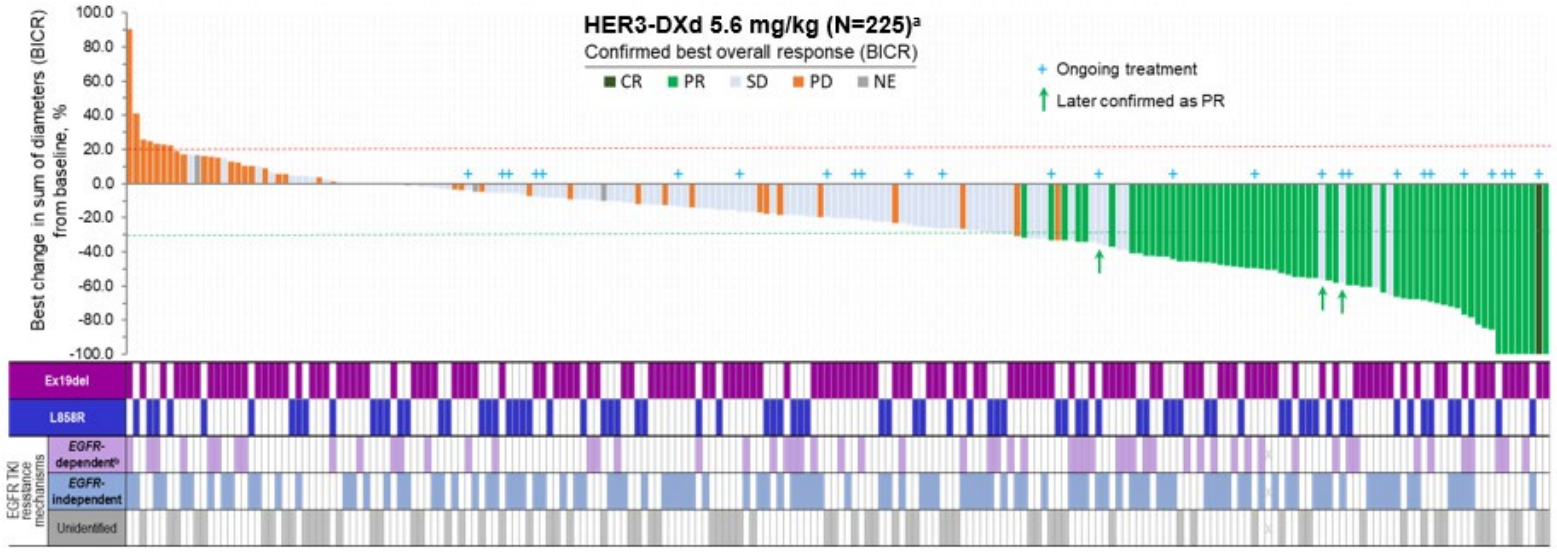
BICR, blinded independent central review; CNS, central nervous system; cORR, confirmed objective response rate; DOR, duration of response; EGFR, epidermal growth factor receptor; HER3-DXd, patritumab deruxtecan; IV, intravenous; NSCLC, non-small cell lung cancer; Q3W, once every 3 weeks; TKI, tyrosine kinase inhibitor.
Yu H, et al. WCLC 2023. Abstract OA05.03.

HERTHENA-Lung 01 Phase 2

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), %		**28.4 (22.6-34.8)**	**28.2 (22.2-34.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	63 (28.0)	58 (27.8)
	SD[a]	102 (45.3)	93 (44.5)
	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		6.0 (4.4-7.2)	6.4 (4.4-7.2)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.8 (11.2-12.6)	11.8 (10.9-12.6)

Median study follow-up, 13.1 (range, 9.0-21.6) months.

Efficacy snapshot (6 months additional follow up): 3 PRs confirmed, cORR 29.8% (95% CI, 23.9%-36.2%)



BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; HER3-DXd, patritumab deruxtecan; NE, not established; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Yu H, et al. WCLC 2023. Abstract OA05.03.

HERTHENA-Lung 01 Phase 2

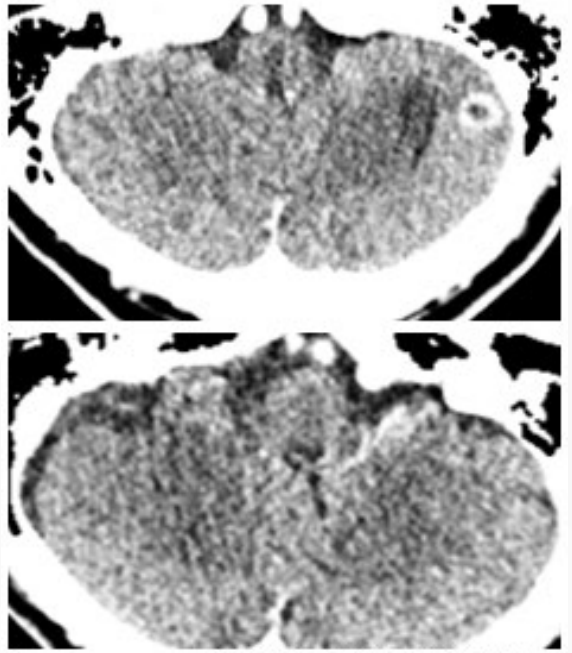
Intracranial Efficacy of HER3-DXd in Patients With Brain Metastases in Baseline

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)
DOR, median (95%, CI), mo	8.4 (5.8-NE)

Complete CNS Response in 1 of 7 Patients With a Measurable CNS BICR Target Lesion

Screening
T1:LD, 11 mm

Week 6
T1:LD, 0 mm



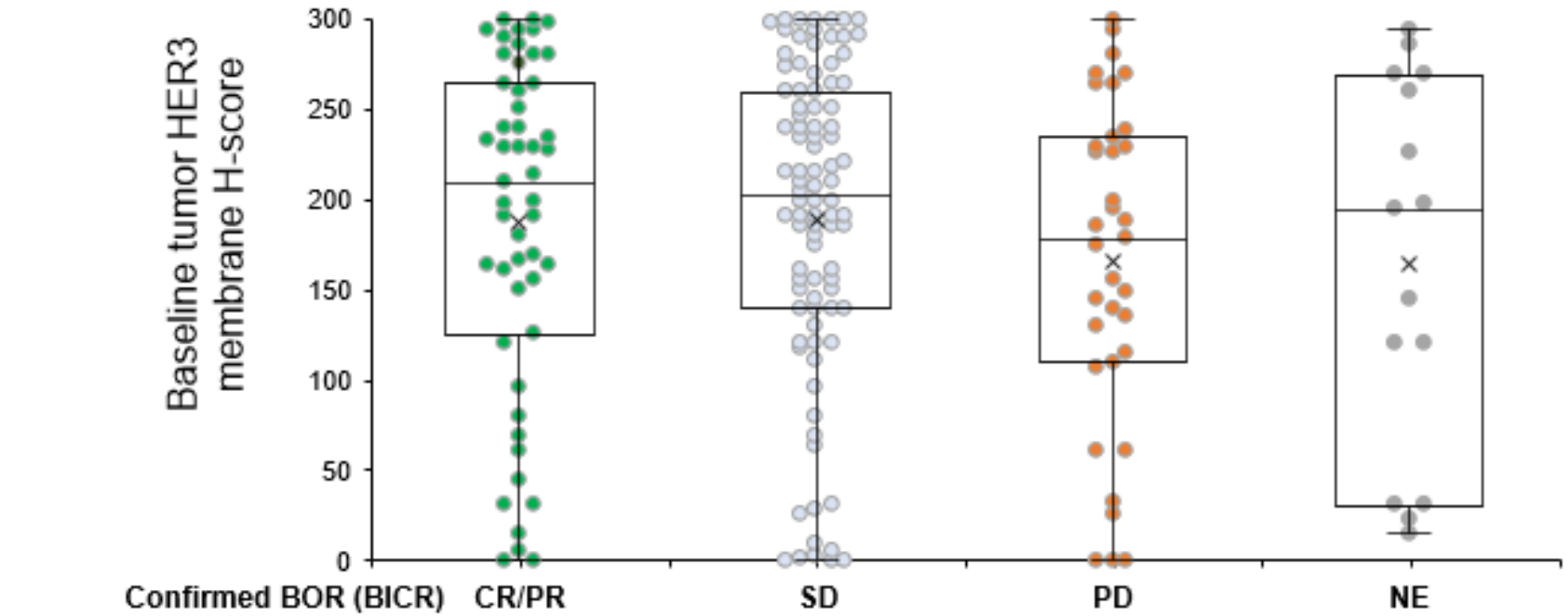
Contrast enhanced CT scans

BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DOR, duration of response; HER3-DXd, patritumab deruxtecan; NE, not established; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

Yu H, et al. WCLC 2023. Abstract OA05.03.

HERTHENA-Lung 01 Phase 2

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]



BICR, blinded independent central review; BOR, best overall response; CR, complete response; HER3, human epidermal growth factor receptor 3; HER3-DXd, patritumab deruxtecan; NE, not established; PD, progressive disease; PR, partial response; SD, stable disease.

