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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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Challenging Cases in… Lung Cancer

Presented virtually March 12th 2024 and in person April 12th 2024

EGFRm NSCLC

Patient case: untreated metastatic disease

- *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 14 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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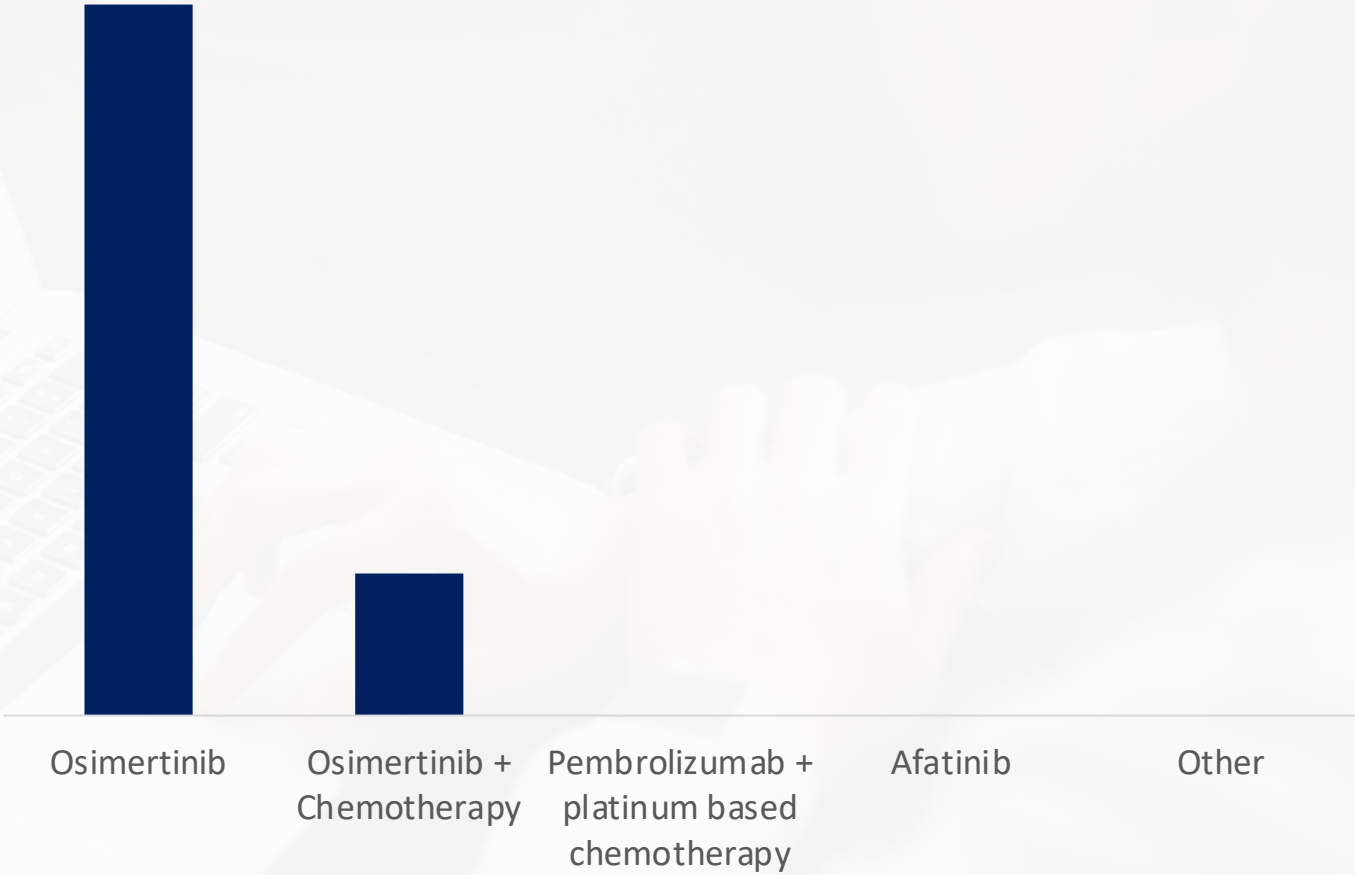
Polling Question

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

1. Osimertinib
2. Osimertinib + platinum-based chemotherapy
3. Erlotinib + VEGFi
4. Afatinib
5. Alternative EGFR TKI
6. 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*
  - *NCCN Preferred category 1 treatment*
  - *Low toxicity with good efficacy*
- *If brain metastases, more likely to push for treatments (osimertinib) in combination with chemotherapy*
- *General awareness of the FLAURA2 trial assessing the combination of osimertinib plus chemotherapy*
  - *"Yet to have a patient"*
  - *"Need the right patient to add more toxicity – depends on PS"*

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*

FDA Applications

- *On **December 21, 2023,** Johnson & Johnson announced the submission of a supplemental Biologics License Application (sBLA) to the U.S. FDA together with a New Drug Application (NDA) seeking the approval of amivantamab-vmjw (RYBREVANT®) in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or L858R substitution mutations, as detected by an FDA-approved test. Application based on the Phase 3 MARIPOSA study.*

FDA Approvals

- *On **February 16, 2024**, the Food and Drug Administration approved osimertinib (Tagrisso®) with platinum-based chemotherapy for patients with locally advanced or metastatic non-small cell lung cancer (la/mNSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. Approval was based on the FLAURA2 study.*

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NCCN Guidelines for EGFR mutations in the 1L setting

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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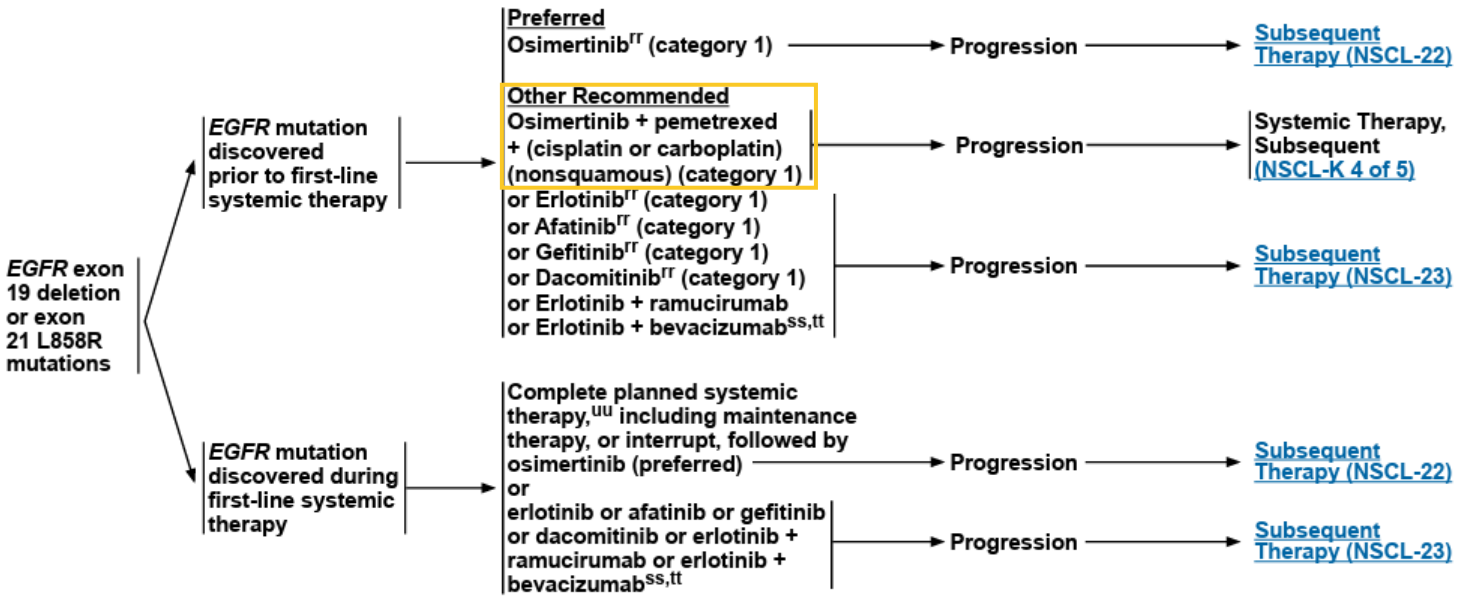
Discussion

***EGFR* EXON 19 DELETION OR EXON 21 L858R MUTATIONS[nn]**

FIRST-LINE THERAPY[qq]



[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[qq] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[rr] For performance status 0–4.
[ss] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[tt] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[uu] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. The rate of side effects (pneumonitis) is higher within 3 months. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516; Gettinger S, et al. J Thorac Oncol 2018;13:1363-1372.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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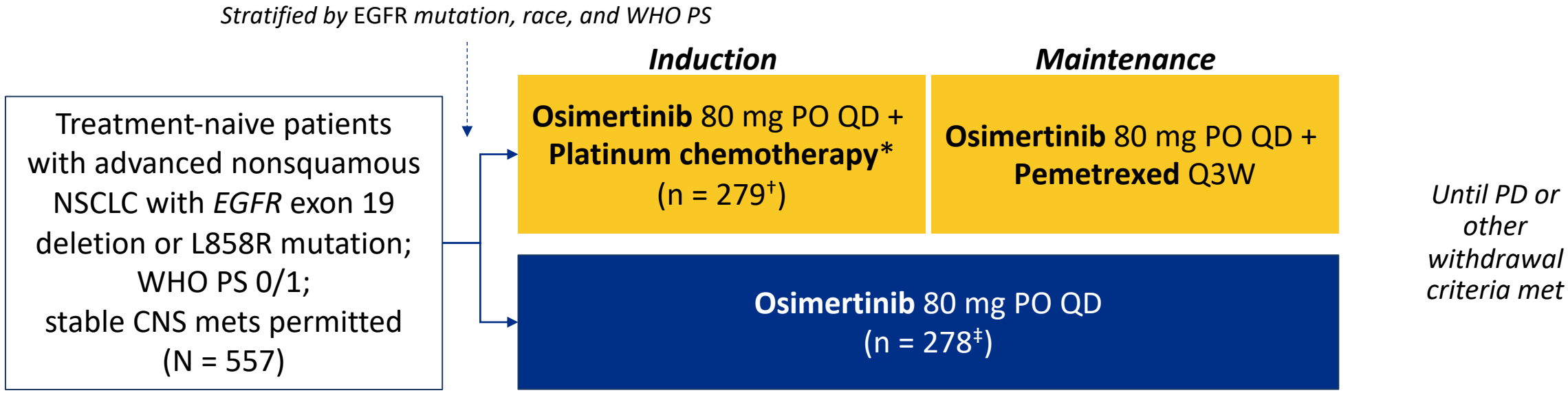
FLAURA2: Does 1L Osimertinib ± platinum-based chemotherapy benefit patients with EGFR-mutated advanced NSCLC?

