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CHALLENGING CASES

Lung Cancer

Challenging Cases in Lung Cancer

Presented by Dr. Lee Schwartzberg

Program Disclosures

COIs: Consultant for Daiichi Sankyo, AstraZeneca, Seagen, Novartis, Foundation Medicine, Spectrum. Speaker for Daiichi Sankyo, Seagen, AstraZeneca, Merck

The information presented is consistent with FDA Guidelines and includes the latest clinical trial data

This program has been provided as an opportunity for discussion and learning, with insights from key opinion leaders

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Renown Oncology/Hematology

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Challenging Cases in… Lung Cancer

Presented virtually
January 9th 2024

EGFRm NSCLC

- *What is the optimal first line therapy? Second line therapy? Third line therapy?*
- *Challenges with biopsy and testing?*
- *Sequencing considerations to provide the best outcomes for patients?*

Note: Aggregated results and discussion are based on 6 oncologists and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated

Patient History

55-year-old female with 5 pack year smoking history

4-month history of cough and SOB

Other medical history includes DM on metformin, otherwise healthy

Diagnosis

CXR: Right upper lobe mass

CT CAP: 4 cm spiculated mass RUL, bilateral mediastinal nodes, 2 liver mets

MRI: head negative

Biopsy of liver: Adenocarcinoma, moderately differentiated, TTF-1 +

NGS: EGFR Exon 19 deletion, PD-L1 30%, TMB 8

What first-line treatment do you recommend?

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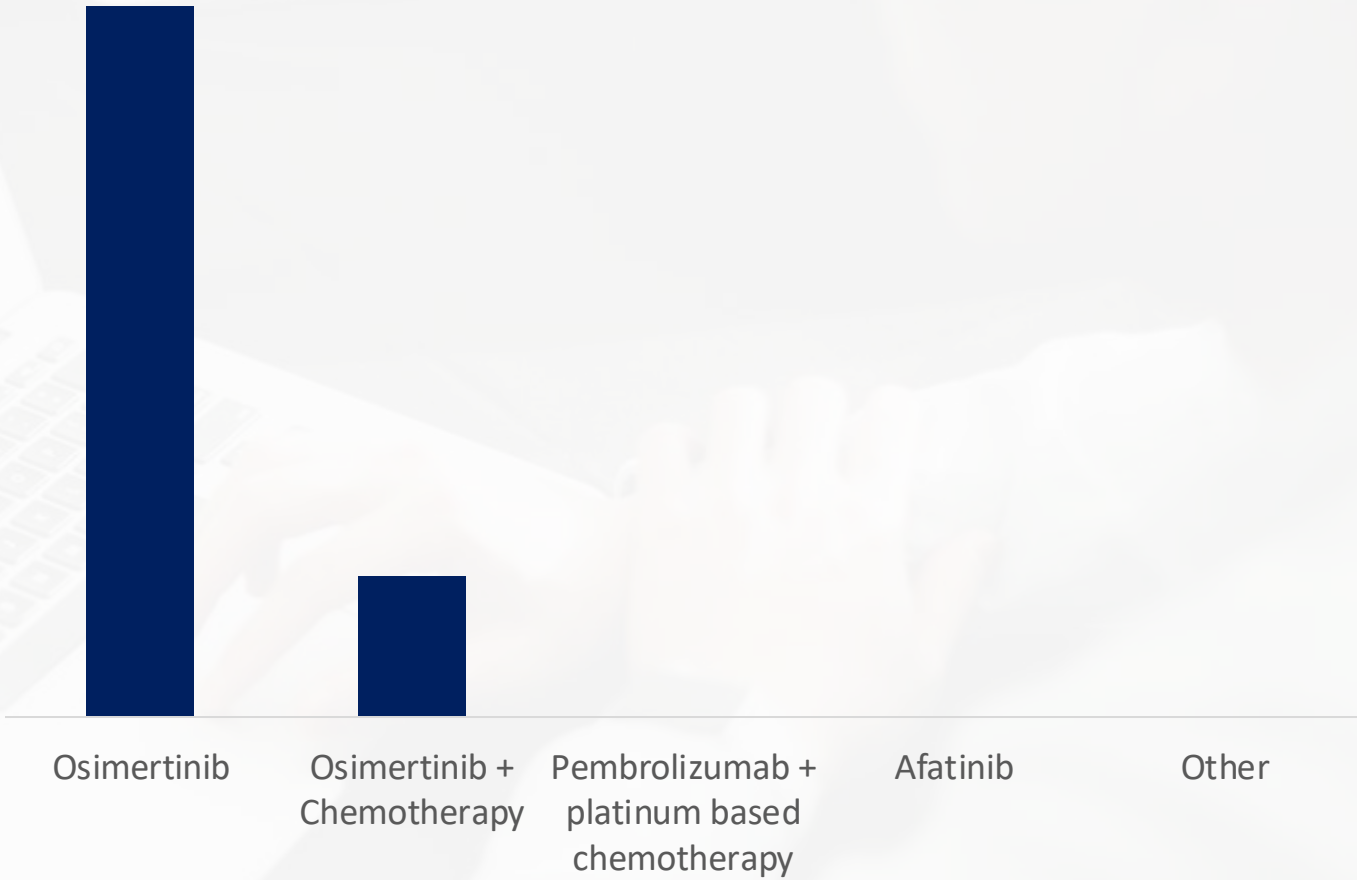
POLLING QUESTION

What first-line treatment do you recommend for EGFR Exon 19 del?

1. Osimertinib
2. Osimertinib + chemotherapy
3. Pembrolizumab + Platinum based chemo
4. Afatinib
5. Other

ARS Results from HCP Participants

What first-line treatment do you recommend for EGFR Exon 19 del?



Discussion with HCP Participants

What first-line treatment do you recommend for EGFR Exon 19 del?

- *Most participants agreed that osimertinib was the 1L standard of care for patients with EGFR Exon19 deletion mNSCLC*
  - *"Long-time responders on osimertinib"*
- *Awareness of the FLAURA2 trial assessing the combination of osimertinib plus chemotherapy exists*
  - *Data is immature*
  - *Not yet included NCCN Guidelines, could result in insurance issues*

KOL insights:

- *Combination of osimertinib and chemotherapy (Flaura2) improved PFS versus chemotherapy alone*
- *Increased toxicity profile with combination regimen*
- *Benefit for use of combination in patients with CNS metastases*

Treatment

Patient had an excellent response to osimertinib

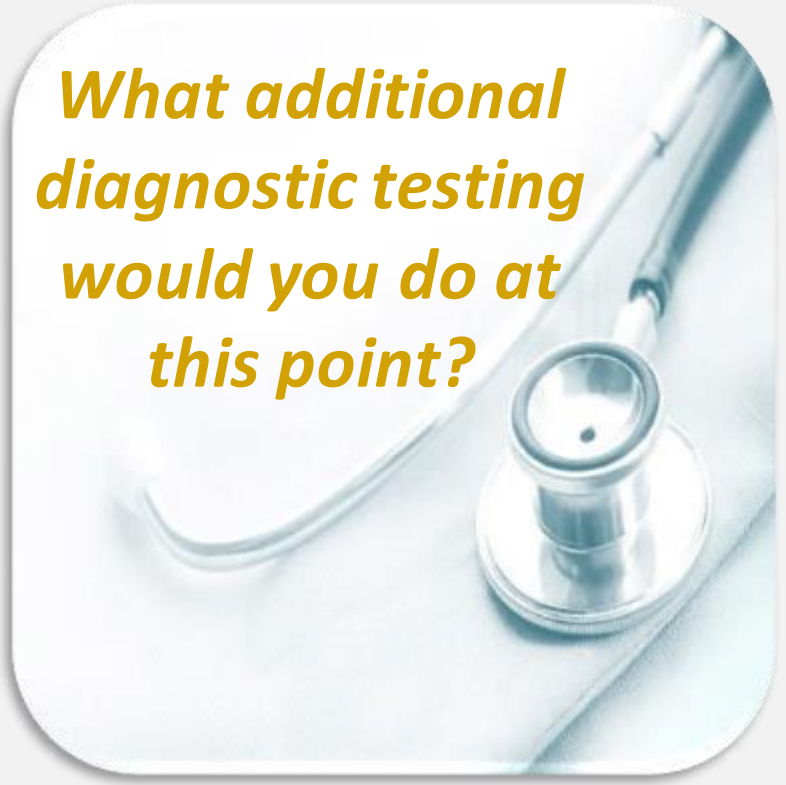
Progression

15 months after initiation, new liver lesions and several bone lesions

MRI: head negative

PS remains excellent

What additional diagnostic testing would you do at this point?