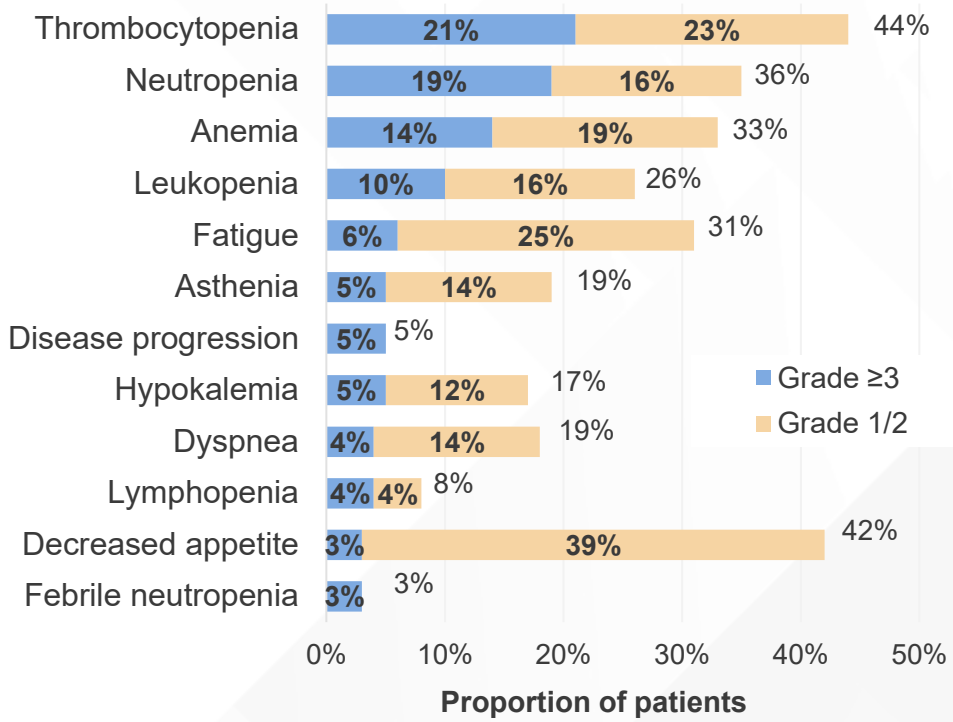
Yu H, et al. WCLC 2023. Abstract OA05.03.

HERTHENA-Lung 01 Phase 2

Safety summary	HER3-DXd 5.6 mg/kg (N=225)
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation	16 (7.1)
Associated with treatment dose reduction	48 (21.3)
Associated with treatment dose interruption	91 (40.4)
Associated with death	24 (10.7)
Grade ≥3 TEAE, n (%)	146 (64.9)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death	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)

Median treatment duration: 5.5 (range, 0.7-18.2) months.

Most Common Grade ≥3 TEAEs Occurring in ≥3% of Patients (N=225)[d]



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

HER3-DXd, patritumab deruxtecan; TEAE, treatment-emergent adverse event.
Yu H, et al. WCLC 2023. Abstract OA05.03.

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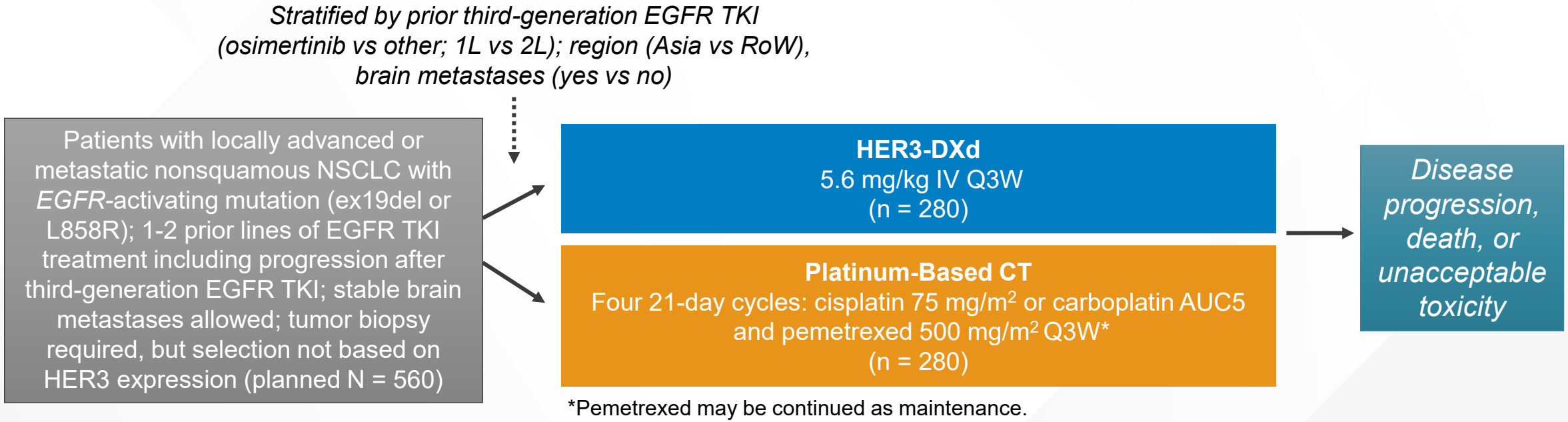
HERTHENA-Lung02: Ongoing Phase III Study of Patritumab Deruxtecan in *EGFR*-Mutated NSCLC

Multicenter, randomized, open-label phase III study



*Pemetrexed may be continued as maintenance.

- **Primary endpoint:** PFS by BICR (RECIST v1.1)
- **Secondary endpoints:** PFS by investigator, OS, ORR, DoR, DCR, TTR, safety

1L/2L, first-line/second-line; BICR, blinded independent central review; CT, chemotherapy; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; HER3-DXd, patritumab deruxtecan; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor; TTR, time to relapse.

Mok TSK, et al. *Future Oncol.* 2024;20(15):969-908.
ClinicalTrials.gov identifier: NCT05338970.

Patritumab Deruxtecan Regulatory Status

- BLA seeking accelerated approval granted priority review by FDA on 12/22/2023[1]
- FDA issued a CRL on 6/25/2024[2]
  - The CRL results from findings **pertaining to an inspection of a third-party manufacturing facility**
  - **The CRL did not identify any issues with the efficacy or safety data submitted**
- The companies developing patritumab deruxtecan are working with the third-party manufacturer to address and resolve the findings to continue the approval process[2]

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BLA, biological license application; CRL, complete response letter; FDA, Food and Drug Administration.

1. Daiichi Sankyo, Inc. https://www.daiichisankyo.com/files/news/pressrelease/pdf/202112/20211223_E1.pdf
2. Daiichi Sankyo, Inc. https://www.daiichisankyo.com/files/news/pressrelease/pdf/202406/20240626_E.pdf

Phase I Combination Study of HER3-DXd With Osimertinib

Multicenter, open-label phase I study

Dose Escalation

Patients with locally advanced or metastatic NSCLC with *EGFR*-activating mutation (ex19del or L858R); prior osimertinib; no prior CT (total target N = 252)

→ **HER3-DXd**
3.2, 4.8, 5.6 mg/kg IV Q3W
+ Osimertinib
80 mg PO QD
(n = 3-6 per dose cohort)

- **Primary endpoint:** Safety
- **Secondary endpoints:** ORR, DoR, DCR, TTR, PFS, OS

Dose Expansion

Patients with locally advanced or metastatic NSCLC with *EGFR*-activating mutation (ex19del or L858R); prior osimertinib; no prior CT

→ **HER3-DXd + Osimertinib**
RCD*
(n = 60)

→ **HER3-DXd**
5.6 mg/kg IV Q3W
(n = 60)

*A third treatment arm may be added if 2 RCDs are determined.

If osimertinib RCD = 80 mg, a cohort of first-line patients will be added (n = 30)

- **Primary endpoint:** ORR by BICR (RECIST v1.1)
- **Secondary endpoints:** ORR by investigator, DoR, DCR, TTR, PFS, OS, safety

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BICR, blinded independent central review; CT, computed tomography; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; HER3-DXd, patritumab deruxtecan; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; Q3W, once every 3 weeks; QD, every day; RCD, recommended combination dose; RECIST, Response Evaluation Criteria in Solid Tumours; TTR, time to relapse.
ClinicalTrials.gov identifier: NCT04676477.