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



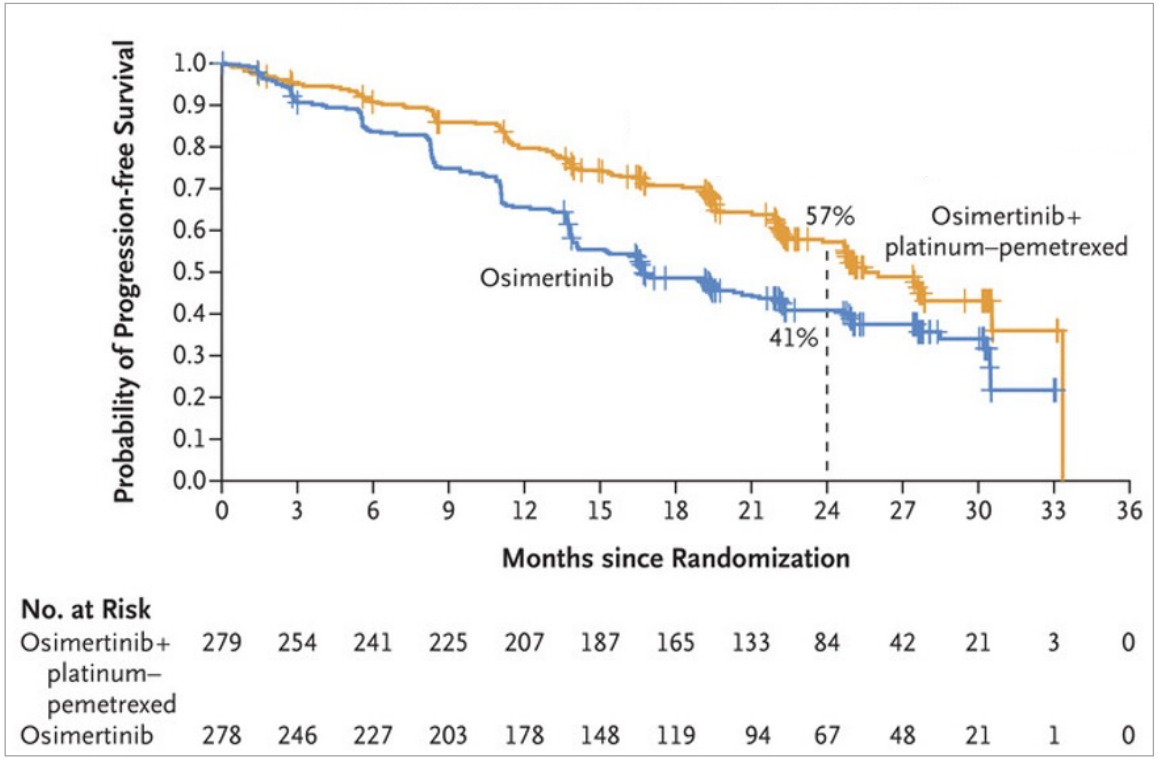
*Pemetrexed 500 mg/m^2 + carboplatin AUC5 or cisplatin 75 mg/m^2 Q3W for 4 cycles.
†n = 276 received tx. ‡n = 275 received tx.

Primary endpoint: investigator-assessed PFS (RECIST v1.1)
Key secondary endpoints: ORR, DoR, DCR, OS, PFS2, HRQoL, safety

Data cutoff: April 3, 2023

Jänne. WCLC 2023. Abstr PL03.13.

FLAURA2 Primary Endpoint: PFS



Median PFS	Osimertinib + Platinum CT (n = 279*)	Osimertinib Monotherapy (n = 278*)	HR (95% CI)	P Value
Per investigator (primary endpoint), mo	**25.5**	**16.7**	**0.62 (0.49-0.79)**	**< 0.0001**
Per BICR, mo	29.4	19.9	0.62 (0.48-0.80)	0.0002
Per investigator by CNS mets at BL, mo (n/N)				
• With CNS mets	24.9 (52/116)	13.8 (79/110)	0.47 (0.33-0.66)	--
• Without CNS mets	27.6 (68/163)	21.0 (87/168)	0.75 (0.55-1.03)	--
Per investigator by EGFR mut at BL, mo (n/N)				
• ex19del	27.9 (65/172)	19.4 (94/169)	0.60 (0.44-0.83)	--
• L858R	24.7 (55/106)	13.9 (70/107)	0.63 (0.44-0.90)	--

*n = 3 in each arm did not receive tx.

- PFS data per investigator currently 51% mature
- Median follow-up 19.5 mo in osimertinib + chemotherapy arm, 16.5 mo in osimertinib monotherapy arm
- PFS benefit with addition of chemotherapy to osimertinib observed across all predefined subgroups

Jänne. WCLC 2023. Abstr PL03.13.

FLAURA2 Secondary Endpoints

Response Outcome	Osimertinib + Platinum CT (n = 279*)	Osimertinib Monotherapy (n = 278*)	Adjusted OR (95% CI)
ORR, %	**83**	**76**	1.61 (1.06-2.44)
• CR	<1	1	
• PR	83	75	
• SD ≥35 days	12	18	
• PD	3	4	
Median best change in target lesion size, % (range)	-52.6 (-100 to 20.0)	-50.0 (-100 to 40.4)	
Median DoR, mo (95% CI)	24.0 (20.9-27.8)	15.3 (12.7-19.4)	

Survival Outcome, Mo	Osimertinib + Platinum CT (n = 279)	Osimertinib Monotherapy (n = 278)	HR (95% CI)	P Value
Median PFS2	30.6	27.8	0.70 (0.52-0.93)	.0132
Median OS	Not reached	Not reached	0.90 (0.65-1.24)	.5238

PFS2, second progression-free survival

- PFS2 and OS data 34% and 27% mature, respectively
- 46% of patients in osimertinib + CT arm and 60% of patients in osimertinib monotherapy arm received subsequent anticancer treatment, typically cytotoxic chemotherapy (33% and 54%, respectively)

Jänne. WCLC 2023. Abstr PL03.13.

FLAURA2 Safety

Safety Outcome	Osimertinib + Platinum CT (n = 276)	Osimertinib Monotherapy (n = 275)
Median osimertinib exposure, mo (range)	22.3 (0.1-33.8)	19.3 (0.1-33.8)
Completed 4 cycles platinum-based chemotherapy, %	76	--
Any AE, n (%)	**276 (100)**	**268 (97)**
• Grade ≥3	176 (64)	75 (27)
• Serious	104 (38)	53 (19)
• Leading to death	18 (7)	8 (3)
• Leading to discontinuation	132 (48)	17 (6)
– Discontinuation of osimertinib | platinum | pemetrexed	30 (11) | 46 (17) | 119 (43)	17 (6) | --|--
Any possibly treatment-related AE, n (%)	**269 (97)**	**241 (88)**
• Grade ≥3	146 (53)	29 (11)
– Related to osimertinib| platinum|pemetrexed	81 (29) |104 (38) | 130 (47)	29 (11) |--|--
• Serious	52 (19)	15 (5)
• Leading to death	5 (2)	1 (< 1)
– Related to osimertinib|platinum|pemetrexed	3 (1) |2 (1) |3 (1)	1 (< 1) |--|--

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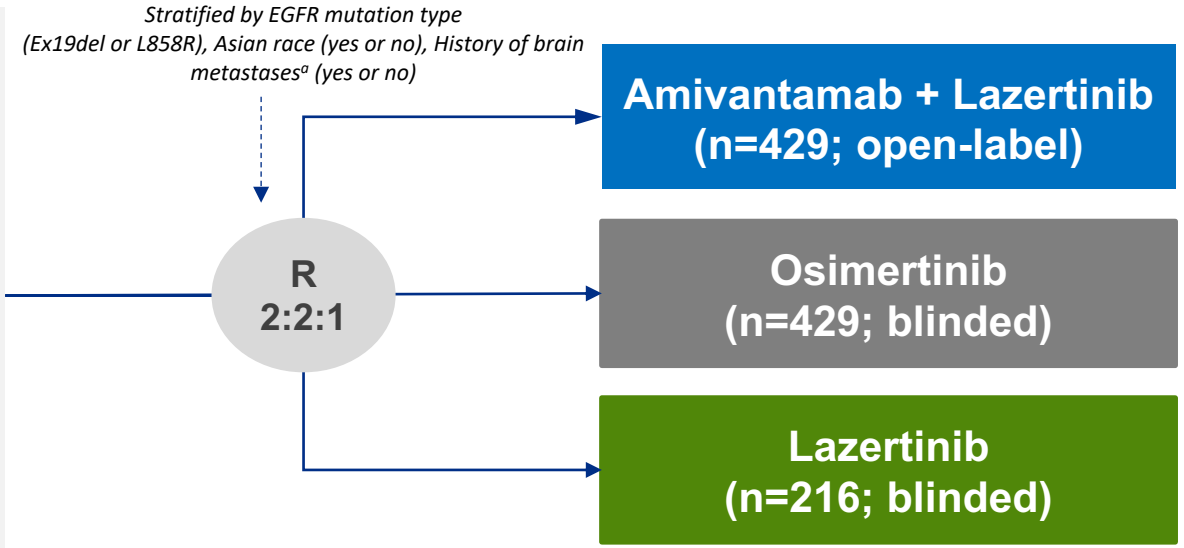
Jänne. WCLC 2023. Abstr PL03.13.