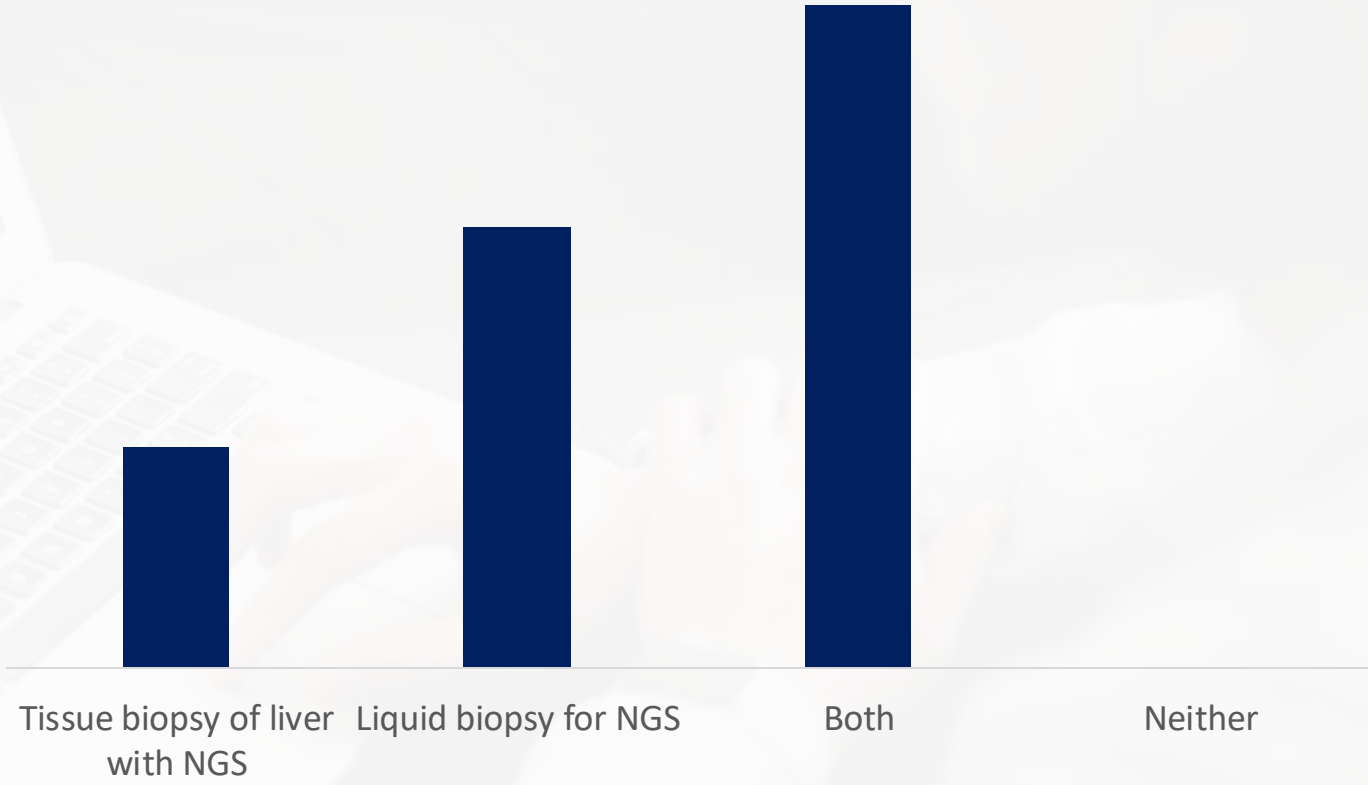
POLLING QUESTION

What additional diagnostic testing would you do at this point?

1. Tissue biopsy of liver with NGS
2. Liquid biopsy for NGS
3. Both
4. Neither

ARS Results from HCP Participants

What additional diagnostic testing would you do at this point?



Discussion with HCP Participants

What additional diagnostic testing would you do at this point?

- *Most participants agreed that doing both tissue and liquid biopsy provides the best information for informing treatment decisions*
  - *Dependent on patient willingness*
- *Sequential testing is preferred with liquid first followed by tissue if nothing is initially revealed*
  - *Some insurance challenges with requesting both tissue and liquid biopsy at the same time*
- *Tissue biopsy is dependent on ease of location; can be more sensitive than liquid*
  - *Biopsy of bone metastases is not always helpful*
- *Some preference for liquid biopsy only on progression after tissue with NGS at initial diagnosis*

Treatment

Excellent response to Osimertinib

Progression

15 months after initiation, new liver lesions and several bone lesions

MRI head negative

PS remains excellent

Test results

Biopsy of new liver lesion shows moderately differentiated adenocarcinoma

NGS shows C797S EGFR mutation

What is your choice of second line therapy?

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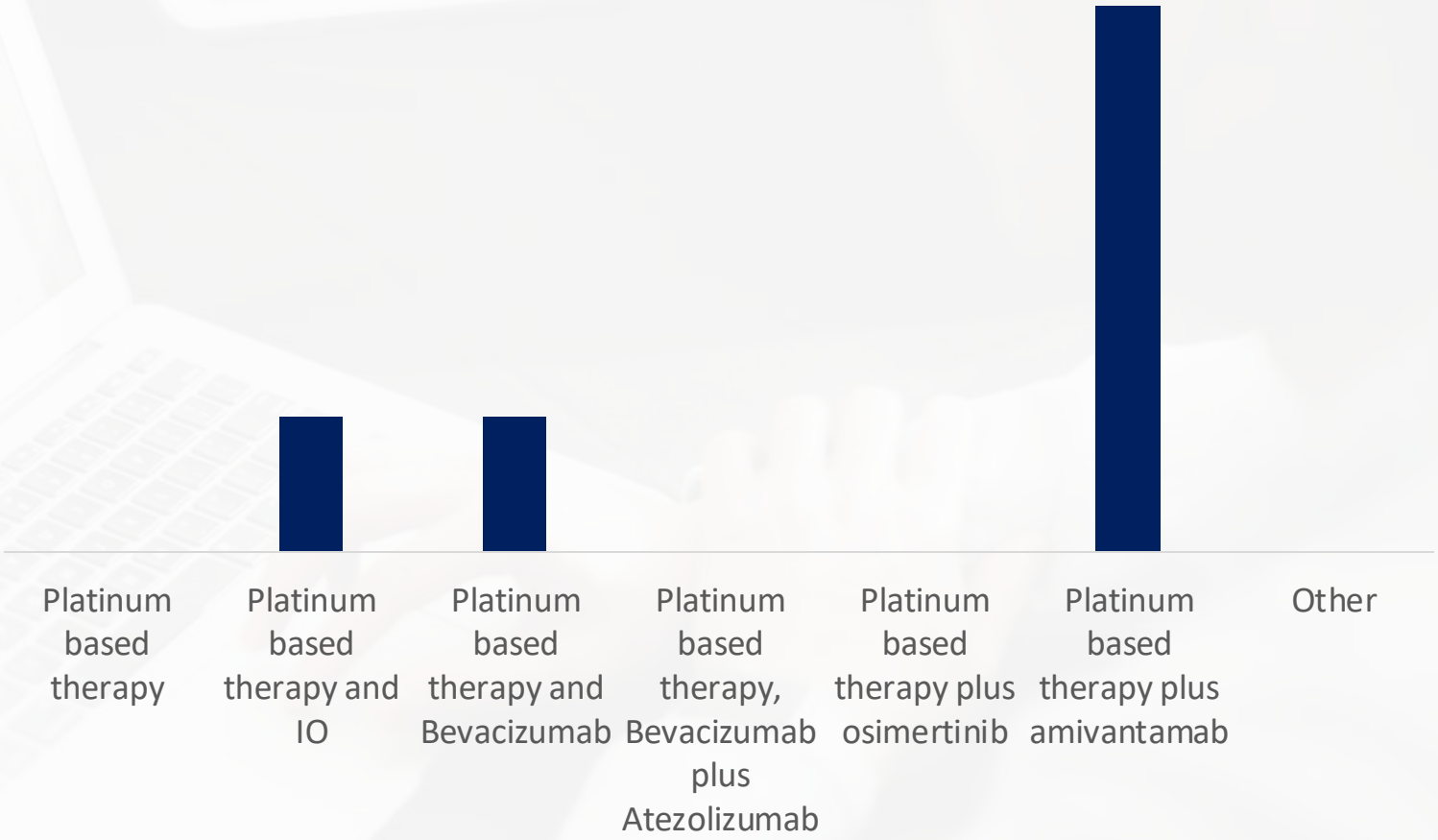
POLLING QUESTION