BL-B01D1: EGFR x HER3 Bispecific ADC

Phase Ia/Ib dose escalation and dose expansion study

Patients with locally advanced or metastatic NSCLC or other solid tumors, with failure of standard therapy or without feasible treatment options; measurable disease per RECIST V1.1; ECOG PS 0-1 (Q3W safety cohort: N = 369; NSCLC cohort: N = 102)

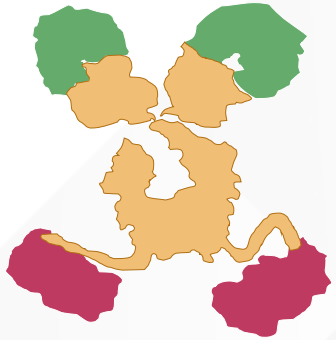
Dose Escalation

- **BL-B01D1** QW dosing 0.27, 1.5, 3.0 mg/kg IV
- **BL-B01D1** D1D8 Q3W dosing 2.5, 3.0, 3.5 mg/kg IV
- **BL-B01D1** D1 Q3W dosing 4.5, 5.0, 6.0 mg/kg IV

Dose Expansion

- **NSCLC (*EGFR*^{wt} and *EGFR*^{mut})**
- **Nasopharyngeal carcinoma**
- **SCLC**
- **Head and neck squamous cell carcinoma**

- **Primary endpoint:** DLT, MTD, RP2D
- **Secondary endpoints:** PK, ADA, ORR, DCR, DoR



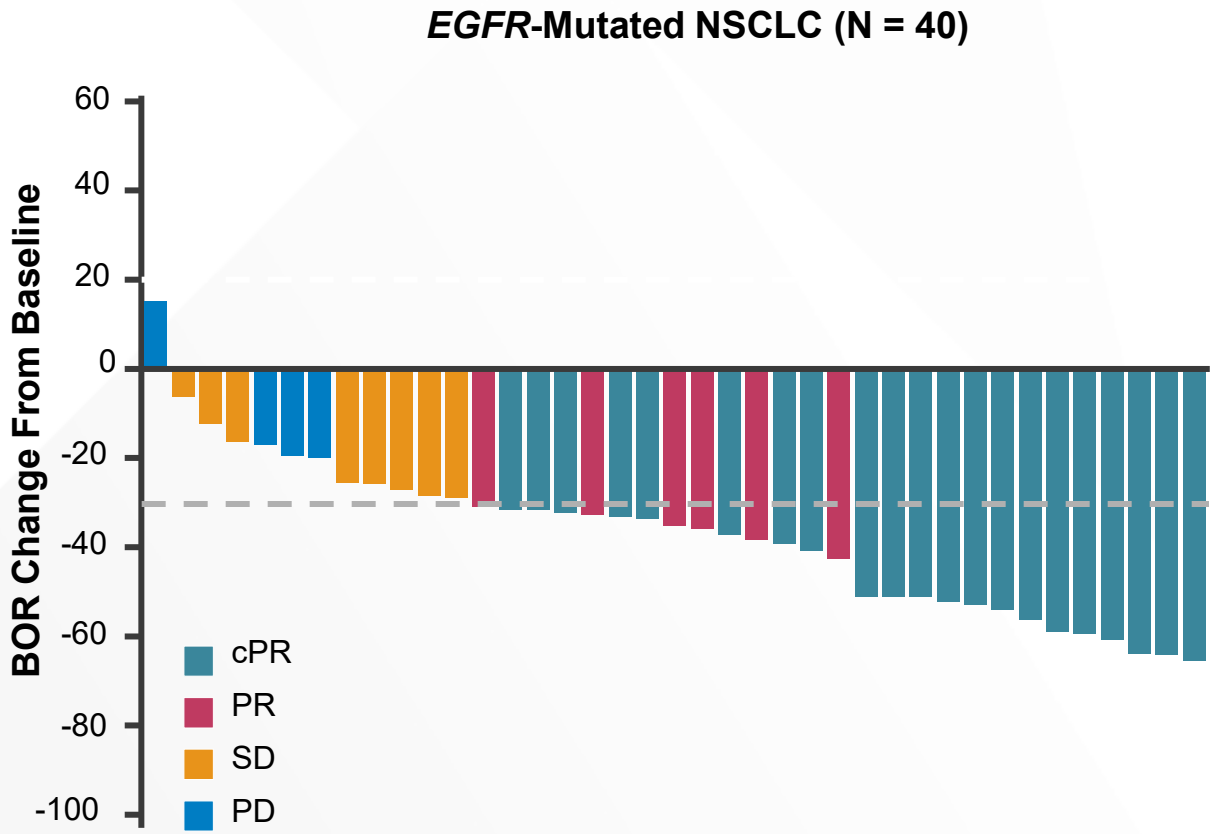
- **αEGFR** Human EGFR affinity: High
- Cat B cleavable linker Ed-04 (TOPI inhibitor)
- wt Fc IgG1
- **αHER3** Human HER3 affinity: Low

ADA, anti-drug antibodies; ADC, antibody-drug conjugate; DCR, disease control rate; DLT, dose-limiting toxicities; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; IgG1, immunoglobulin G1; IV, intravenous; MTD, maximum-tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; PK, pharmacokinetic; Q3W, once every 3 weeks; QW, once weekly; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended phase II dose; SCLC, small cell lung cancer; TOPI, topoisomerase I.

Zhang L, et al. ESMO 2023. Abstract 1316MO. Zhang L, et al. ASCO 2023. Abstract 3001.

BL-B01D1: Response Rates in *EGFR*-Mutated NSCLC

- All patients in the current analysis received Q3W dose regimens



	EGFR-Mutated NSCLC		*EGFR* Wild-Type NSCLC	
	All (n = 40)	Treated/No CNS Mets (n = 13)	All (n = 62)	2L Post PBC (n = 26)
Prior CT lines, % • 0 • 1 • 2+	 25 50 25	 8 46 46	 0 42 56	 0 100 0
ORR, %	67.5	69.2	40.3	50.0
cORR, %	52.5	61.5	30.6	38.5
DCR, %	87.5	92.3	87.1	80.8
mDoR, mo	8.5	12.3	NR	NR
mPFS, mo	5.6	15.0	5.4	6.7

2L, second-line; CNS, central nervous system; cORR, confirmed objective response rate; cPR, confirmed partial response; CT, computed tomography; DCR, disease control rate; EGFR, epidermal growth factor receptor; mDoR, median duration of response; mPFS, median progression-free survival; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PBC, platinum-based chemotherapy; PD, progressive disease; PR, partial response; Q3W, once every 3 weeks; SD, stable disease.

Zhang L, et al. ESMO 2023. Abstract 1316MO. Zhang L, et al. ASCO 2023. Abstract 3001.

BL-B01D1: Safety in All Tumor Types

Overall Safety Summary	All Q3W (N = 369)
Median follow-up (months)	3.9
TEAE, n (%) ▪ ≥ Grade 3 ▪ ≥ Grade 4 ▪ Serious ▪ Associated with death ▪ Associated with dc ▪ Associated with delay ▪ Associated with reduction	363 (98) 249 (67) 125 (34) 142 (38) 17 (5) 12 (3) 102 (28) 50 (14)
TRAE, n (%) ▪ ≥ Grade 3 ▪ ≥ Grade 4 ▪ Serious ▪ Associated with death*	351 (95) 226 (61) 115 (31) 108 (29) 8 (2)

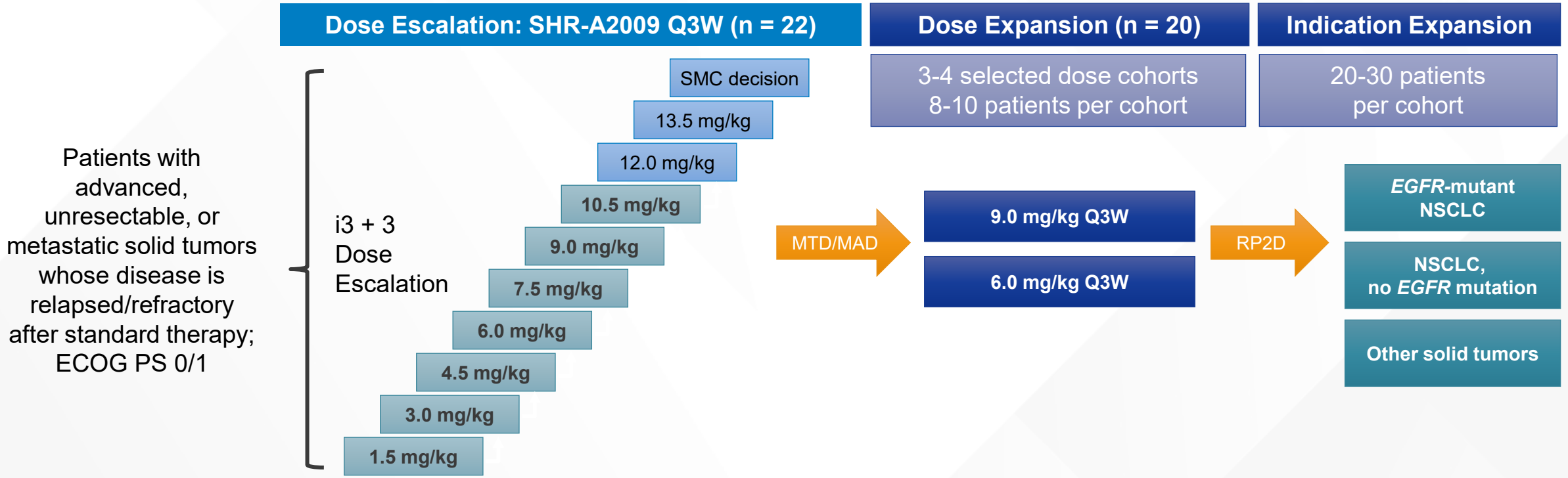
TRAE ≥15%, %	All Q3W (N = 369)		2.5 mg/kg D1D8 Q3W (N = 278)		4.5 mg/kg D1 Q3W (N = 40)	
	Any	≥G3	Any	≥G3	Any	≥G3
Leukopenia	65	32	61	27	73	33
Anemia	64	24	64	22	73	25
Neutropenia	59	36	53	29	70	45
Thrombocytopenia	55	28	53	27	58	23
Nausea	36	<1	33	1	40	0
Asthenia	31	<1	28	1	33	0
Decreased appetite	29	<1	26	<1	38	0
Alopecia	25	0	21	0	43	0
Stomatitis	25	1	22	1	28	3
Vomiting	22	1	20	1	33	3
Diarrhea	17	<1	15	<1	30	0
Skin disorders	17	<1	14	<1	25	3
Hypokalemia	15	2	16	1	5	3
Hypoalbuminemia	13	0	15	0	5	0

- One grade 2 ILD was observed

*Septic shock (n = 3); pneumonia (n = 2); respiratory failure, myelosuppression, gastrointestinal infection (n = 1 each).
G, grade; ILD, interstitial lung disease; Q3W, once every 3 weeks; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
Zhang L, et al. ESMO 2023. Abstract 1316MO. Zhang L, et al. ASCO 2023. Abstract 3001.