MARIPOSA: Does 1L amivantamab plus lazertinib benefit patients with EGFR-mutated advanced NSCLC?

Study Design: Global, randomized, controlled phase III trial

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented EGFR Ex19del or L858R
- ECOG PS 0 or 1

N=1074



Dosing (in 28-day cycles)

- Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks
- Lazertinib: 240 mg daily
- Osimertinib: 80 mg daily

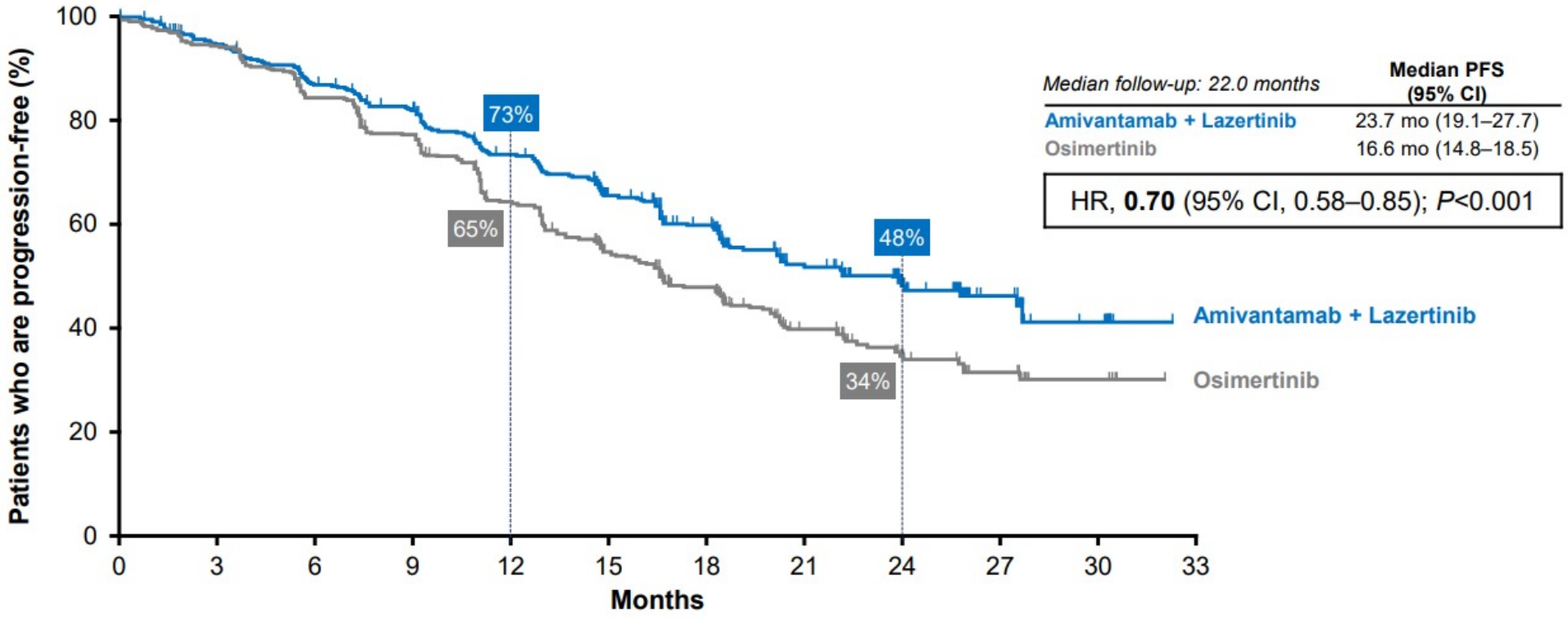
Data cut-off: 11-Aug-2023.

Primary endpoints: Amivantamab + lazertinib vs osimertinib - PFS by BICR per RECIST v1.1

Secondary endpoints: Amivantamab + lazertinib vs osimertinib - OS, ORR, DoR PFS after first subsequent therapy (PFS2) and safety

[a]Serial brain MRIs were required for all patients. Baseline brain MRI was required for all patients and performed ≤28 days prior to randomization; patients who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis. Extracranial tumor assessments were conducted every 8 weeks for the first 30 months and then every 12 weeks until disease progression is confirmed by BICR. bKey statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS. c These secondary endpoints (symptomatic and intracranial PFS) will be presented at a future congress.

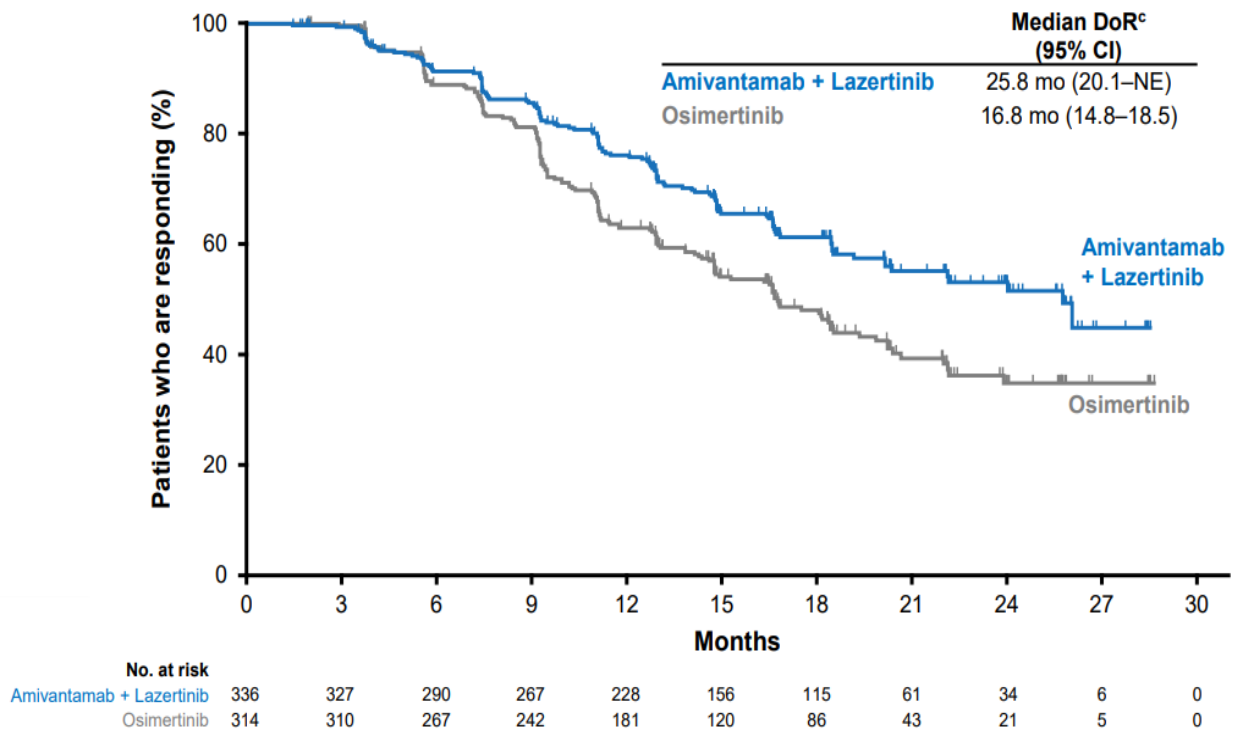
MARIPOSA Primary endpoint: Progression-free survival by BICR



No. at risk												
Amivantamab + Lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

ESMO 2023. Abstr LBA14

MARIPOSA DoR by BICR



MARIPOSA ORR by BICR

BICR-assessed response, n (%)	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)
ORR		
• All responders	**86%** (95% CI, 83–89)	**85%** (95% CI, 81–88)
• Confirmed responders	80% (95% CI, 76–84)	76% (95% CI, 71–80)
Best Response		
• CR	**29 (7)**	**15 (4)**
• PR	334 (79)	335 (81)
• SD	30 (7)	42 (10)
• PD	7 (2)	11 (3)
• NE/Unknown	21 (5)	11 (3)
Ongoing responses	**209 of 336 (62%)**	**151 of 314 (48%)**

MARIPOSA Safety

TEAEs, n (%)	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)
All grades	421 (100)	425 (99)
Grade ≥3	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
Associated with dose reduction	249(59)	23 (5)
Associated with dose delay	350 (83)	165 (39)
Associated with discontinuation	147 (35)	58 (14)
AEs Associated with death[a]	34 (8)	31 (7)

Treatment-related AEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab + lazertinib and 3% with osimertinib