What is your choice of second line therapy?

1. Platinum based therapy
2. Platinum based therapy and IO
3. Platinum based therapy and Bevacizumab
4. Platinum based therapy, Bevacizumab + Atezolizumab
5. Platinum based therapy + Osimertinib
6. Platinum based therapy + Amivantamab
7. Other

ARS Results from HCP Participants

What is your choice of second line therapy?



Discussion with HCP Participants

What is your choice of second line therapy?

- *Most participants agreed that platinum-based therapy with amivantamab was the preferred treatment choice in the second line setting on identification of C797S EGFR mutation by NGS*
- *Acknowledgement that platinum-based therapy with bevacizumab is an accepted treatment option*
- *General awareness that immunotherapy is not as effective in patients with EGFR mutations*

Resistance Mechanisms to Osimertinib

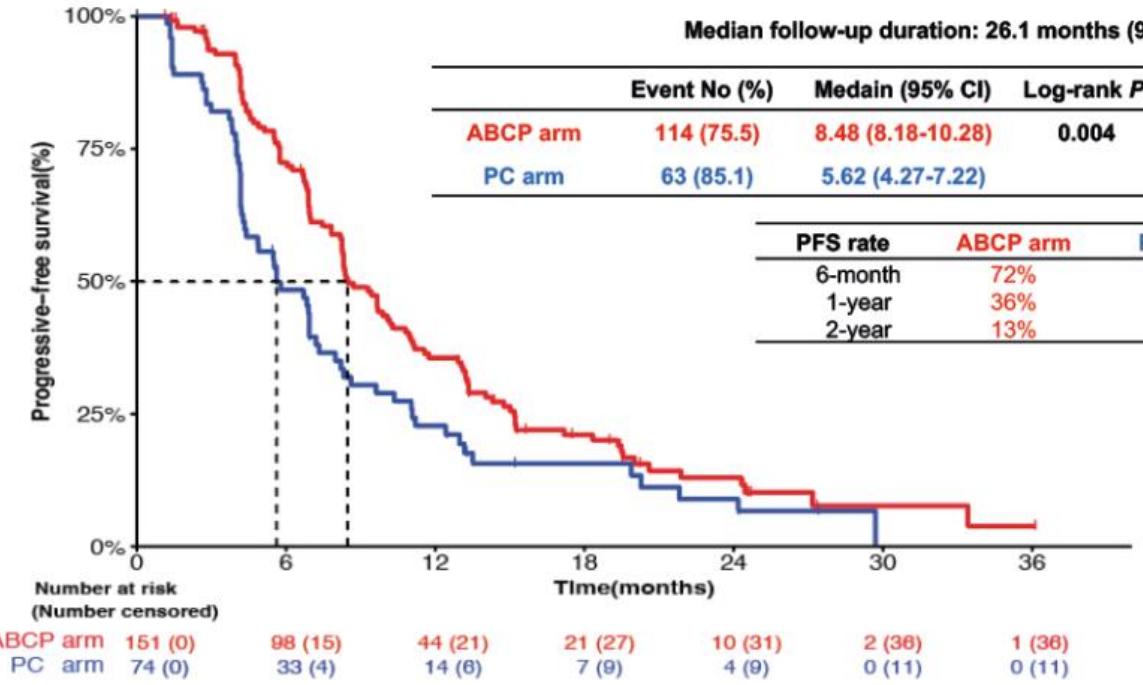
* Other EGFR tertiary mutations include G719X, G724S AND S768I
▲Mutations have also been reported

Leonetti, A., Sharma, S., Minari, R. et al. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer 121, 725–737 (2019).

ATTLAS: Atezo/Bev + Chemo vs. Chemo

Progression-Free Survival

(RECIST v1.1, investigator assessed)



Median follow-up duration: 26.1 months (95% CI 24.7-28.2)

	Event No (%)	Medain (95% CI)	Log-rank *P*	HR (95% CI)
ABCP arm	114 (75.5)	8.48 (8.18-10.28)	0.004	0.62
PC arm	63 (85.1)	5.62 (4.27-7.22)		(0.45-0.86)

PFS rate	ABCP arm	PC arm	P
6-month	72%	48%	0.163
1-year	36%	23%	0.012
2-year	13%	9%	0.006

The ATTLAS trial met its primary endpoint, with significantly longer PFS with ABCP than chemotherapy in patients with EGFR- or ALK-mutated NSCLC after progression on TKI therapy

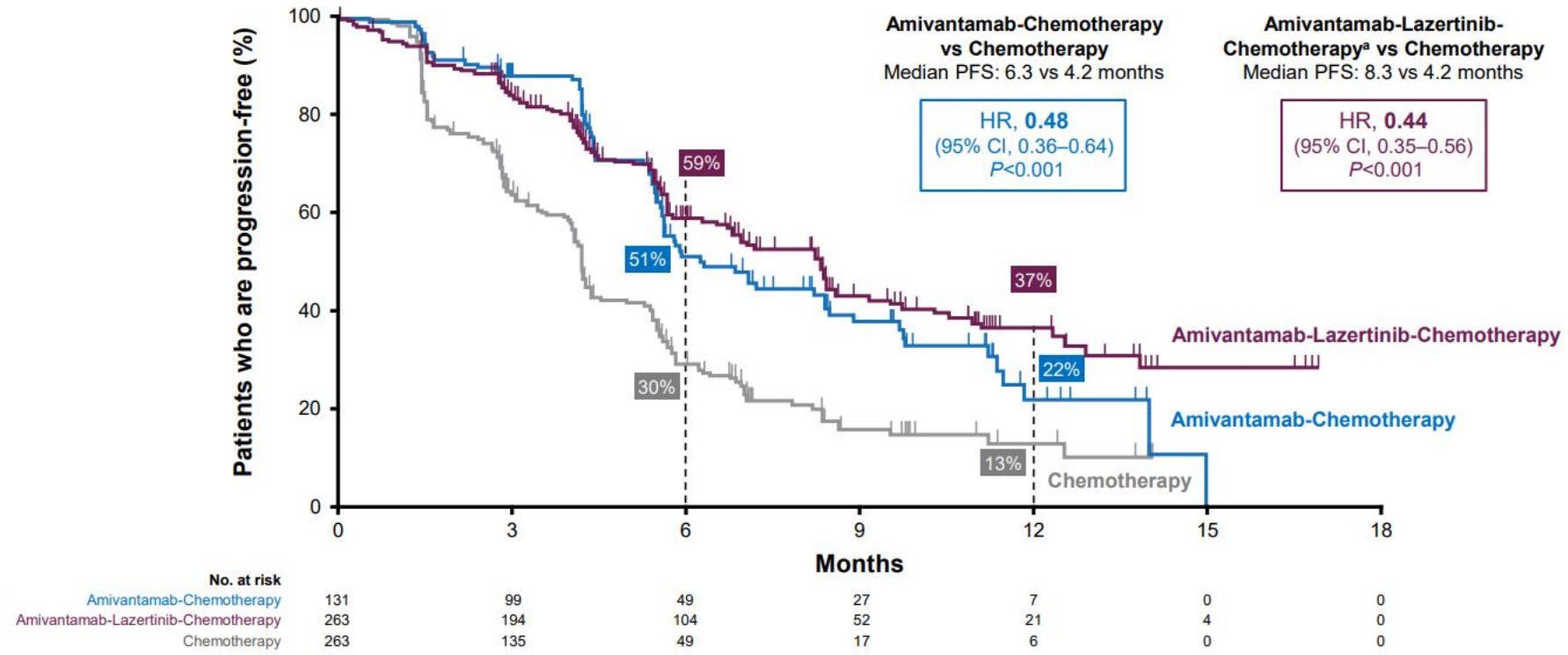
2nd line EGFRm (N=215) or ALK (N=13)