Phase I Study of SHR-A2009, a HER3-Targeted ADC, in Advanced Solid Tumors

- First-in-human, multinational phase I trial of SHR-A2009, novel ADC comprising a fully human anti-HER3 IgG1 mAb with cleavable peptide linker and DNA topoisomerase I inhibitor payload



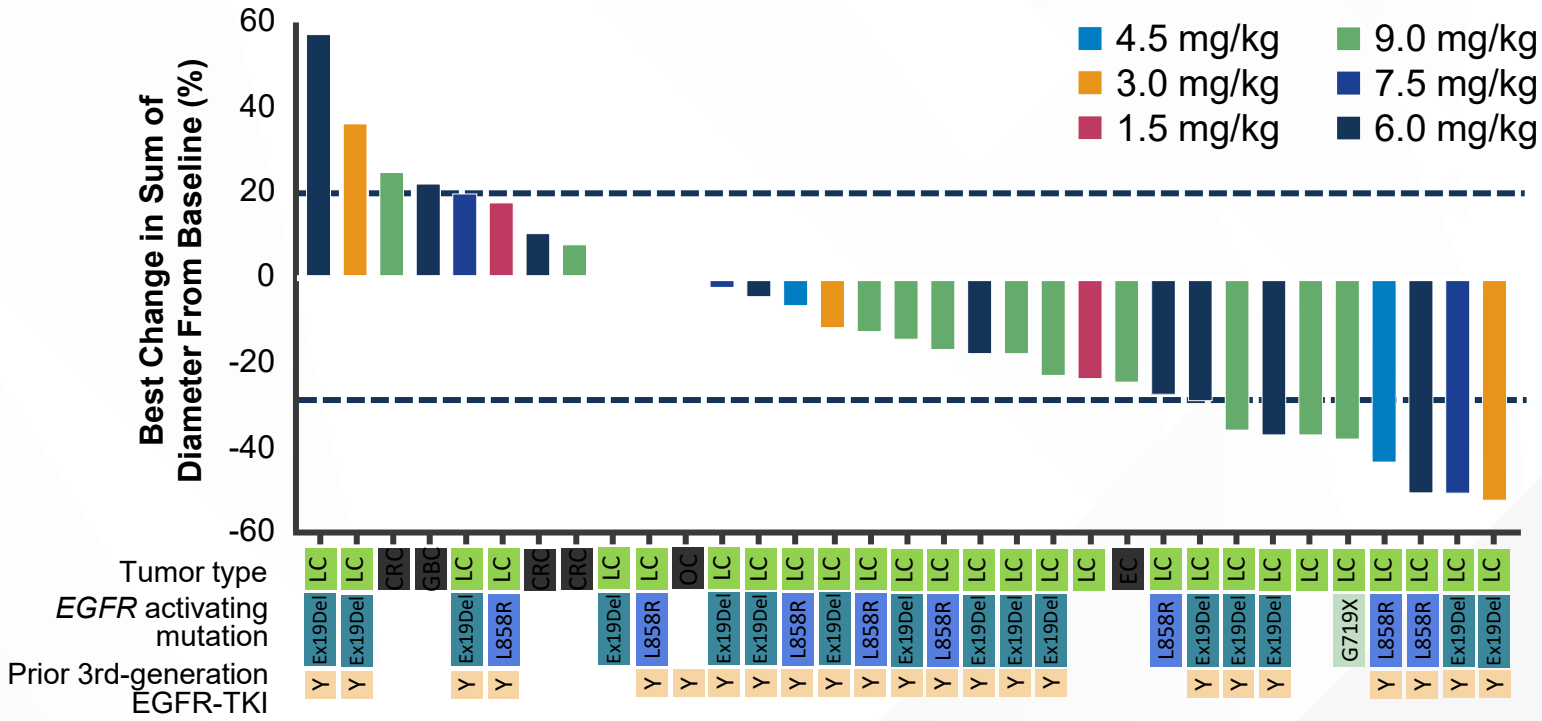
- Primary endpoints: safety, tolerability, RP2D
- Secondary endpoints: preliminary efficacy, PK, immunogenicity

ADC, antibody-drug conjugate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; IgG1, immunoglobulin G1; mAb, monoclonal antibody; MTD/MAD, maximum tolerated dose/maximum administered dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetic; Q3W, once every 3 weeks; RP2D, recommended phase II dose.

Zhou Q, et al. ESMO 2023. Abstract 658MO.

SHR-A2009: Tumor Response in Advanced Solid Tumors

All Solid Tumors	All Doses (n = 36)
ORR, n (%)	**9 (25.0)**
DCR, n (%)	26 (72.2)
Median DoR, mo (range)	7.0 (2.8-8.5)
6-mo PFS, % (95% CI)	46.4 (27.0-63.8)
Patients With NSCLC	**All Doses (n = 30)**
ORR, n (%)	9 (30.0)
DCR, n (%)	23 (76.7)
Median DoR, mo (range)	7.0 (2.8-8.5)
6-mo PFS, % (95% CI)	49.8 (28.8-67.8)



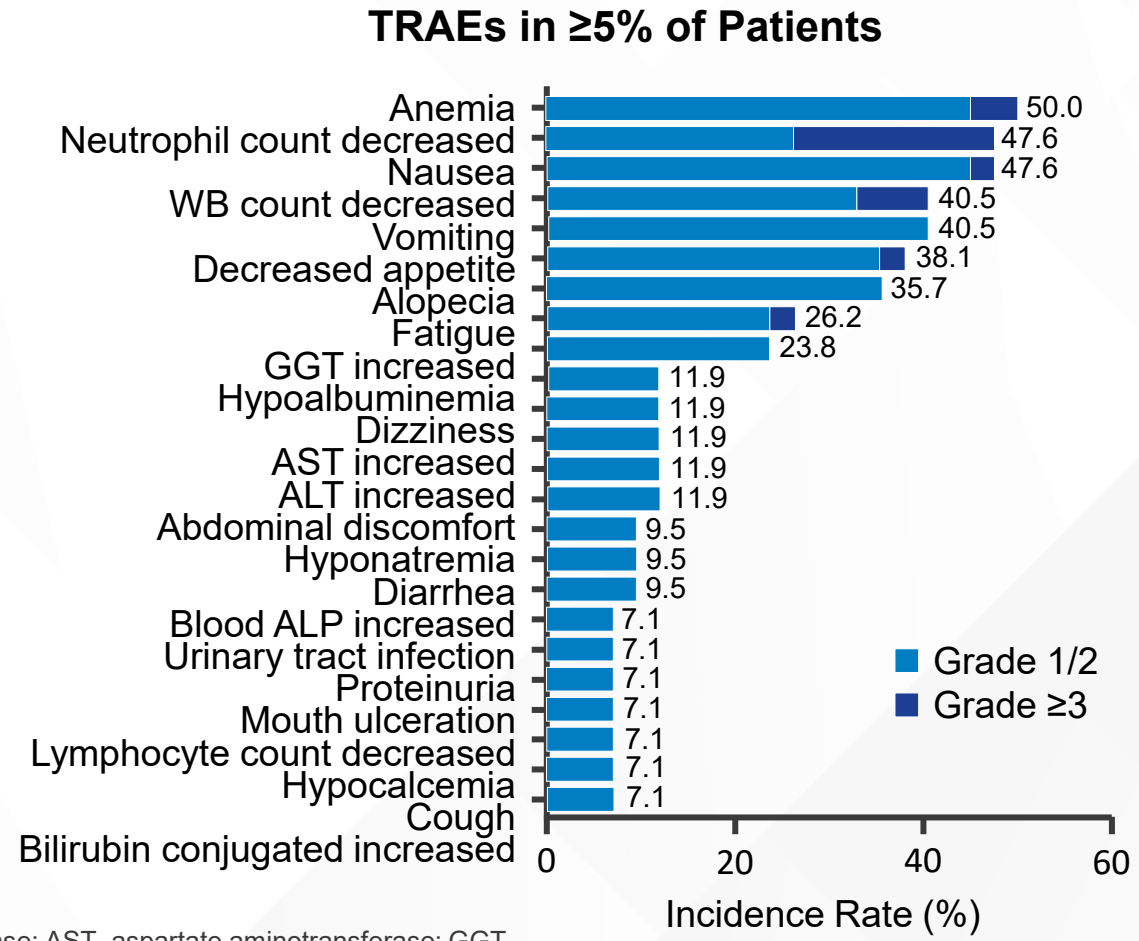
- Among patients with NSCLC (n = 36), 94.4% had an EGFR mutation and all were resistant to EGFR-TKI, with 85.3% (29/34) previously treated with third-generation agents
- Grade ≥3 TRAEs: 13 (31.0%), leading to drug discontinuation in 3 (7.1%) patients
  - Interstitial lung disease occurred in 2 (4.8%) patients

DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine-kinase inhibitor; TRAE, treatment-related adverse event.
Zhou Q, et al. ESMO 2023. Abstract 658MO.