COMPARISON

	MARIPOSA			FLAURA2	
Current FDA approval	• ***Amivantamab in combination with carboplatin and pemetrexed:*** *for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test.* • ***Amivantamab as a single agent****: locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has* ***progressed on or after platinum-based chemotherapy****.*			• ***1L treatment*** *of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test* • ***In combination with pemetrexed and platinum-based chemotherapy****, for the* ***1L treatment*** *of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.*	
Inclusion Criteria	Locally advanced or metastatic NSCLC **Treatment-naïve** for advanced disease with EGFR Ex19del or L858R; ECOG PS 0 or 1			**Treatment-naive** patients with advanced nonsquamous NSCLC With *EGFR* exon 19 deletion or L858R mutation; WHO PS 0/1 Stable CNS mets permitted	
N	1074			557	
Study design	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)	Lazertinib (n=216)	Osimertinib + Platinum chemotherapy (n = 279)	Osimertinib (n = 278)
Median PFS	**23.7**	**16.6** **0.70 (0.58-0.85) *P* < 0.001**	**18.5**	**25.5**	**16.7** **0.62 (0.49-0.79) *P* < 0.0001**
ORR %	86	85	---	83	76
Median DoR	25.8	16.8	---	24.0	15.3
AE Grade ≥3	316 (75)	183 (43)	---	176 (64)	75 (27)
Reference	ESMO 2023. Abstr LBA14			WCLC 2023 Abstr PL03	

Treatment

Patient had an excellent response to osimertinib

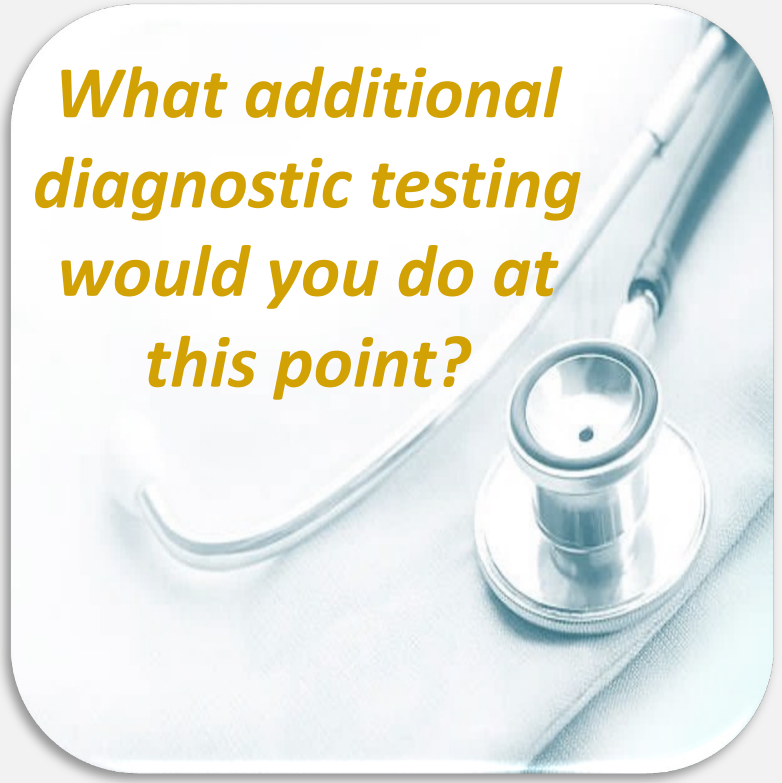
Progression

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?



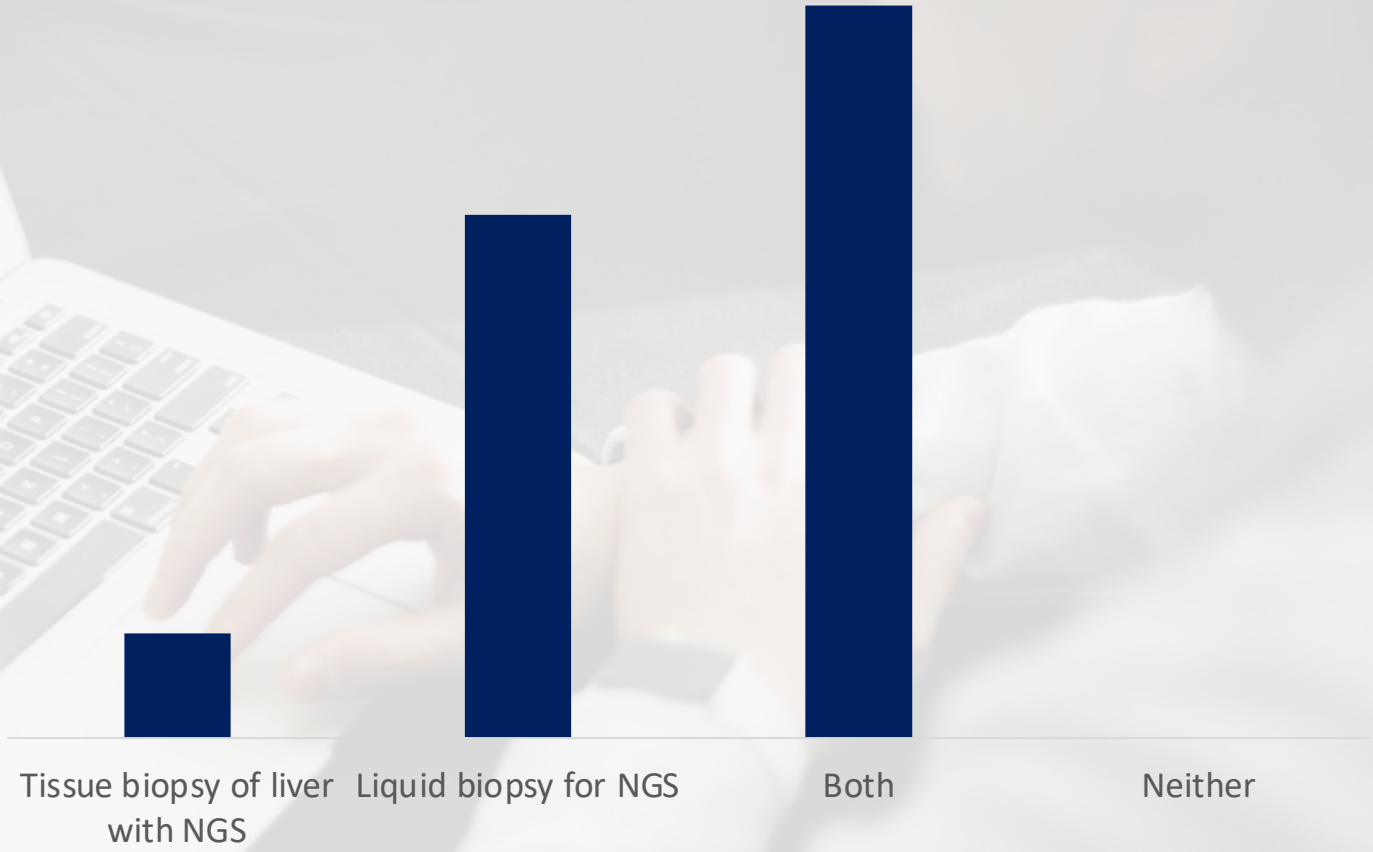
Polling Question

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?

- *General understanding is tissue and liquid are done concurrently or sequentially; combination viewed as superior at catching mutations*
- *Recognition that logistics are easier for liquid with a faster turnaround*
  - *Scheduling can be challenging for patients; with liquid it can be done same day*
  - *Liquid to start, and if unrevealing, then followed by tissue*
- *Some view that tissue is superior for EGFRm, especially to rule out transformations.*
- *Recognition that tissue can be challenging to do sometimes; try to do it at progression if patient is amenable*

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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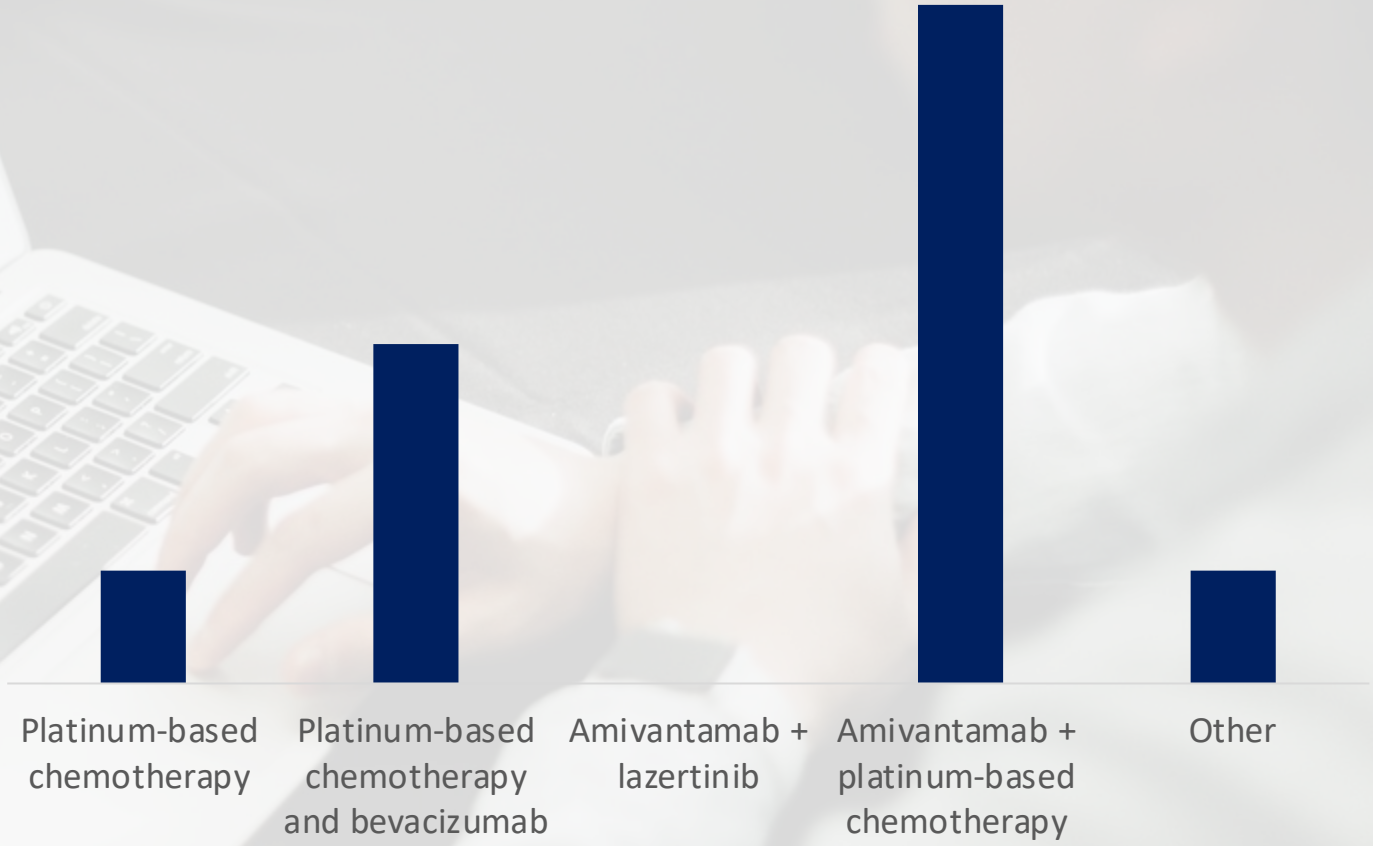
Polling Question