- ORR: **69.5%** vs **41.9%**, p<0.001

Ahn M-J, et al. A phase 3, randomized study of atezolizumab plus bevacizumab and chemotherapy in patients with EGFR or ALK mutated in non-small cell lung cancer (ATTLAS, KCSG-LU19-04). ESMO Congress 2023, LBA67

MARIPOSA2: Amivantamab Plus Chemotherapy (With or Without Lazertinib) vs Chemotherapy

Primary Endpoint: Progression-free Survival by BICR

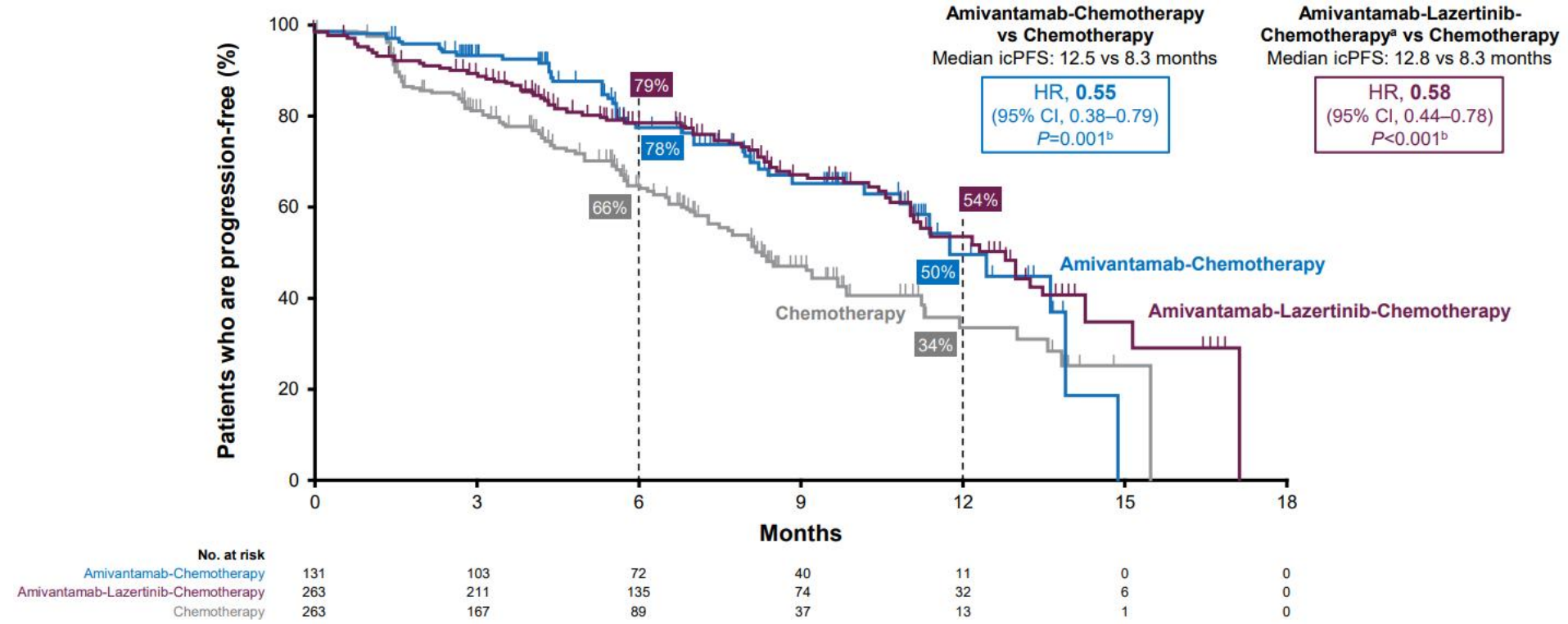


At a median follow-up of 8.7 months, amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of progression or death by 52% and 56%, respectively

Passaro, et al. Amivantamab plus chemotherapy (with or without lazertinib) vs chemotherapy in EGFR-mutated advanced NSCLC after progression on osimertinib: MARIPOSA-2, a phase III, global, randomized, controlled trial. ESMO Congress 2023, LBA15
Ann Oncol. 2023 Oct 23:S0923-7534(23)04281-3.

MARIPOSA2: Amivantamab Plus Chemotherapy (With or Without Lazertinib) vs Chemotherapy

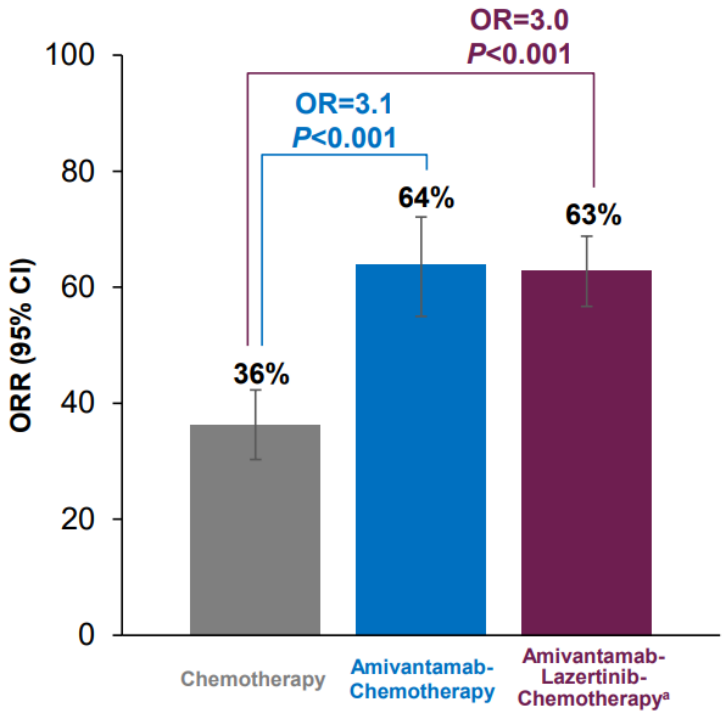
Intracranial Progression-free Survival by BICR



Amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of intracranial progression or death by 45% and 42%, respectively

Passaro, et al. Amivantamab plus chemotherapy (with or without lazertinib) vs chemotherapy in EGFR-mutated advanced NSCLC after progression on osimertinib: MARIPOSA-2, a phase III, global, randomized, controlled trial. ESMO Congress 2023, LBA15
Ann Oncol. 2023 Oct 23:S0923-7534(23)04281-3.