SHR-A2009: AE Profile

- No dose-limiting toxicities occurred up to 10.5 mg/kg Q3W dose level

Event, n (%)	All patients (n = 42)
Median duration of treatment, mo (range)	2.8 (0.3-12.4)
Any AE	42 (100)
Grade ≥3 AE	21 (50.0)
Any TRAE	39 (92.9)
Grade ≥3 TRAE	13 (31.0)
TRAE leading to dose reduction	3 (7.1)
TRAE leading to dose hold	8 (19.0)
TRAE leading to discontinuation	3 (7.1)
TRAE leading to death	1 (2.4)
Serious TRAE	4 (9.5)
ILD	2 (4.8)

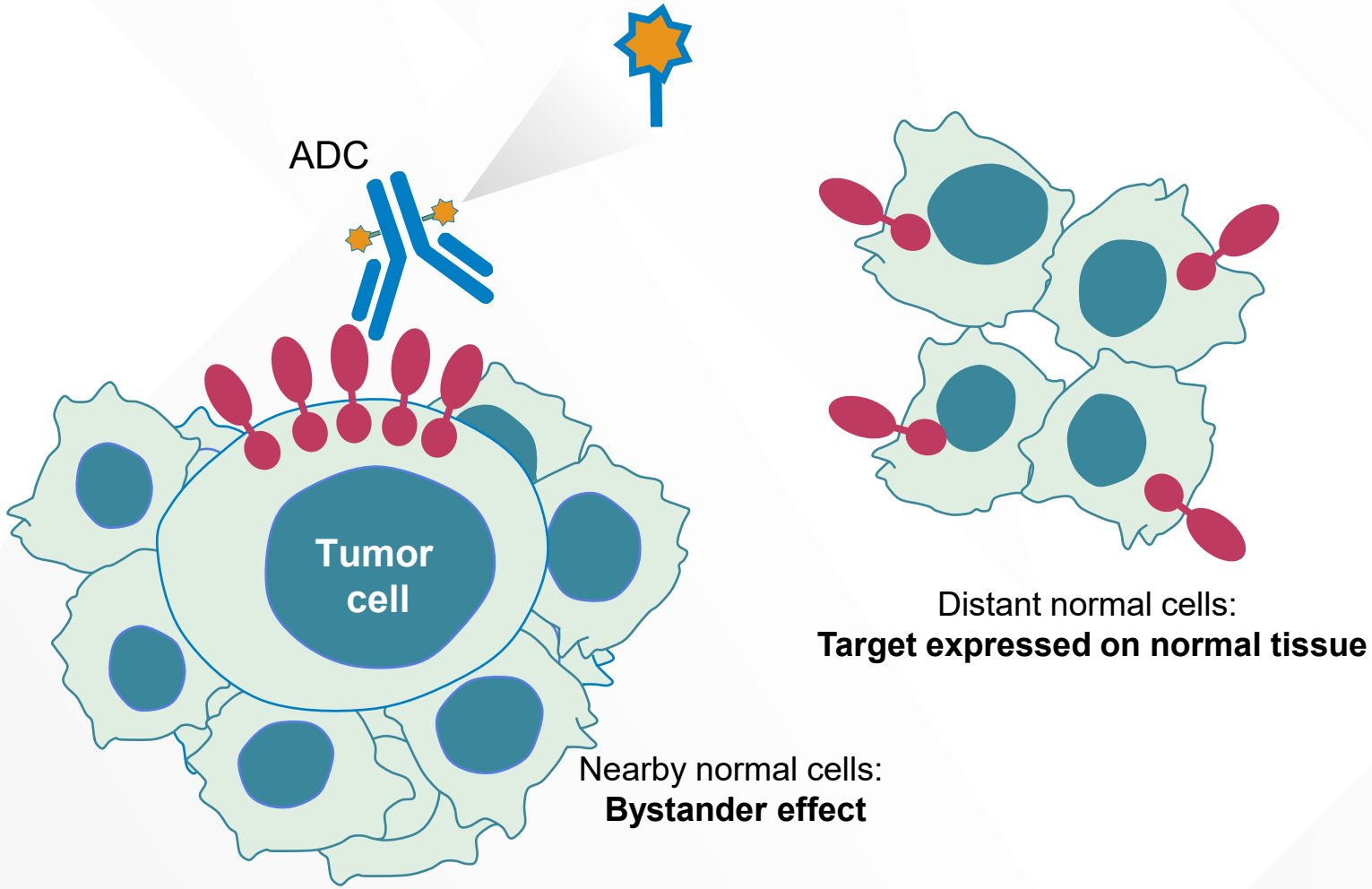


AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ILD, interstitial lung disease; Q3W, once every 3 weeks; TRAE, treatment-related adverse event; WB, white blood cell.

Zhou Q, et al. ESMO 2023. Abstract 658MO.

Treatment Emergent Adverse Events (TEAEs): Detection and Management

ADC Mechanisms of Toxicity



Cytotoxic payload:

- Intrinsic toxicity
- Drug-to-antibody ratio
- Membrane permeability (bystander effect)

Linker:

- Cleavable vs noncleavable

Tumor Antigen Target:

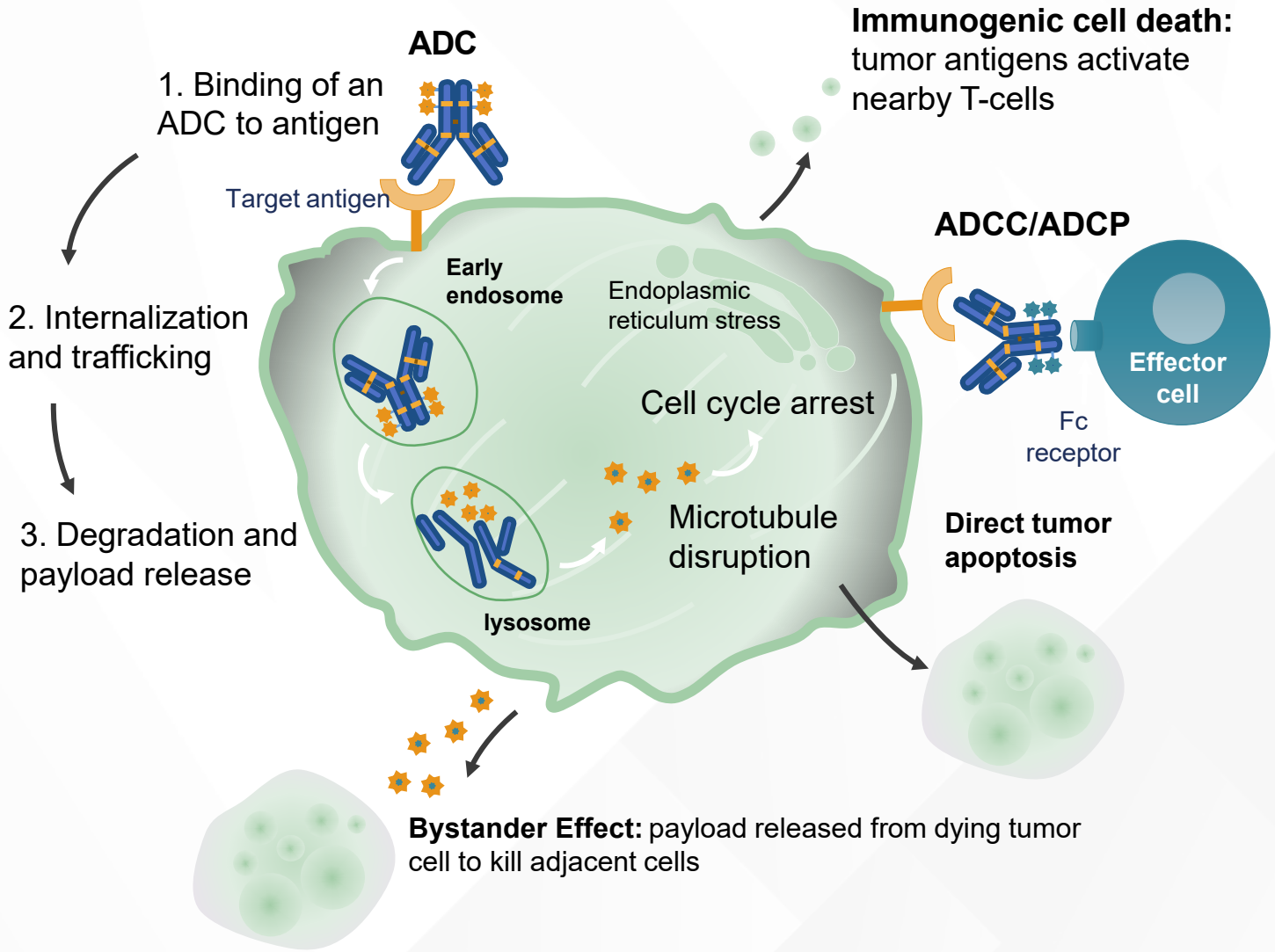
- Expression of target protein on noncancer cells

ADC, antibody-drug conjugate.

Johns AC, Campbell MT. *Cancer J.* 2022;28(6):469-478.

ADC Mechanisms of Toxicity: Bystander Effect

- Internalized ADC degraded by target cell and payload exits cell and enters neighbor cell
- Payload released in extracellular space without ADC entering target cell (acidic)



ADC, antibody-drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis.