What is your choice of second line therapy?

1. Platinum-based chemotherapy
2. Platinum-based chemotherapy and bevacizumab
3. Amivantamab + lazertinib
4. Amivantamab + platinum-based chemotherapy
5. Other

ARS Results from HCP Participants

What is your choice of second line therapy?

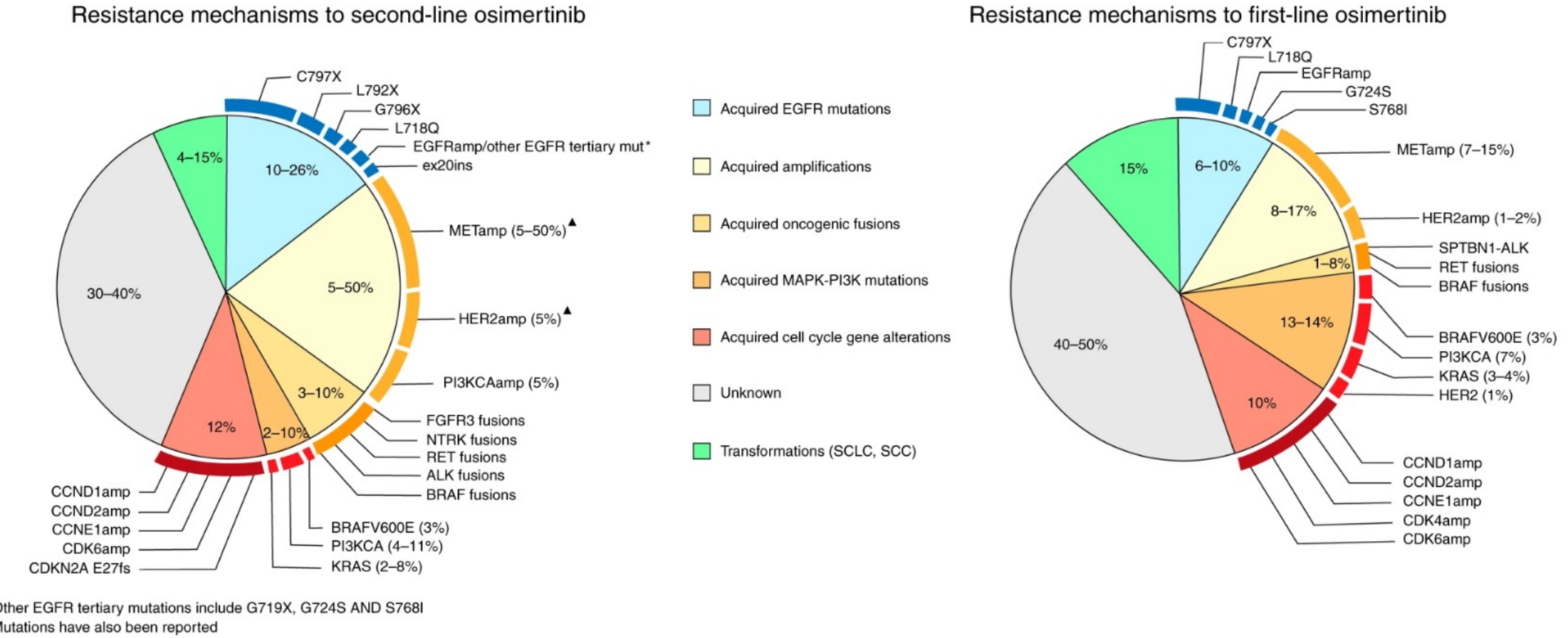


Discussion with HCP Participants

What is your choice of second line therapy?

- *In general, responses reflect the variation in available treatments*
- *Most have used amivantanab with chemotherapy at this point*
  - *Acknowledgement that amivantamab combo had better PFS than chemo alone.*
  - *Some use of platinum doublet + beva; but believe data is better for amivantamab with chemotherapy*
- *Transformations happen 15% of time; broad range can happen and does impact future options*

Resistance Mechanisms to Osimertinib

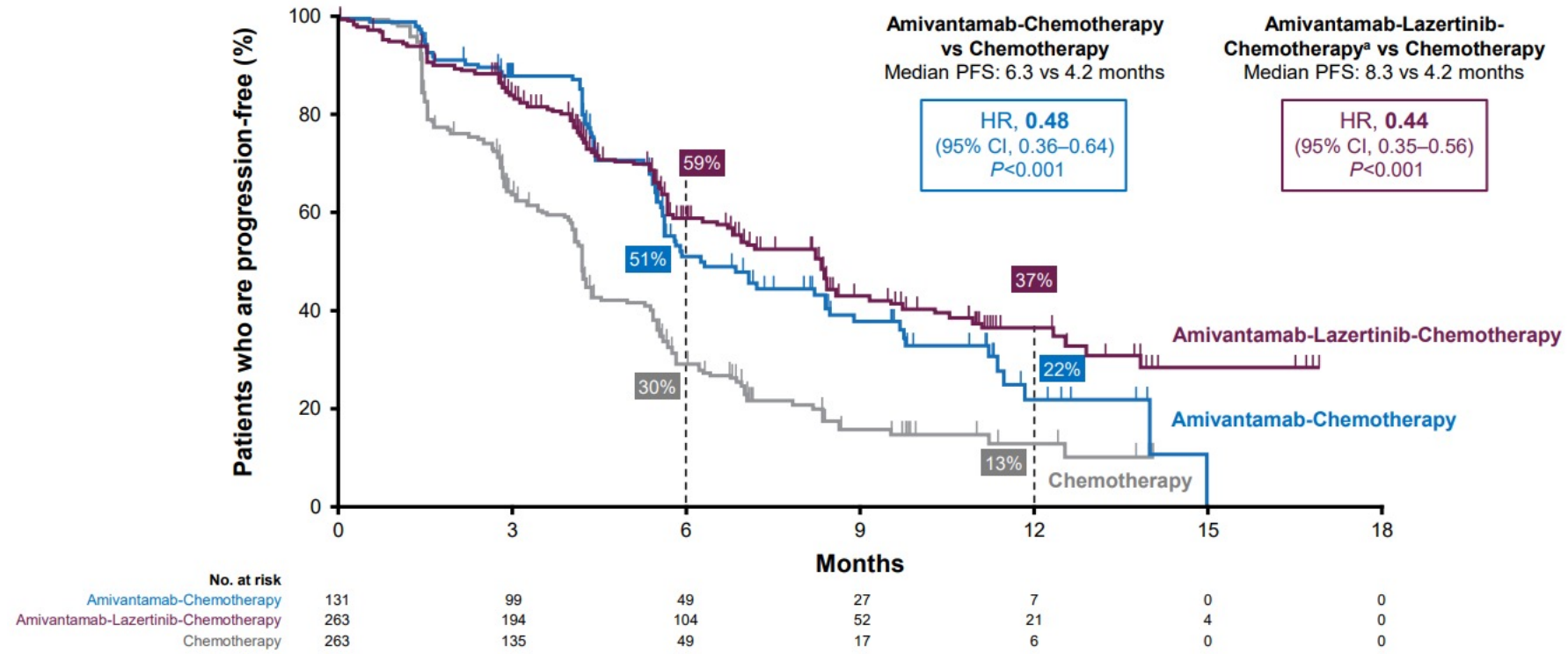


* Other EGFR tertiary mutations include G719X, G724S AND S768I
▲Mutations have also been reported

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).