MARIPOSA2: Amivantamab Plus Chemotherapy (With or Without Lazertinib) vs Chemotherapy



BICR-assessed Response, n (%)[b]	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Best Response			
CR	1 (0.4)	2 (2)	6 (2)
PR	93 (36)	81 (62)	157 (61)
SD	82 (32)	30 (23)	61 (24)
PD	52 (20)	10 (8)	14 (5)
NE/UNK	32 (12)	7 (5)	21 (8)
Median DoR[c]	5.6 mo (95% CI, 4.2–9.6)	6.9 mo (95% CI, 5.5–NE)	9.4 mo (95% CI, 6.9–NE)

Passaro, et al. Amivantamab plus chemotherapy (with or without lazertinib) vs chemotherapy in EGFR-mutated advanced NSCLC after progression on osimertinib: MARIPOSA-2, a phase III, global, randomized, controlled trial. ESMO Congress 2023, LBA15
Ann Oncol. 2023 Oct 23:S0923-7534(23)04281-3.

Treatment

Patient receives Platinum based chemo + bevacizumab

Progression

Patient has stable disease for 4 months, then progresses in liver

PS now 1

Brain MRI shows one 1 cm lesion w/o edema in temporal lobe. Treated with SRS

What is your choice of third line therapy?

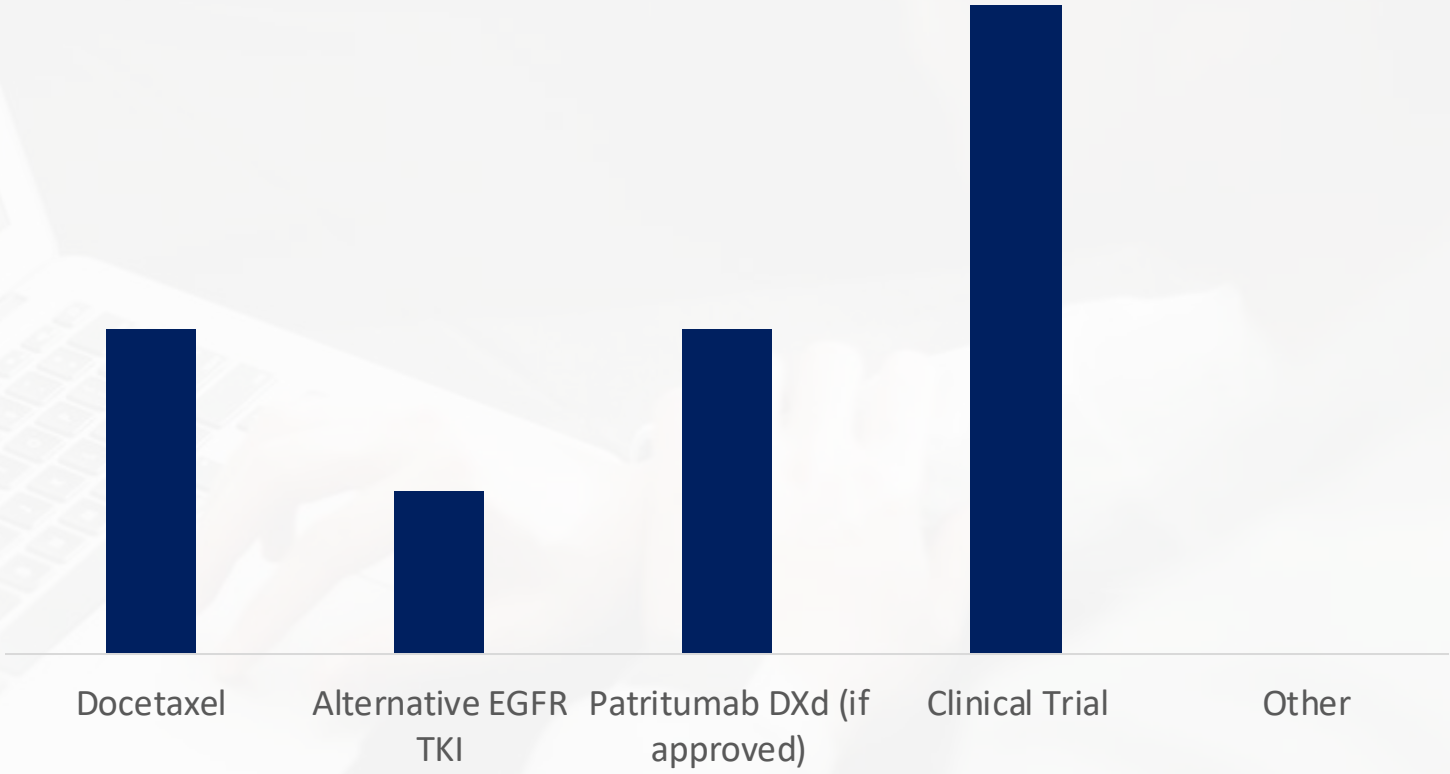
POLLING QUESTION

What is your choice of third line therapy?

1. Docetaxel
2. Alternative EGFR TKI
3. Patritumab DXd (if approved)
4. Clinical trial
5. Other

ARS Results from HCP Participants

What is your choice of third line therapy?



Discussion with HCP Participants

What is your choice of third line therapy?

- *Treatment choice in the third line setting varies*
- *Clinical trial is considered in the 3L setting, providing greater options for patients*
  - *Some community oncology practices have a robust research program and screen patients for eligibility*
- *Awareness of initial promising data with patritumab-DXd warrants consideration*
- *Some consideration of an alternative EGFR TKI in the 3L setting but likelihood of utilizing docetaxel is greater*

Investigational Agents Targeting HER3

Anti-HER3 Monoclonal Abs

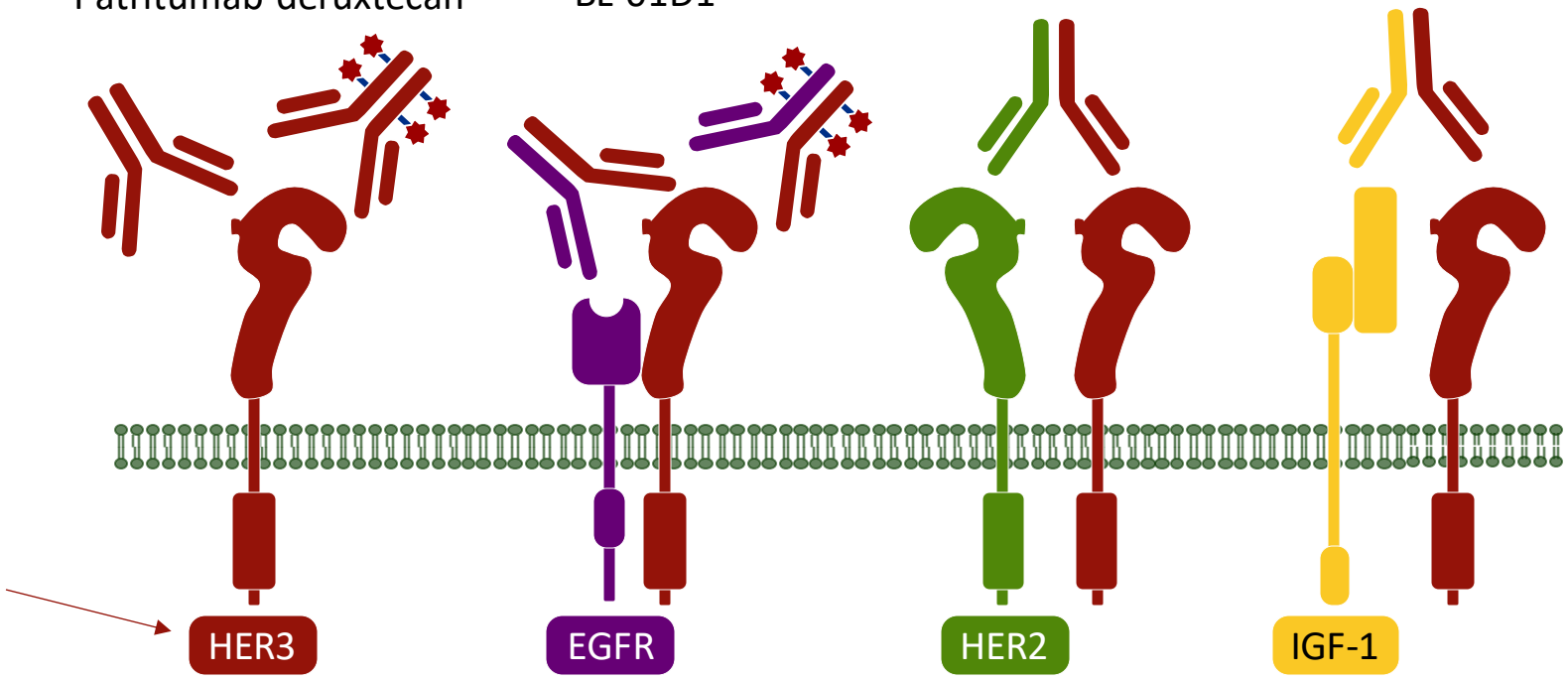
- Patritumab
- Seribantumab
- Lumretuzumab
- GSK2849330
- CDX-3379
- Barecetamab
- AV-203
- Elgemtumab
- HMBD-001
- U3P1287/01
- SIBP-03