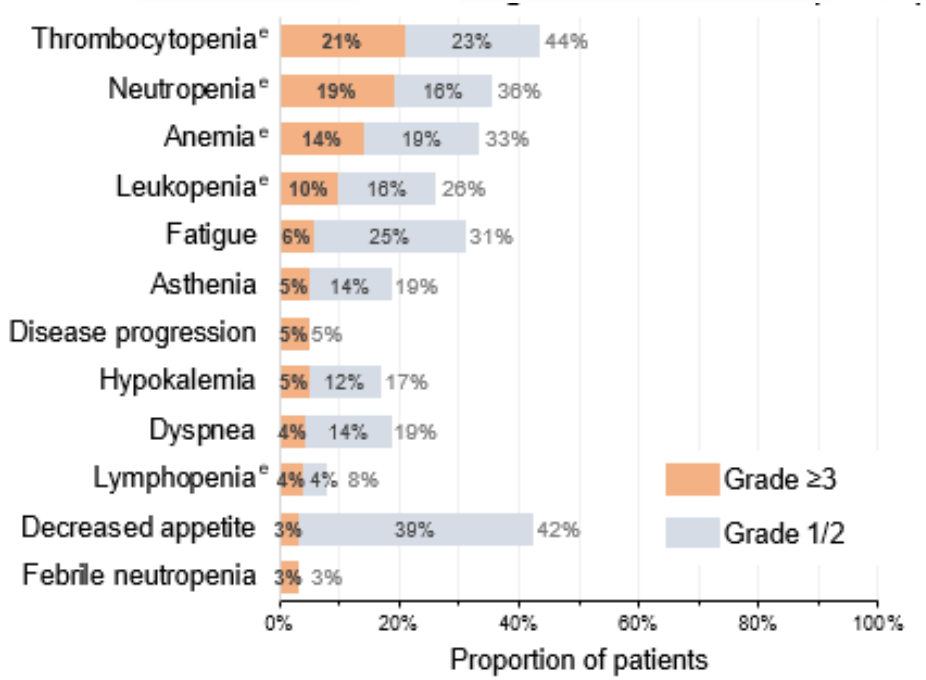
Johns AC, Campbell MT. *Cancer J.* 2022;28(6):469-478. Drago JZ, et al. *Nat Rev Clin Oncol.* 2021;18(6):327-344.

HER3-DXd – Adverse Events

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)
Associated with death[b]	24 (10.7)
Grade ≥3 TEAE, n (%)	146 (64.9)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[c]	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)

Median treatment duration: 5.5 (range, 0.7-18.2) months.

Most Common Grade >3 TEAEs Occurring in ≥3% of Patients (N=225)[d]



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

HER3-DXd, patritumab deruxtecan; TEAE, treatment-emergent adverse event.
Yu H, et al. WCLC 2023. Abstract OA05.03.

Workup for Suspected ADC-Related ILD

- Hold ADC pending more information
- History and physical exam
- Rule out other causes of ILD (eg, other drugs or RT toxicity) and other pathologies with similar presentation (eg, infection, PD, or PE)
  - High-resolution CT scan of chest
  - Pulmonology consult with pulmonary function testing
  - Bronchoscopy and BAL ± transbronchial lung biopsy
- Laboratory tests
  - CBC, liver and kidney function tests, electrolytes, CRP, ESR, procalcitonin, LDH, other
  - Analysis for infection based on suspected pathogen (blood culture, expectorated sputum, urinary antigens, β-D-glucan, other)
  - Tumor markers and autoimmune antibodies, if indicated

AXIS Medical Education

ADC, antibody-drug conjugate; BAL, bronchoalveolar lavage; CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; LDH, lactate dehydrogenase; PD, progressive disease; PE, pulmonary embolism.

Tarantino P, et al. *JAMA Oncol.* 2021;7(12):1873-1881.

Detecting and Managing T-DXd–Related Interstitial Lung Disease: The 5 “S” Rules

T-DXd, trastuzumab deruxtecan.

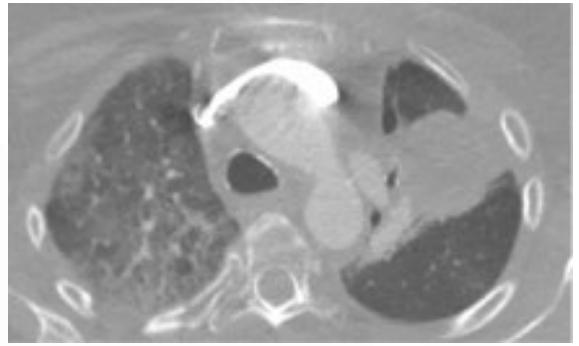
Tarantino P, Tolaney SM. *JCO Oncol Pract.* 2023;19(8):526-527.

Management of ILD Associated With HER3-DXd

What to Look for

- **Shortness of breath, particularly on exertion**
- **Dry cough**
- **Chest discomfort**
- **Fatigue**

Promptly investigate any evidence of suspected ILD/pneumonitis with high-resolution CT, pulmonologist consult, and blood cultures/CBC



Grade and Description	Protocol Management Recommendations

1: asymptomatic; clinical or diagnostic observations only	▪ Hold patritumab deruxtecan until resolution to grade 0
	  ▪ If AE resolves in ≤28 days, resume with same dose of patritumab deruxtecan
	  ▪ If AE resolves in >28 days, resume with reduced dose of patritumab deruxtecan
	▪ Consider corticosteroid treatment (eg, prednisone ≥0.5 mg/kg/day)

2: symptomatic; limiting instrumental ADL **3:** severe symptoms; limiting self-care ADL or life-threatening respiratory compromise	▪ **Permanently discontinue patritumab deruxtecan** ▪ Promptly initiate corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent) and continue for ≥14 days followed by gradual taper for ≥4 weeks
For all grades	▪ Oxygen supplementation for hypoxia ▪ Monitor closely for worsening symptoms, re-image as clinically indicated ▪ Supportive treatment for prolonged corticosteroid use ▪ Consider infliximab, mycophenolate mofetil, IVIG, etc if corticosteroid refractory

Dose reductions: Starting Dose 5.6 mg/kg Q3W → Reduction 1: 4.8 mg/kg → Reduction 2: 3.2 mg/kg → Discontinue

Image courtesy of Rebecca Heist, MD, MPH.
ADL, activities of daily living; AE, adverse event; CBC, complete blood count; CT, computed tomography; HER3-DXd, patritumab deruxtecan; ILD, interstitial lung disease.
Yu HA, et al. *J Clin Oncol.* 2023;41(35):5363-5375.
Jänne PA, et al. *Cancer Discov.* 2022;12(7):74-89.

Managing Clinically Significant Nausea and Vomiting With HER3-DXd

- Premedicate with 3-drug regimen for CINV (eg, dexamethasone + 5-HT_3 receptor antagonist + NK1 receptor antagonist)
- ***Onset may be delayed:*** Provide patient with take-home antiemetics (eg, dexamethasone, ondansetron)
- Manage with antiemetics, dose reductions; withhold if high grade until resolved to grade ≤1

AXIS Medical Education

CINV, chemotherapy-induced nausea and vomiting; HER3-DXd, patritumab deruxtecan.

Stankowicz M, et al. *Breast Care (Basel).* 2021;16(4):408-411.
Rugo HS, et al. *ESMO Open.* 2022;7(4):100553.
Trastuzumab deruxtecan. Package insert. Daiichi Sankyo, Inc; 2024.

Management of Select AEs Associated With HER3-DXd: Neutropenia

Grade/Description	Protocol Management Recommendations
Grade 1: <LLN - 1500 neutrophils/mm^3; <LLN - 1.5 x 10^9 neutrophils/L	• Continue patritumab deruxtecan and monitor for worsen neutropenia
Grade 2: <1500 - 1000 neutrophils/mm^3; <1.5 - 1.0 x 10^9 neutrophils/L	• Continue patritumab deruxtecan and monitor for worsen neutropenia
Grade 3: 500 to <1000 neutrophils/mm^3; 0.5-1 x 10^9 neutrophils/L	• Hold patritumab deruxtecan until resolution to grade ≤2 • Then resume with **same** dose of patritumab deruxtecan
Grade 4: <500 neutrophils/mm^3; <0.5 x 10^9 neutrophils/L	• Hold patritumab deruxtecan until resolution to grade ≤2 • Then resume with **reduced** dose of patritumab deruxtecan

Dose reductions: Starting Dose 5.6 mg/kg Q3W → Reduction 1: 4.8 mg/kg → Reduction 2: 3.2 mg/kg → Discontinue

AXIS Medical Education

AE, adverse event; HER3-DXd, patritumab deruxtecan; Q3W, once every 3 weeks.

Yu HA, et al. *J Clin Oncol.* 2023;41(35):5363-5375.
Clinical Study Protocol. https://ascopubs.org/doi/suppl/10.1200/JCO.23.01476/suppl_file/protocol_JCO.23.01476.pdf

Management of Select AEs Associated With HER3-DXd: Febrile Neutropenia

Grade/Description	Protocol Management Recommendations
Grade 3: ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or sustained temperature of ≥38°C (100.4°F) for ≥1 hr	• Hold patritumab deruxtecan until resolution • Then resume with patritumab deruxtecan and **consider** dose reduction • Consider administration of G-CSF as prophylaxis for all subsequent cycles and according to local guidelines
Grade 4: Life-threatening consequences; urgent intervention indicated	• Hold patritumab deruxtecan until resolution • Then resume with **reduced** dose of patritumab deruxtecan • Administer of G-CSF as prophylaxis for all subsequent cycles and according to local guidelines

Dose reductions: Starting Dose 5.6 mg/kg Q3W → Reduction 1: 4.8 mg/kg → Reduction 2: 3.2 mg/kg → Discontinue

AXIS Medical Education

AE, adverse event; ANC, absolute neutrophil count; HER3-DXd, patritumab deruxtecan; G-CSF, granulocyte colony-stimulating factor.