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

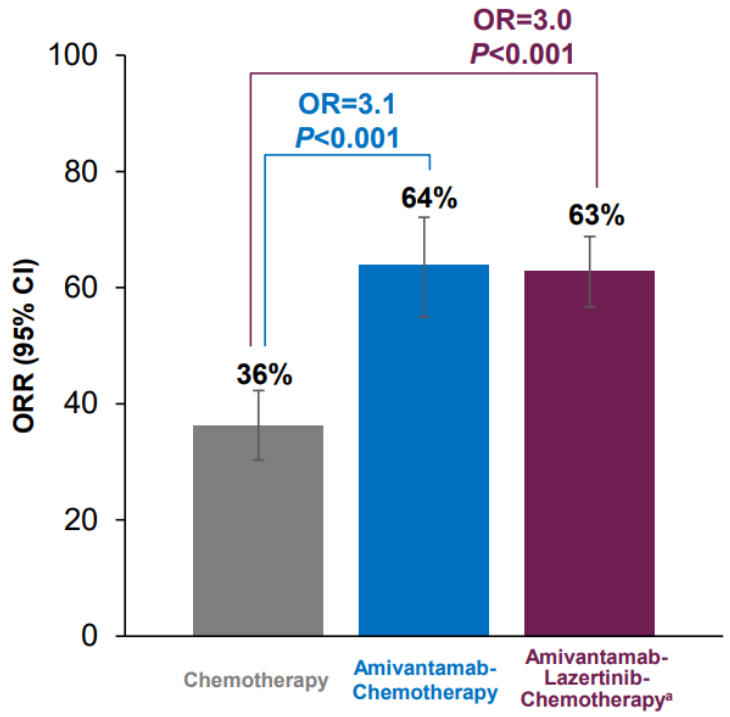
Primary Endpoint: Progression-free Survival by BICR



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



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?

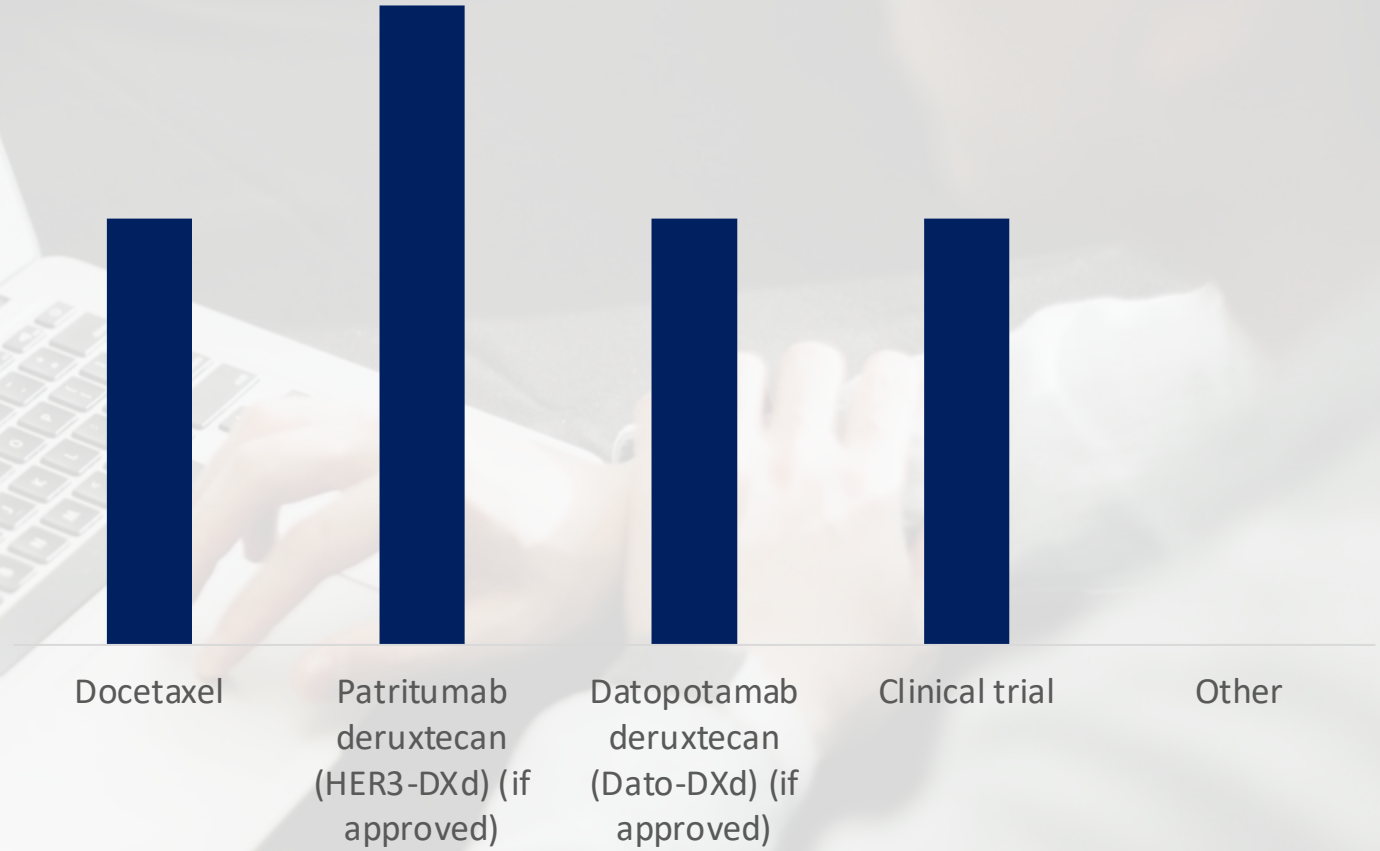
Polling Question

What is your choice of third line therapy?

1. Docetaxel
2. Patritumab deruxtecan (HER3-DXd) (*if approved*)
3. Datopotamab deruxtecan (Dato-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?

- ***Differing opinion, not surprising, given 3rd line setting***
- ***Antibody Drug Conjugates (ADCs), in general, are viewed as promising with a good therapeutic index***
  - ***"Pack a punch with less toxicity"***
- ***Most do not have a favorable impression of docetaxel but are unfamiliar to date with the other options***
- ***Clinical trial is considered a good 3L option when not familiar with the latest data as well as viewing docetaxel as "underwhelming and toxic"***

HERTHENA-Lung01: Phase II Study of Patritumab Deruxtecan (HER3-DXd) 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†)

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

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)

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.

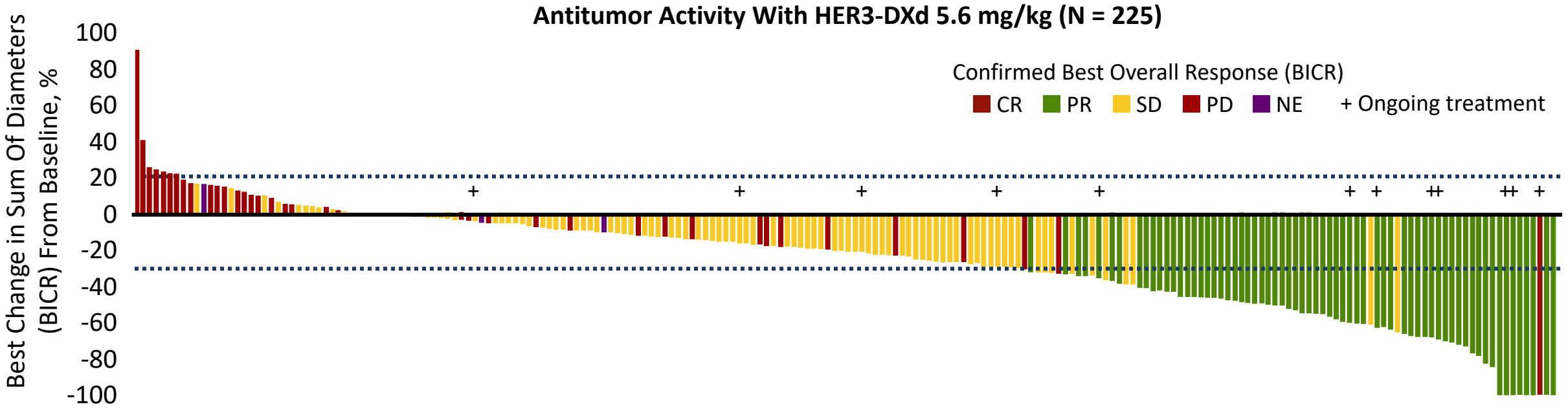
Yu. Future Oncol. 2023;19:1319.
Yu. WCLC 2023. Abstr OA05.03.
Yu. JCO. 2023; JCO2301476.