Anti-HER3 ADCs

- Patritumab deruxtecan

Bispecific EGFR/HER3 ADC

- BL-01D1



Bispecific EGFR/HER3 Abs

- SI-B001
- Duligotuzumab

Bispecific HER2/HER3 Abs

- Zenocutuzumab
- MM-111

Bispecific IGF-1/HER3 Abs

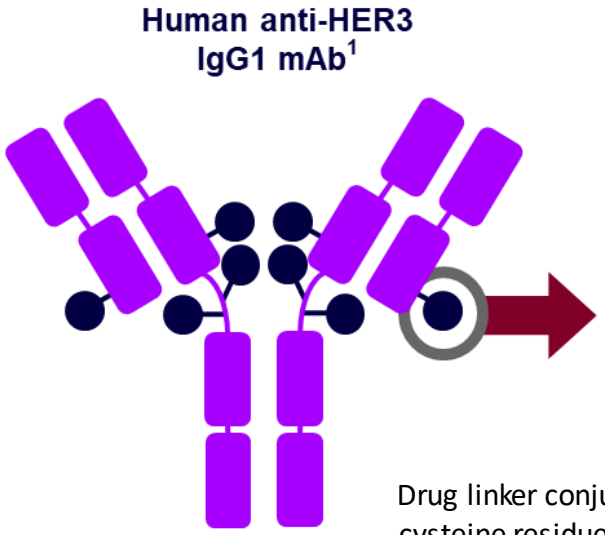
- Isitarumab

Uliano et al., Targeting HER3 for cancer treatment: a new horizon for an old target. ESMO Open. 2023;8:100790.

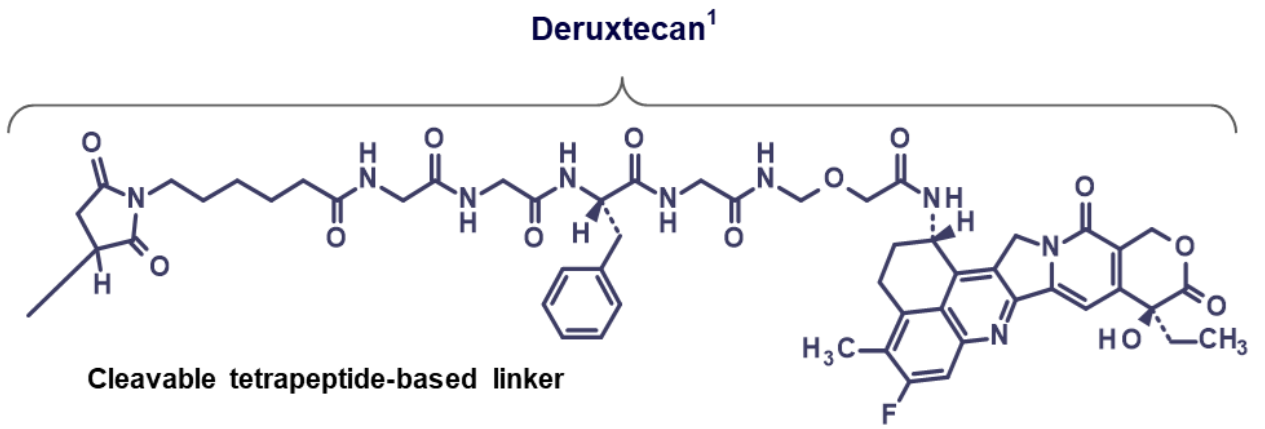
Patritumab Deruxtecan (HER3-DXd): Novel HER3-Targeted Antibody-Drug Conjugate

HER3-DXd is an ADC composed of 3 components:

- A fully human anti-HER3 IgG1 mAb (patritumab)
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker that joins the antibody and the payload



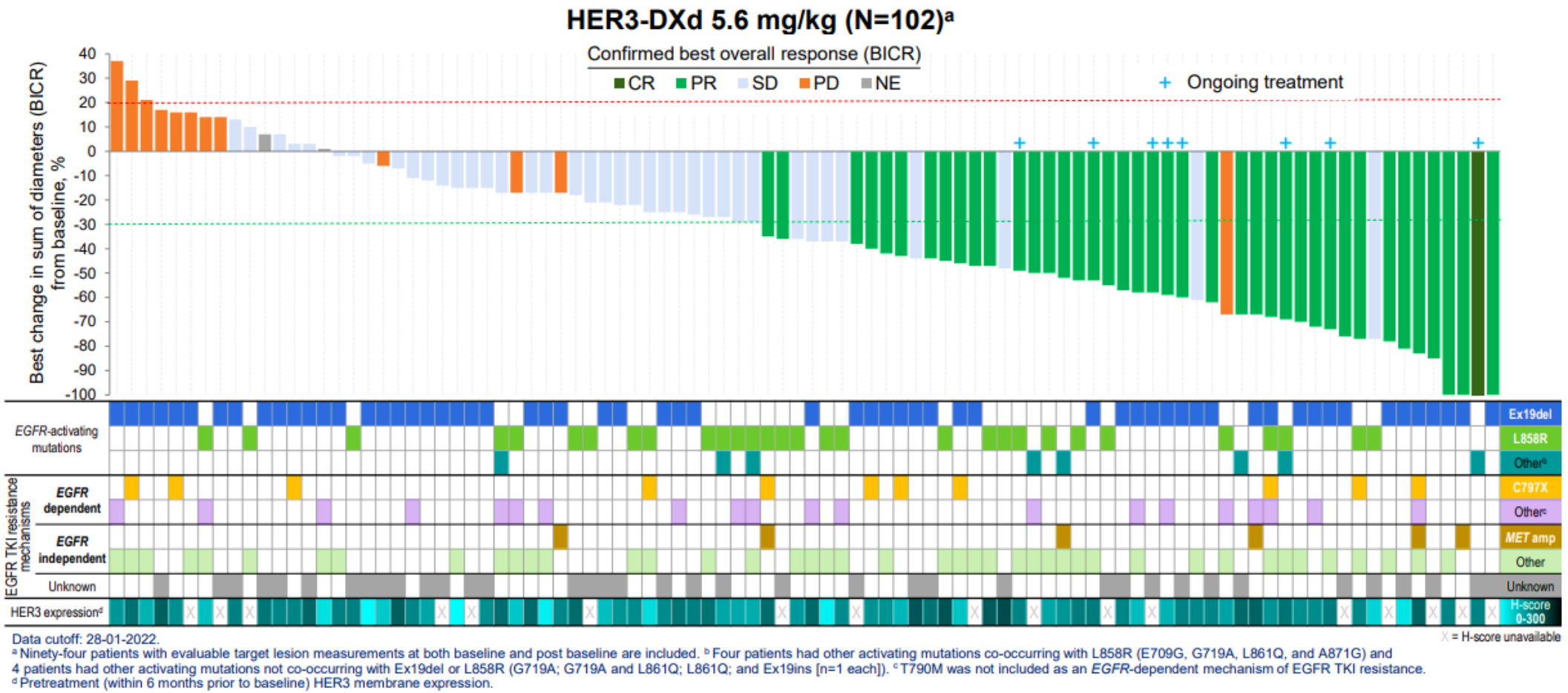
Drug linker conjugated to cysteine residues of mAb



Exatecan derivative

1. **1.** Hashimoto Y, et al. *Clin Cancer Res*. 2019;25:7151-7161.
2. **2.** Koganemaru S, et al. *Mol Cancer Ther*. 2019;18:2043-2050.
3. **3.** Haratani K, et al. *J Clin Invest*. 2020;130(1):374-388.