Yu HA, et al. *J Clin Oncol.* 2023;41(35):5363-5375.
Clinical Study Protocol. https://ascopubs.org/doi/suppl/10.1200/JCO.23.01476/suppl_file/protocol_JCO.23.01476.pdf

Management of Select AEs Associated With HER3-DXd: Thrombocytopenia

Grade/Description	Protocol Management Recommendations
Grade 1: <LLN - 75,000 platelets/mm^3; <LLN - 75.0 x 10^9 platelets/L	• Continue patritumab deruxtecan and monitor for worsen neutropenia
Grade 2: <75,000 - 50,000 platelets/mm^3; <75.0 - 50.0 x 10^9 platelets/L	• Continue patritumab deruxtecan and monitor for worsen neutropenia
Grade 3: <50,000 - 25,000/mm^3 platelets; <50.0 - 25.0 x 10^9 platelets/L	• Hold patritumab deruxtecan until resolution to grade ≤1 ▪ If AE resolves in ≤14 days, resume with **same** dose ▪ If AE resolves in >14 days, resume but **consider reduced** dose
Grade 4: <25,000 platelets/mm^3; <25.0 x 10^9 platelets/L	• Hold patritumab deruxtecan until resolution to grade ≤1 • Then resume with **reduced** dose of patritumab deruxtecan

Dose reductions: Starting Dose 5.6 mg/kg Q3W → Reduction 1: 4.8 mg/kg → Reduction 2: 3.2 mg/kg → Discontinue

AXIS Medical Education

AE, adverse event; ANC, absolute neutrophil count; HER3-DXd, patritumab deruxtecan; LLN, lower limit of normal.

Yu HA, et al. *J Clin Oncol.* 2023;41(35):5363-5375.
Clinical Study Protocol. https://ascopubs.org/doi/suppl/10.1200/JCO.23.01476/suppl_file/protocol_JCO.23.01476.pdf

Shared Decision-Making (SDM) and Individualized Treatment Planning

The Importance of the MDT in NSCLC Care

- The wide range of treatment modalities requires collaboration among multiple specialists to develop individualized management strategies and provide optimal staging in the complex NSCLC setting
- The lung cancer MDT includes a medical oncologist, thoracic surgeon, pulmonologist, and radiation oncologist,
  - Other specialists (eg, radiologists, pathologists, nurse navigator, nutritionists, nuclear medicine specialists, clinical pharmacists, molecular biologists, psychologists) may also be included

- **MDT-based patient care in NSCLC has been associated with longer overall survival and better quality-of-care–related outcomes**

AXIS Medical Education

NSCLC, non-small cell lung cancer; MDT, multi-disciplinary team.
De Castro Jr G, et al; for the Grupo Brasiliero de Oncologia Toracica. *JTO Clin Res Rep.* 2023;4(12):1-20.

Treatment Shared Decision-Making (SDM) in NSCLC

In recent years, treatment options for NSCLC have rapidly expanded to include novel immunotherapies, targeted therapies, and combination and multidisciplinary approaches

Patients and their families are bombarded by multitudes of information about cancer, especially through social media and the internet

The complexity of cancer care and the abundance of cancer-related information can complicate the development of individualized care plans

AXIS Medical Education

NSCLC, non-small cell lung cancer.

Shickh S, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389516.

Treatment SDM in Cancer Care

- Definition: a collaborative, patient-centered process in which the clinical team:
  - Provides patients and caregivers with information about the diagnosis, prognosis, and available treatment options
  - Elicits patient values related to recommended treatment alternatives
  - Clarifies patient/family personal preference for treatment
  - Helps the patient choose an option that is consistent with personal goals and optimal clinical care
  - Supports decision interventions (or “decision aids”) that can facilitate treatment SDM

AXIS Medical Education

SDM, shared decision-making.
Myers RE, et al. *J Pers Med.* 2021;11(10):998.

The Role of SDM in Planning Treatment Regimens

- SDM is a fundamental method of care that is central to individualizing treatment
- It involves an MDT approach to ensure optimal care for and communication with the patient and their family
- The initial step involves promoting productive dialogues that encourage active patient-clinician collaboration, facilitating the process of care plan development, and supporting the cocreation of a comprehensive care plan

MDT, multi-disciplinary team; SDM, shared decision-making.

Shickh S, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389516.

Downloadable Shared Decision-Making Guide

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HERTHENA-Lung01: A Phase 2 Randomized Open-Label Study of Patritumab Deruxtecan (U3-1402) in Subjects with Previously Treated Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer (NSCLC) (Patritumab Deruxtecan in Subjects with Metastatic or Locally Advanced EGFR-mutated NSCLC). Clinical Study Protocol. Protocol Number: U31402-A-U201; IND Number 133343; EudraCT Number 2020-000730-17. Version 3.0, March 31, 2021. https://ascopubs.org/doi/suppl/10.1200/JCO.23.01478/suppl_file/protocol_JCO.23.01478.pdf

Kumagai K, Shao Y, Qin H-F, Tai Y-H, Gao H-J. ALK-rearrangement in non-small-cell lung cancer (NSCLC). Thorac Cancer. 2018;9(4):423-430.

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Lyu H, Han A, Polsdofer E, Liu B, Liu B. Understanding the biology of HER3 receptor as a therapeutic target in human cancer. Acta Pharm Sin B. 2018;8(4):503-510.

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Scherpereel 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. 2019;9:7406.

Sithanandam G, Anderson LM. The ERBB3 receptor in cancer and cancer gene therapy. Cancer Gene Ther. 2008;15(7):413-448.

Sienkowicz M, Mauro L, Hamden K, Pennisi A. Management of chemotherapy-induced nausea and vomiting with trastuzumab deruxtecan: a case series. Breast Care (Basel). 2021;16(4):408-411.

Tarantino P, Modi S, Tolaney S, et al. Interstitial lung disease induced by anti-ERBB2 antibody-drug conjugates: A review. JAMA Oncol. 2021;7(12):1873-1881.

Trastuzumab deruxtecan. Package insert. Daiichi Sankyo, Inc; 2024.

Yu H, Goto Y, Hayashi H, et al. Patritumab deruxtecan (HER3-DXd) in EGFR-mutated NSCLC following EGFR TKI and platinum-based chemotherapy: HERTHENA-Lung01. Abstract presented at IASLC World Conference on Lung Cancer; Singapore; September 9-12, 2023. Abstract OA05.03.

Yu HA, Goto Y, Hayashi H, et al. 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. J Clin Oncol. 2023;41(35):5363-5375.

Provided by AXIS Medical Education

This resource is supported by an educational grant from Daiichi Sankyo.

Targeting Resistance in EGFRm NSCLC with HER3-Directed ADCs in the Community Setting

A PATIENT/CLINICIAN DECISION SUPPORT AID

What is Shared Decision-Making?

Shared decision-making (SDM) occurs when a healthcare provider and a patient work together to make a healthcare decision that is best for the patient. Optimal decision making takes into account evidence-based information about available options; the provider's knowledge and experience; and the patient's values, goals, and preferences. Patients and their families/caregivers who are engaged in an SDM process are more likely to arrive at a treatment decision that works best for all those involved.

What Are the Best Practices for Discussing the Risk/Benefits of Therapy?

For patients and clinicians alike, it is essential to weigh the risks and benefits of different treatment options and to be aware of the potential for both acute and long-term side effects of different treatment options. Individual patient goals and preferences should be considered, including desire for curative treatment. The effects of treatment options on patient quality of life and independence are crucial. The American Society of Clinical Oncology recommends several strategies that may help to appropriately weigh the balance of risks and benefits of different treatment options, including:

- Getting a second opinion
- Understanding the latest guideline recommendations
- Incorporating other decision-making tools
- Encouraging patient discussions with people they trust (family, social workers, clergy, etc.)
- Understanding statistical data for key outcomes and what these may mean (or not mean) for each individual patient

Additional considerations can be found at the American Cancer Society website:
https://www.cancer.org/cancer/managing-cancer/making-treatment-decisions/making-decisions.html

The AXIS 6 Ease ("Es") to SDM

ENSURE
Ensure you see and treat the patient as an individual not a disease.