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



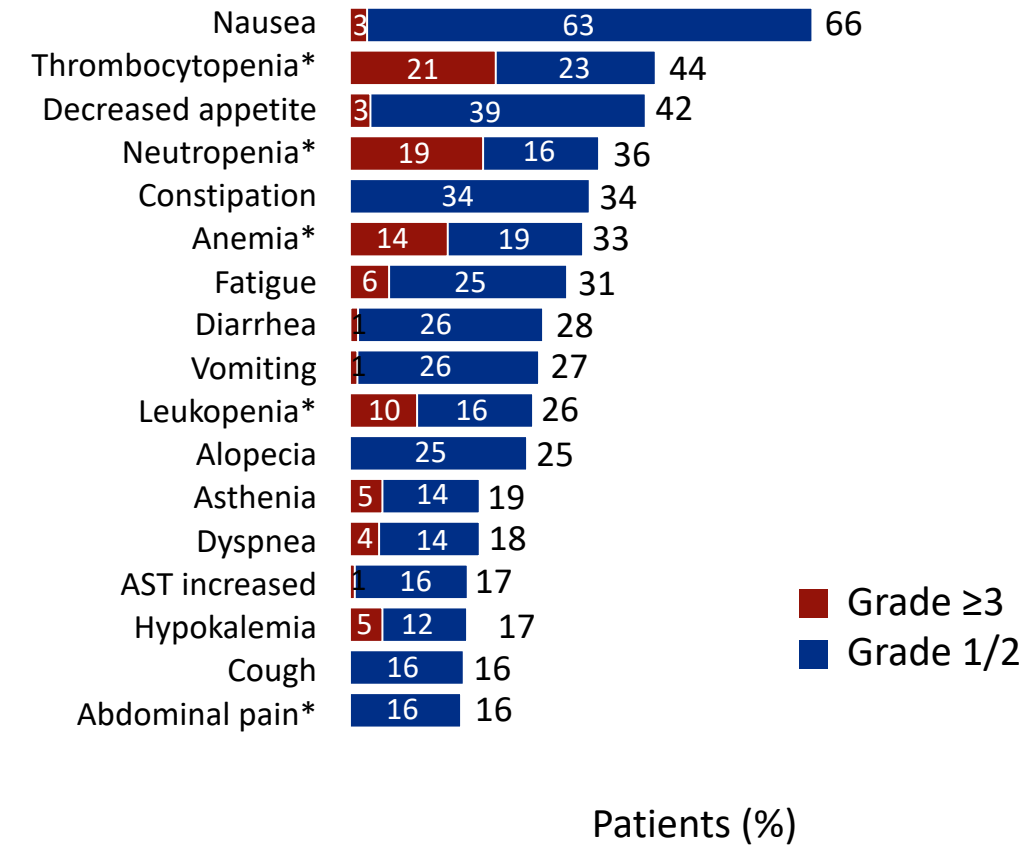
	Type of EGFR TKI Resistance Mechanism			
	EGFR Dependent Only (n = 34)	**EGFR Independent Only (n = 81)**	**Both EGFR Dependent and Independent (n = 32)**	**None Identified (n = 77)**
Confirmed ORR, % (95% CI)	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)

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.

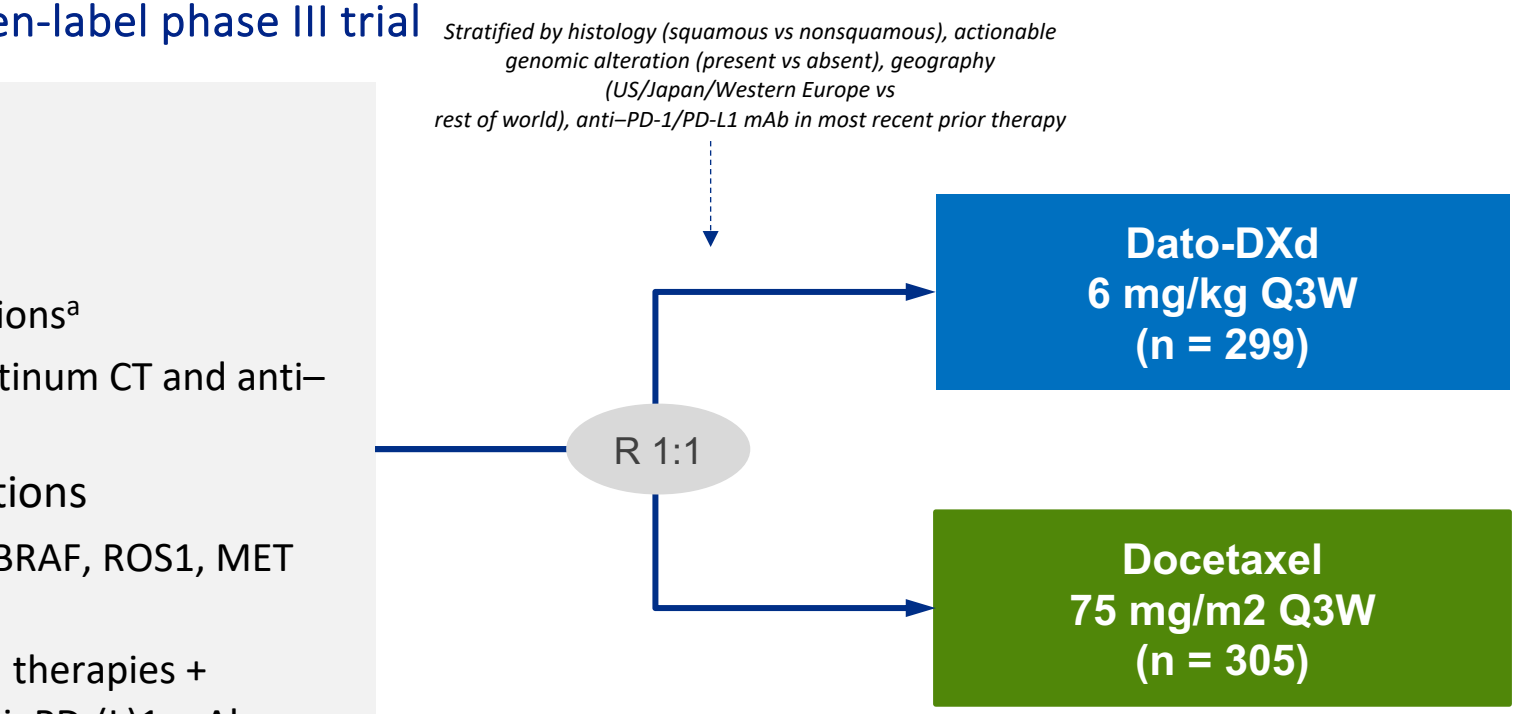
Yu. WCLC 2023. Abstr OA05.03. Yu. JCO. 2023;JCO2301476.

TROPION-Lung01: Does datopotamab deruxtecan (Dato-DXd) provide benefit for previously treated advanced/metastatic NSCLC?

Study Design: Global, randomized, open-label phase III trial

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS 0 or 1
- No prior docetaxel
  - Without actionable genomic alterations[a]
    - 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy
  - With actionable genomic alterations
    - Positive for EGFR, ALK, NTRK, BRAF, ROS1, MET exon 14 skipping, or RET
    - 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

(N = 604)

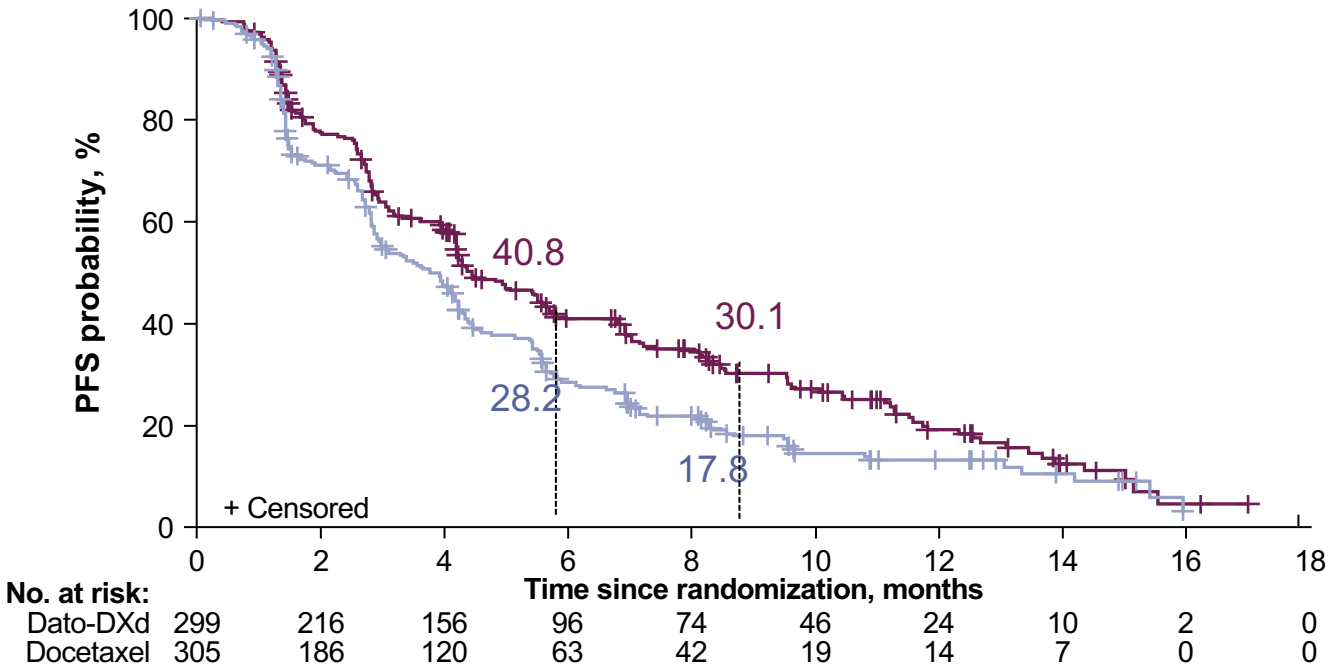


aPatients with KRAS mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. bSquamous vs non-squamous. cPresence vs absence. dUnited States/Japan/Western Europe vs rest of world.