Patritumab Deruxtecan in *EGFR*-Mutated NSCLC (Phase I): Efficacy With Diverse EGFR TKI Resistance



Data cutoff: 28-01-2022.

[a] Ninety-four patients with evaluable target lesion measurements at both baseline and post baseline are included. [b] Four patients had other activating mutations co-occurring with L858R (E709G, G719A, L861Q, and A871G) and 4 patients had other activating mutations not co-occurring with Ex19del or L858R (G719A; G719A and L861Q; L861Q; and Ex19ins [n=1 each]). [c] T790M was not included as an *EGFR*-dependent mechanism of EGFR TKI resistance. [d] Pretreatment (within 6 months prior to baseline) HER3 membrane expression.

Hayashi. JSMO 2023. Abstr PS1-2.

HERTHENA-Lung01: Phase II Study of Patritumab Deruxtecan in *EGFR*-Mutated NSCLC

Study Design: Multicenter, randomized, open-label phase II trial

- Patients with advanced *EGFR*-mutated NSCLC progressing on most recent systemic therapy
- Prior treatment with EGFR TKI* and platinum-based chemotherapy;
- Inactive or previously treated asymptomatic brain mets allowed
- Pretreatment tissue biopsy required but not selected for by HER3 expression

(N = 277)

Current Report

HER3-DXd
5.6 mg/kg IV Q3W fixed dose
(n = 226†)

Median f/u for efficacy:
18.9 mo (range: 14.9-27.5)

Median tx duration for safety:
5.5 mo (range: 0.7-18.2)

HER3-DXd
IV Q3W uptitration‡
(n = 51§)

Primary endpoint: confirmed ORR by BICR

Key secondary endpoint: DoR by BICR

*Protocol amended to require prior osimertinib.
†n = 226 enrolled; n = 225 received ≥1 dose.
‡Dosing: 3.2 mg/kg C1D1, 4.8 mg/kg C2D1, 6.4 mg/kg C3D1+. §n = 51 enrolled; n = 50 received ≥1 dose. Enrollment discontinued after risk–benefit assessment.

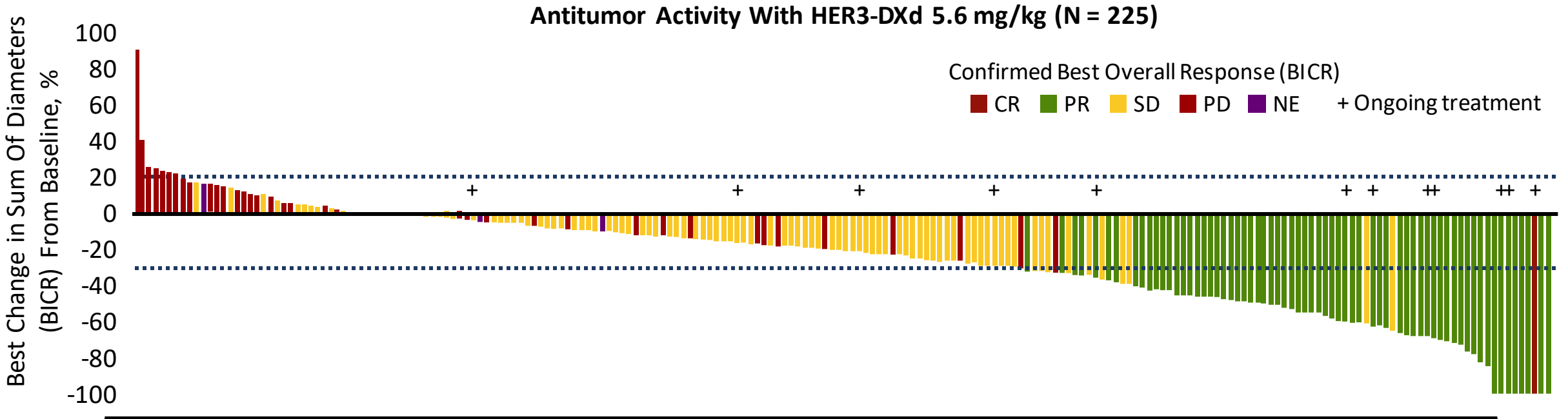
Yu. Future Oncol. 2023;19:1319.
Yu. WCLC 2023. Abstr OA05.03.
Yu. JCO. 2023; JCO2301476.

HERTHENA-Lung01: Responses

Efficacy Outcome	HER3-DXd 5.6 mg/kg	
	All Patients (N = 225)	Patients Who Received 3G EGFR TKI (n = 209)
Confirmed ORR, % (95% CI)	29.8 (23.9-36.2)	29.2 (23.1-35.9)
Best overall response, n (%)		
• CR	1 (0.4)	1 (0.5)
• PR	66 (29.3)	60 (28.7)
• SD	99 (44.0)	91 (43.5)
• 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)
Median DoR, mo (95% CI)	6.4 (4.9-7.8)	6.4 (5.2-7.8)
Median PFS, mo (95% CI)	5.5 (5.1-5.9)	5.5 (5.1-6.4)
Median OS, mo (95% CI)	11.9 (11.2-13.1)	11.9 (10.9-13.1)

Yu. WCLC 2023. Abstr OA05.03.

HERTHENA-Lung01: Antitumor Activity Across EGFR TKI Resistance Mechanisms



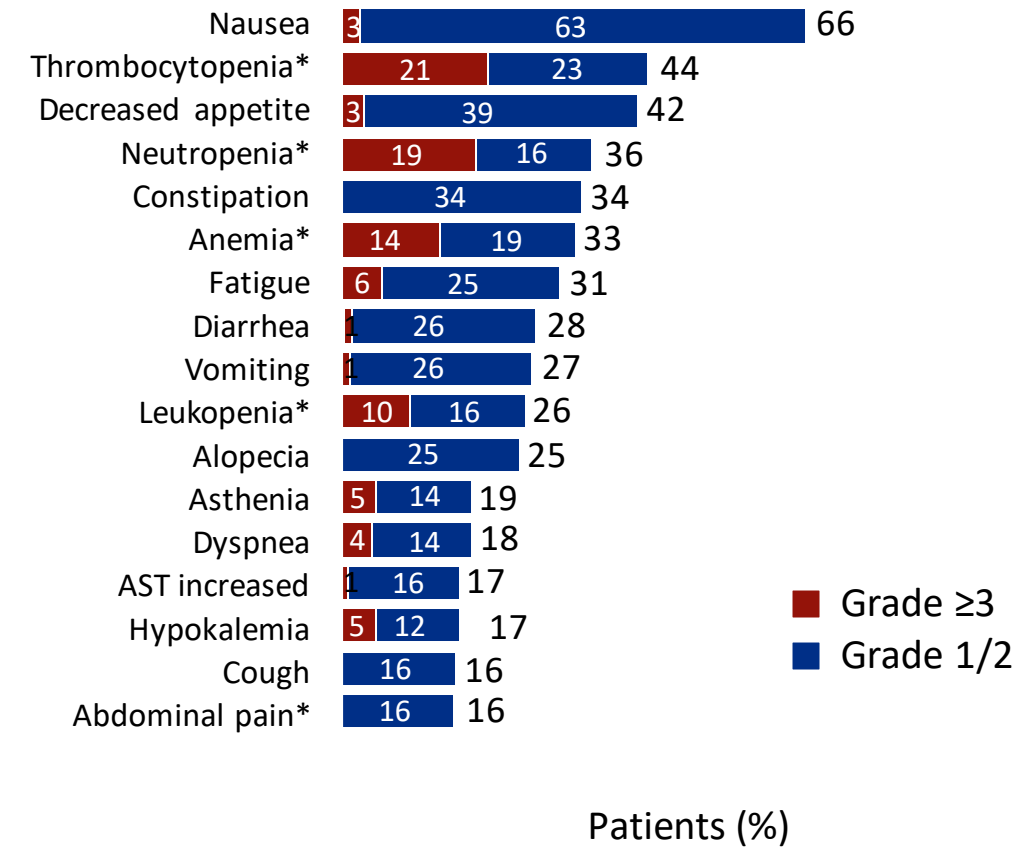
	Type of EGFR TKI Resistance Mechanism			
	EGFR Dependent Only (n = 34)	**EGFR Independent Only (n = 81)**	**Both EGFR Dependent and Independent (n = 32)**	**None Identified (n = 77)**
Confirmed ORR, % (95% CI)	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)

Yu. WCLC 2023. Abstr OA05.03. Yu. JCO. 2023; JCO2301476.