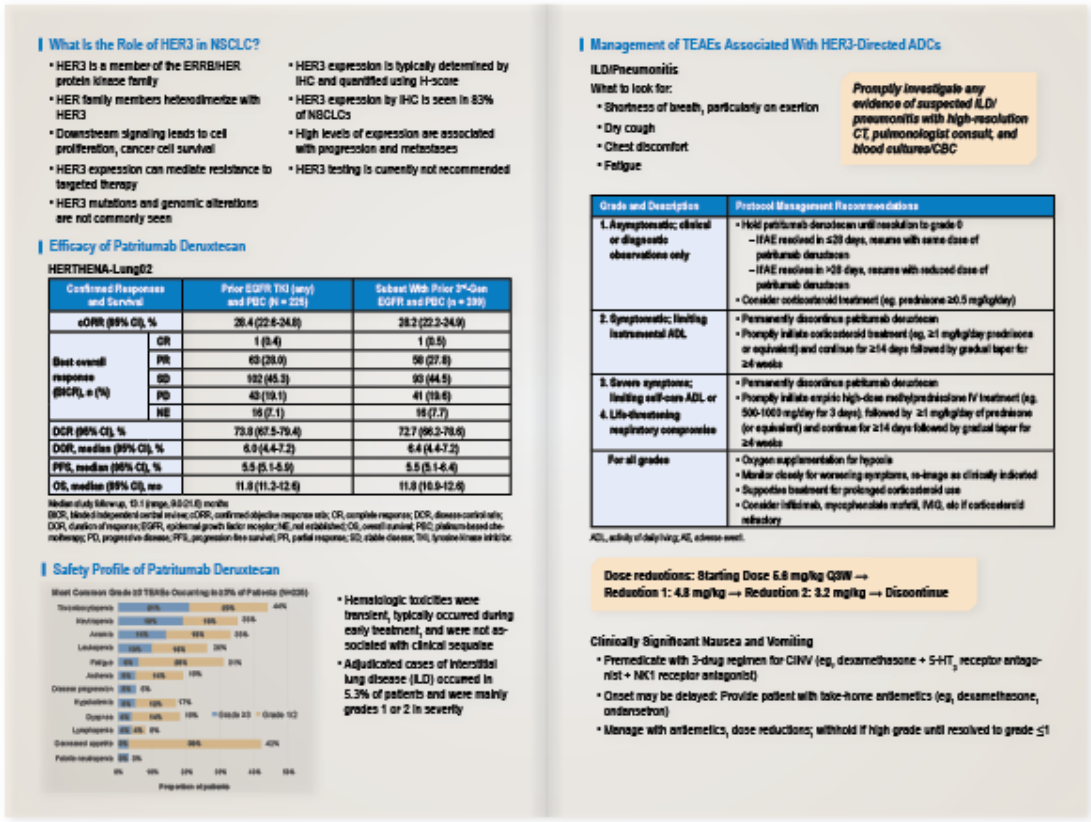
ELEVATE
Elevate the patient-centric experience and improve satisfaction with care.

ENABLE
Enable a long-term personal connection with your patients.

ESTABLISH
Establish co-created treatment plans that align medical evidence with patient preferences to foster adherence and optimize outcomes

ELICIT
Elicit patient/caregiver preferences, values, and goals for therapy.

EVALUATE
Evaluate the risk/benefits and costs of treatment so that they are aligned with patient expectations.



What Is the Role of HER3 in NSCLC?

- HER3 is a member of the ERRB/HER protein kinase family
- HER family members heterodimerize with HER3
- Downstream signaling leads to cell proliferation, cancer cell survival
- HER3 expression can mediate resistance to targeted therapy
- HER3 mutations and genomic alterations are not commonly seen
- HER3 expression is typically determined by IHC and quantified using H-score
- HER3 expression by IHC is seen in 83% of NSCLCs
- High levels of expression are associated with progression and metastases
- HER3 testing is currently not recommended

Efficacy of Patritumab Deruxtecan

HERTHENA-Lung02

Confirmed Response and Survival		Prior EGFR TKI (any) and PBC (N = 225)	Subset With Prior 3rd-Gen EGFR and PBC (n = 139)
cORR (95% CI), %		28.4 (22.6-34.8)	28.2 (22.3-34.9)
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	63 (28.0)	38 (27.8)
	SD	102 (45.3)	93 (44.5)
	PD	43 (19.1)	41 (19.6)
	NE	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), %		6.9 (4.4-7.2)	6.4 (4.4-7.2)
PFS, median (95% CI), %		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.3-12.6)	11.9 (10.9-12.6)

Median study follow-up, 13.1 (range, 9.0-21.6) months
BICR, blinded independent central review; cDCR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; NE, not established; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Safety Profile of Patritumab Deruxtecan

- Hematologic toxicities were transient, typically occured during early treatment, and were not associated with clinical sequelae
- Adjudicated cases of interstitial lung disease (ILD) occured in 5.3% of patients and were mainly grades 1 or 2 in severity

Management of TEAEs Associated With HER3-Directed ADCs

ILD/Pneumonitis

What to look for:

- Shortness of breath, particularly on exertion
- Dry cough
- Chest discomfort
- Fatigue

Promptly investigate any evidence of suspected ILD/pneumonitis with high-resolution CT, pulmonologist consult, and blood cultures/CBC

Grade and Description	Protocol Management Recommendations
1. Asymptomatic; clinical or diagnostic observations only	• Hold patritumab deruxtecan until resolution to grade 0 – If AE resolved in ≤28 days, resume with same dose of patritumab deruxtecan – If AE resolves in >28 days, resume with reduced dose of patritumab deruxtecan • Consider corticosteroid treatment (eg, prednisone ≥0.5 mg/kg/day)
2. Symptomatic; limiting instrumental ADL	• Permanently discontinue patritumab deruxtecan • Promptly initiate corticosteroid treatment (eg, ≥1 mg/kg/day prednisone or equivalent) and continue for ≥14 days followed by gradual taper for ≥4 weeks
3. Severe symptoms; limiting self-care ADL, or 4. Life-threatening respiratory compromise	• Permanently discontinue patritumab deruxtecan • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by ≥1 mg/kg/day of prednisone (or equivalent) and continue for ≥14 days followed by gradual taper for ≥4 weeks
For all grades	• Oxygen supplementation for hypoxia • Monitor closely for worsening symptoms, re-image as clinically indicated • Supportive treatment for prolonged corticosteroid use • Consider infliximab, mycophenolate mofetil, IVIG, etc if corticosteroid refractory

ADL, activity of daily living; AE, adverse event.

Dose reductions: Starting Dose 5.6 mg/kg Q3W →
Reduction 1: 4.8 mg/kg → Reduction 2: 3.2 mg/kg → Discontinue

Clinically Significant Nausea and Vomiting

- Premedicate with 3-drug regimen for CINV (eg, dexamethasone + 5-HT_3 receptor antagonist + NK1 receptor antagonist)
- Onset may be delayed: Provide patient with take-home antiemetics (eg, dexamethasone, ondansetron)
- Manage with antiemetics, dose reductions; withhold if high grade until resolved to grade ≤1

AXIS Medical Education

Case-Based Learning Lab

Case Study 1

- 46-year-old woman with EGFR exon 19 deletion positive lung cancer who was initially started on osimertinib plus chemotherapy and had an initial good response but subsequent progression 22 months later
- She has multi-site progression in the liver, bone, and lung.
- Repeat biopsy shows continued EGFR exon 19 deletion but no additional acquired genomic alterations

EGFR, epidermal growth factor receptor.

Case Study Audience Question

What is the next best treatment option for this patient?

a) Single agent docetaxel
b) Carboplatin, pemetrexed, and amivantamab
c) Osimertinib + capmatinib
d) Patritumab deruxtecan

Rationale for Best/Correct Answer

Data from HERTHENA-Lung01 trial showed that the HER3-directed ADC patritumab deruxtecan yielded durable responses in patients with *EGFR*-mutated NSCLC that progressed following therapy with an EGFR TKI and platinum-based therapy.

ADC, antibody-drug conjugate; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Yu HA, et al. *J Clin Oncol.* 2023;41(35):5363-5375.

Case Study 2

- 63-year-old woman with L858R positive lung cancer who has metastases to bone, brain, and lung
- She was initially treated with osimertinib for 15 months, followed by carboplatin/pemetrexed for 8 months, and then develops progression in the lung with a new pleural effusion, dyspnea on exertion and a dry cough
- She is started on patritumab deruxtecan and after 3 cycles, her dyspnea on exertion and cough resolved
- Imaging shows resolution of the pleural effusion and shrinkage of her pulmonary mets
- She presents for cycle 6 of HER3-DXd with new onset dyspnea and with oxygen saturation of 87% on room air. She admits to a productive cough with some yellow sputum

HER3-DXd, patritumab deruxtecan.

Case Study Audience Question

What is the appropriate next step for this patient?

a) Hold patritumab deruxtecan
b) Start antibiotics for possible pneumonia
c) Start prednisone at 1mg/kg
d) Refer to pulmonary for workup and evaluation
e) All of the above

Case Study Conclusion and Rationale for Best/Correct Answer

- Current management recommendations for patients who develop grade 1 ILD while on patritumab deruxtecan include:
  - Holding patritumab deruxtecan until resolution to grade 0
  - Starting antibiotics for possible pneumonia
  - Starting prednisone at 1 mg/kg
  - Referring to pulmonary for workup and evaluation

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ILD, interstitial lung disease.

Yu HA, et al. *J Clin Oncol.* 2023;41(35):5363-5375. Jänne PA, et al. *Cancer Discov.* 2022;12(7):74-89.

Key Takeaways

- HER3-directed ADC therapies may be a new treatment option for EGFR-mutated NSCLC with prior EGFR TKI exposure
  - ORR was similar for patients regardless of the type of prior EGFR TKI
- Management of TEAEs related to HER3-directed ADCs requires a multidisciplinary approach, with proactive monitoring for ILD/pneumonitis and early management of nausea/vomiting
- SDM is crucial to ensure that the patient's goal of therapy are included when selecting treatment

AXIS Medical Education

ADC, antibody-drug conjugate; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; SDM, shared decision-making; TEAE, treatment-emergent adverse event.

AXIS Medical Education

Targeting Resistance in EGFRm NSCLC with HER3-Directed ADCs in the Community Setting