Primary endpoints: PFS by BICR and OS

Secondary endpoints: ORR (BICR), DoR (BICR), safety

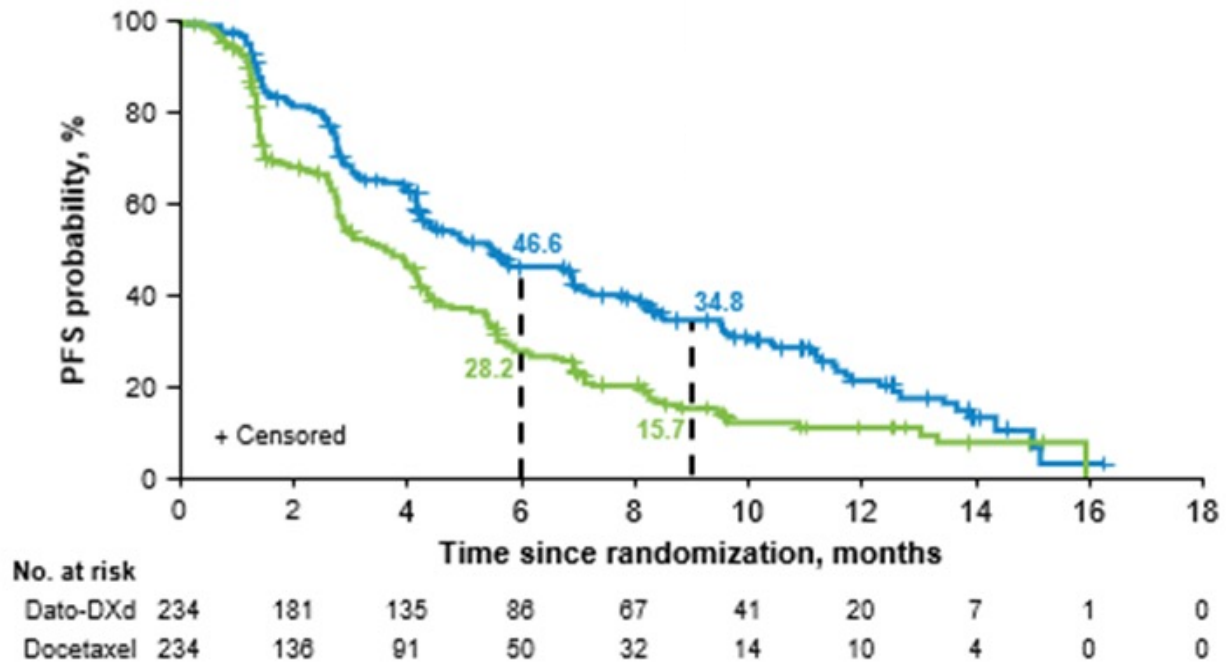
TROPION-Lung01 Primary Endpoint: ITT PFS by BICR



	Dato-DXd	Docetaxel
Median (95% CI), months	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
P-value	**0.004**	
ORR (95% CI), %	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

Dato-DXd met primary endpoint of PFS in the ITT population with a significant improvement vs docetaxel

TROPION-Lung01: Dato-DXd in Non–Squamous 2L+ mNSCLC



	Dato-DXd n=234	Docetaxel n=234
Median PFS (95% CI), months	**5.5** (4.3 - 6.9)	**3.6** (2.9 - 4.2)
HR	**0.63** (0.51 - 0.79)	
Interim medium OS (95% CI), months	**13.4** (12.1-16.4)	**11.4** (10.1-13.8)
HR	**0.79** (0.60-1.02)	
ORR, n (%)	**73 (31)**	**30 (13)**
CR	4 (2)	0
PR	69 (30)	30 (13)
DOR, (95% CI), mo	**7.7** (5.6-11.1)	**5.6** (5.4-6.0)

Note: PFS HR for non–squamous without actionable genomic alterations (AGAs): 0.71

Patritumab Deruxtecan

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.

Datopotamub Deruxtecan

February 19, 2024 *– Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) Biologics License Application (BLA) for datopotamab deruxtecan (Dato-DXd) has been accepted in the U.S. for the treatment of adult patients with locally advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC) who have received prior systemic therapy. Datopotamab deruxtecan is a specifically engineered TROP2 directed DXd antibody drug conjugate (ADC) being jointly developed by Daiichi Sankyo and AstraZeneca.*

The Prescription Drug User Fee Act (PDUFA) date, the U.S. Food and Drug Administration (FDA) action date for its regulatory decision, is December 20, 2024.

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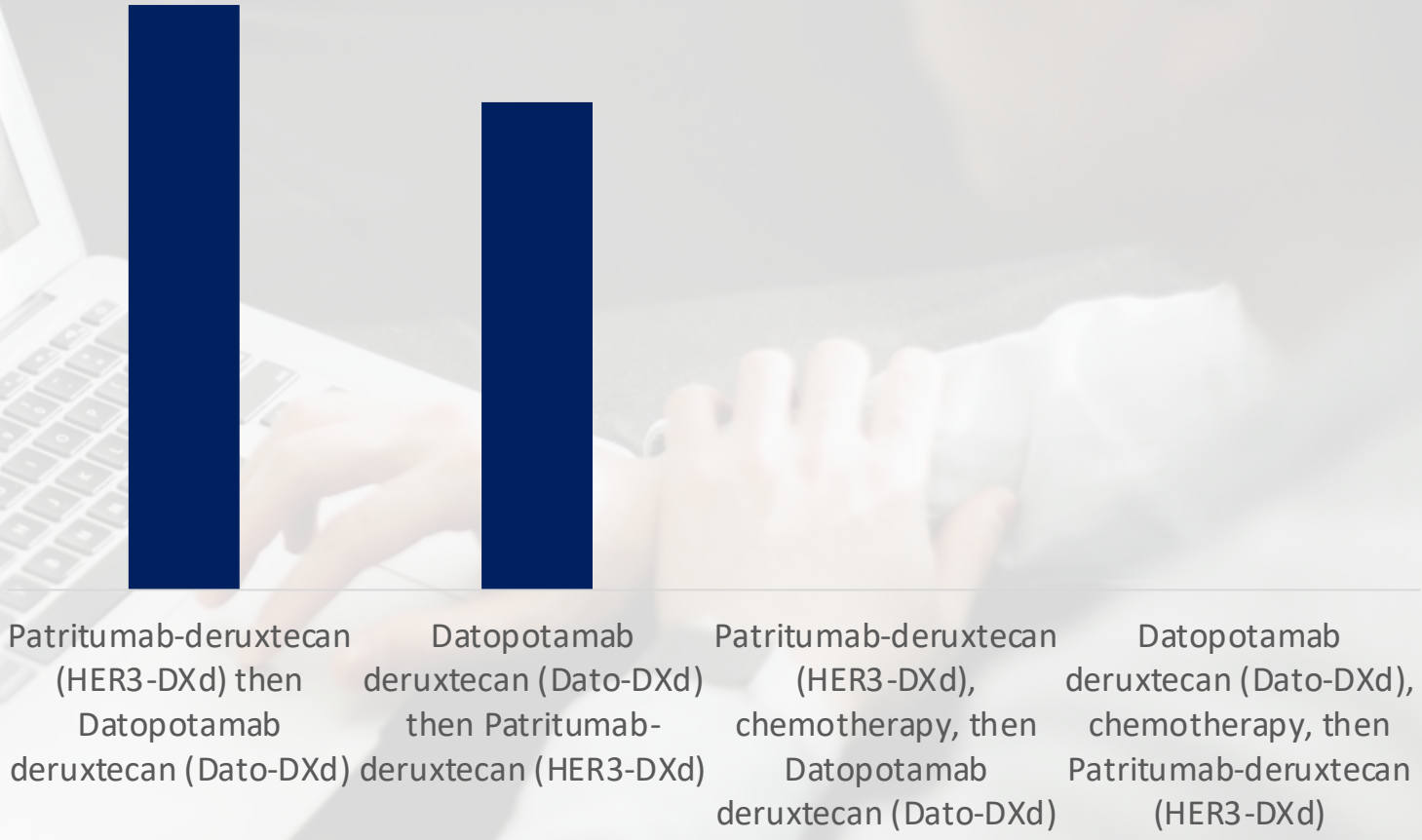
Polling Question

If approved, what would be your preferred order for sequencing ADCs?

1. Patritumab-deruxtecan (HER3-DXd) then Datopotamab deruxtecan (Dato-DXd)
2. Datopotamab deruxtecan (Dato-DXd) then Patritumab-deruxtecan (HER3-DXd)
3. Patritumab-deruxtecan (HER3-DXd), chemotherapy, then Datopotamab deruxtecan (Dato-DXd)
4. Datopotamab deruxtecan (Dato-DXd), chemotherapy, then Patritumab-deruxtecan (HER3-DXd)

ARS Results from HCP Participants

If approved, what would be your preferred order for sequencing ADCs?



Discussion with HCP Participants

If approved, what would be your preferred order for sequencing ADCs?

- ***Some preference for HER3-DXD prior to Dato-DXD based on a more favorable toxicity profile***
- ***Some preference for Dato-DXd prior to HER3-DXd based on the phase 3 clinical trial data versus phase 2 clinical trial data, respectively***
- ***Would be nice to see head-to-head of HER3-DXd and Dato-DXd***
- ***Familiarity based on ENHERTU; comfortable to manage toxicities***
- ***Overall preference for ADC(s) prior to docetaxel***
  - ***Potential use of an ADC in the 2L setting for non-driver mutation disease and in the 3L+ for driver-mutation disease***

KOL insights:

- ***For HER3-DXd: no testing required; suitable for use on progression EGFRm NSCLC; works across all resistance mechanisms; low discontinuation rate; low ILD incidence***
- ***For Dato-DXd: use in non-squamous patients***

Key Takeaways

Lung Cancer

Patient case: untreated metastatic disease

- *Osimertinib is the clear winner in the 1L setting*
- *New treatment landscape anticipated by the end of the year based on FDA approvals and NCCN Guideline updates*
- *Exciting to have alternative options to docetaxel*

Thank you!

Lee Schwartzberg, MD

Renown
Oncology/Hematology

Reno, Nevada

Sponsored by:

Daiichi-Sankyo