HERTHENA-Lung01: Safety Summary

Safety Outcome, n (%)	HER3-DXd 5.6 mg/kg (N = 225)
Any TEAE	224 (99.6)
• **Associated with treatment d/c**	**16 (7.1)**
• Associated with dose reduction	48 (21.3)
• Associated with dose interruption	91 (40.4)
TEAE grade ≥3	146 (64.9)
Treatment-related TEAE	215 (95.6)
• Grade ≥3	102 (45.3)
• Serious TEAE	34 (15.1)
• Associated with death	4 (1.8)
Adjudicated ILD (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 time to onset, days (range)	53 (9-230)

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



*Grouped preferred terms.

Yu. WCLC 2023. Abstr OA05.03. Yu. JCO. 2023;JCO2301476.

HERTHENA-Lung01 CNS Analysis: Study Design

- Multicenter, randomized, open-label phase II trial

- Patients with advanced *EGFR*-mutated NSCLC progressing on most recent systemic therapy
- Prior treatment with EGFR TKI* and platinum-based chemotherapy;
- Inactive or previously treated asymptomatic brain mets allowed
- Pretreatment tissue biopsy required but not selected for by HER3 expression

(N = 277)

*Protocol amended to require prior osimertinib.

HER3-DXd
5.6 mg/kg IV Q3W fixed dose
(n = 225)

HER3-DXd
IV Q3W uptitration

Cohorts evaluated for intracranial response

- Patients with brain mets at baseline (n = 95)
- Patients with brain mets at baseline and no prior irradiation (n = 30)

Cohorts evaluated for site of first progression

- Patients with PD on study (n = 143)
- Patients with history of brain mets (n = 115) and PD on study (n = 76)
- Patients with no history of brain mets (n = 110) and PD on study (n = 67)

Primary endpoint: confirmed ORR by BICR

Current analysis: intracranial response by BICR, site of first progression (CNS vs non-CNS) by BICR

Johnson. ESMO 2023. Abstr 1319MO. Yu. J Clin Oncol. 2023;[Epub].

HERTHENA-Lung01 CNS Analysis: Intracranial Response

Response by CNS BICR	Patients With Baseline Brain Mets (n = 95)	Patients With Baseline Brain Mets That Were Not Irradiated (n = 30)*
CNS confirmed ORR, n (%) [95% CI]	19 (20.0) [12.5-29.5]	10 (33.3) [17.3-52.8]
• CR	15 (15.8)	9 (30.0)†
• PR	4 (4.2)	1 (3.3)
• SD/non-CR/non-PD	57 (60.0)	13 (43.3)
• PD	13 (13.7)	4 (13.3)
• NE	6 (6.3)	3 (10.0)
CNS DCR, % (95% CI)	80.0 (70.5-87.5)	76.7 (57.7-90.1)
Median CNS DoR, mo (95% CI)	9.2 (8.1-11.1)	8.4 (5.8-9.2)

*Patients with measurable target lesions = 7; Those with nontarget lesions only = 23.

†Patients with nontarget only lesions = 8.

Johnson. ESMO 2023. Abstr 1319MO.

HERTHENA-Lung01 CNS Analysis: Site of First Progression

Site of First Progressive Disease (by BICR), n (%)	History of Brain Mets		All Patients (N = 225)
	Yes (n = 115)	No (n = 110)	
All sites	76 (66)	67 (61)	143 (64)
• Non-CNS	63 (55)	65 (59)	128 (57)
• CNS	24 (21)	3 (3)	27 (12)
• CNS and non-CNS	11 (10)	1 (1)	12 (5)

- Progression in brain at first progressive disease occurred in 21% of patients with a history of brain mets and 3% of patients without a history of brain mets

Johnson. ESMO 2023. Abstr 1319MO.

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

Study Design: Multicenter, randomized, open-label phase III study

Stratified by prior third-generation EGFR TKI (osimertinib vs other; 1L vs 2L); region (Asia vs RoW), brain metastases (yes vs no)

- Patients with locally advanced or metastatic nonsquamous NSCLC with *EGFR*-activating mutation (ex19del or L858R)
- 1-2 prior lines of EGFR TKI treatment including progression after third-generation EGFR TKI
- Stable brain metastases allowed
- Tumor biopsy required, but selection not based on HER3 expression

(planned N = 560)

HER3-DXd
5.6 mg/kg IV Q3W
(n = 280)

Platinum-Based CT
Four 21-day cycles: cisplatin 75 mg/m^2 or carboplatin AUC5 and pemetrexed 500 mg/m^2 Q3W*
(n = 280)

Disease progression, death, or unacceptable toxicity

*Pemetrexed may be continued as maintenance.

Primary endpoint: PFS by BICR (RECIST v1.1)

Secondary endpoints: PFS by investigator, ORR, DoR, DCR, TTR, safety

Mok. ESMO 2022. Abstr 1095. NCT05338970.

Ongoing Phase I Combination Study of Patritumab Deruxtecan With Osimertinib

Study Design: 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

(total target N = 252)

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

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

*Recommended combination dose; 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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ClinicalTrials.gov Identifier: NCT04676477.

Patritumab Deruxtecan Granted Priority Review in the U.S. for Certain Patients with Previously Treated Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer

Submission based on HERTHENA-Lung01 results showing patritumab deruxtecan demonstrated clinically meaningful and durable responses in patients with advanced EGFR-mutated non-small cell lung cancer previously treated with two or more systemic therapies

Application being evaluated under FDA Real-Time Oncology Review

If approved, patritumab deruxtecan would be a first-in-class HER3 directed DXd antibody drug conjugate for these patients

RAHWAY, N.J. and BASKING RIDGE, N.J. December 22, 2023 – Daiichi Sankyo (TSE: 4568) and Merck, known as MSD outside of the United States and Canada, (NYSE: MEK) announced today that the U.S. Food and Drug Administration (FDA) has accepted and granted Priority Review to the Biologics License Application (BLA) for patritumab deruxtecan (HER3-DXd) for the treatment of adult patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) previously treated with two or more systemic therapies.

The Prescription Drug User Fee Act (PDUFA) date, the FDA action date for their regulatory decision, is ***June 26, 2024***. The Priority Review follows receipt of Breakthrough Therapy Designation granted by the FDA in December 2021.

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Key Takeaways

EGFRm NSCLC

Patient case: untreated metastatic disease

- *Testing and retesting drives treatment strategies*
  - *Difficult to treat due to multiple mechanisms of resistance; need to test as more treatments become available*
- *Awareness of clinical trial data provides new treatment options for patients*
  - *Very active area of research with many novel treatment options such as bispecifics being studied*
- *FDA approvals and NCCN Guidelines play a pivotal role in directing treatment pathways*
  - *Potential approval of Patritumab-DXd in 2024 will provide more treatment options for patients*

Program Sponsor