IASLC
2023 World Conference on Lung Cancer
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Therapies for advanced EGFR-mutated lung cancers

Collin Blakely MD, PhD
Associate Professor
UCSF

Best of IASLC-WCLC 2023
San Francisco

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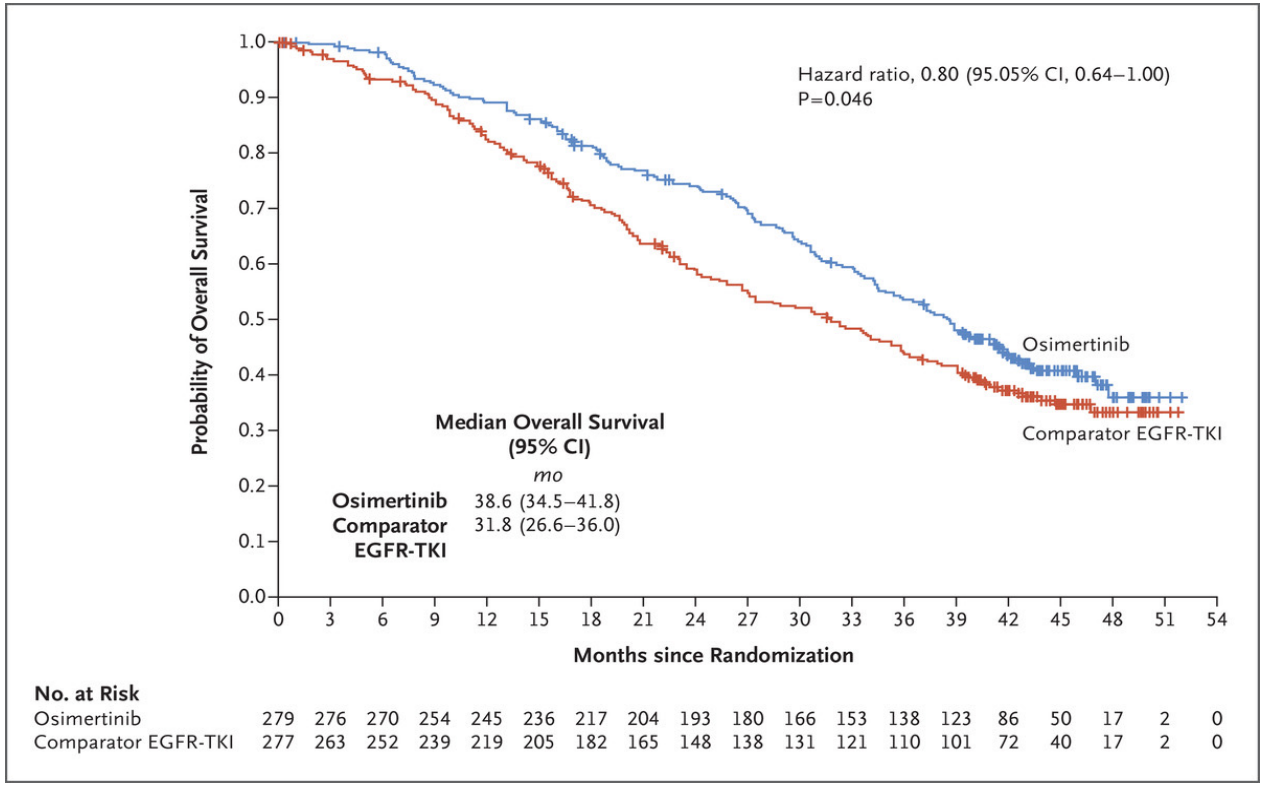
FLAURA trial established Osimertinib as the standard 1st line therapy for metastatic EGFR-mutated NSCLC



Resistance inevitably occurs

Median PFS 18.9 months

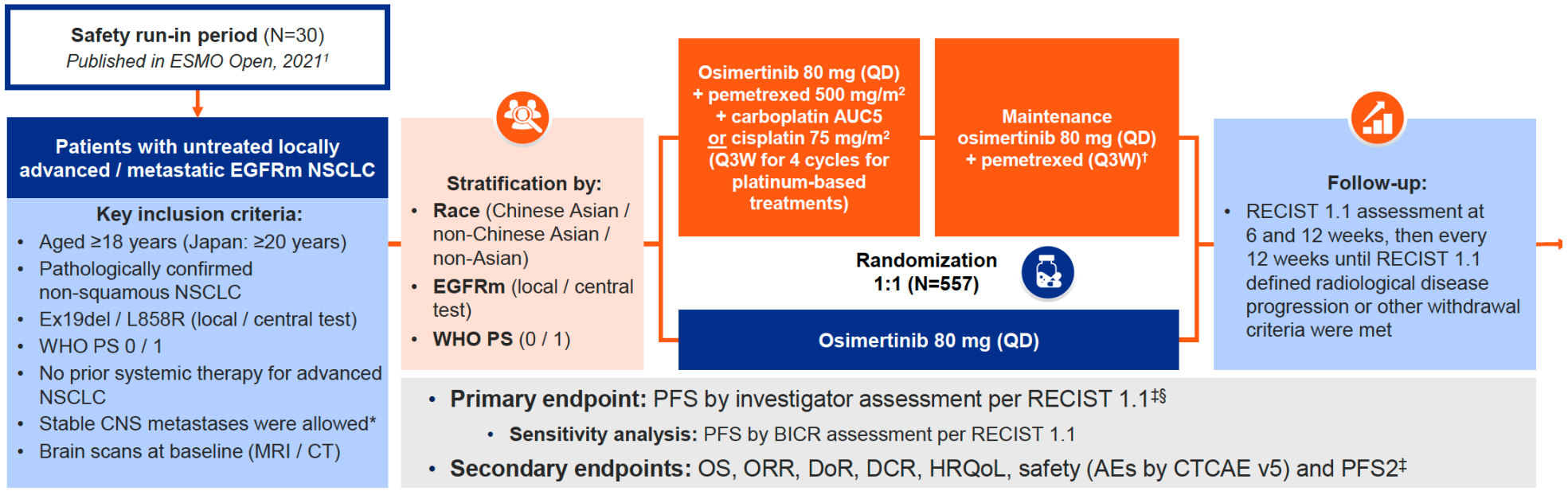
Median OS 38.6 months

Decreased PFS benefit observed in patients with CNS metastases at baseline and in patients with EGFR p.L858R mutated tumors

SS Ramalingam et al. N Engl J Med 2020;382:41-50

- **How can we improve PFS and OS for patients treated with 1st line osimertinib?**
- **Are there specific patient populations who would benefit from upfront combination therapy approaches?**
- **What are the best therapeutic options for treating osimertinib resistant EGFR-mutated lung cancers?**

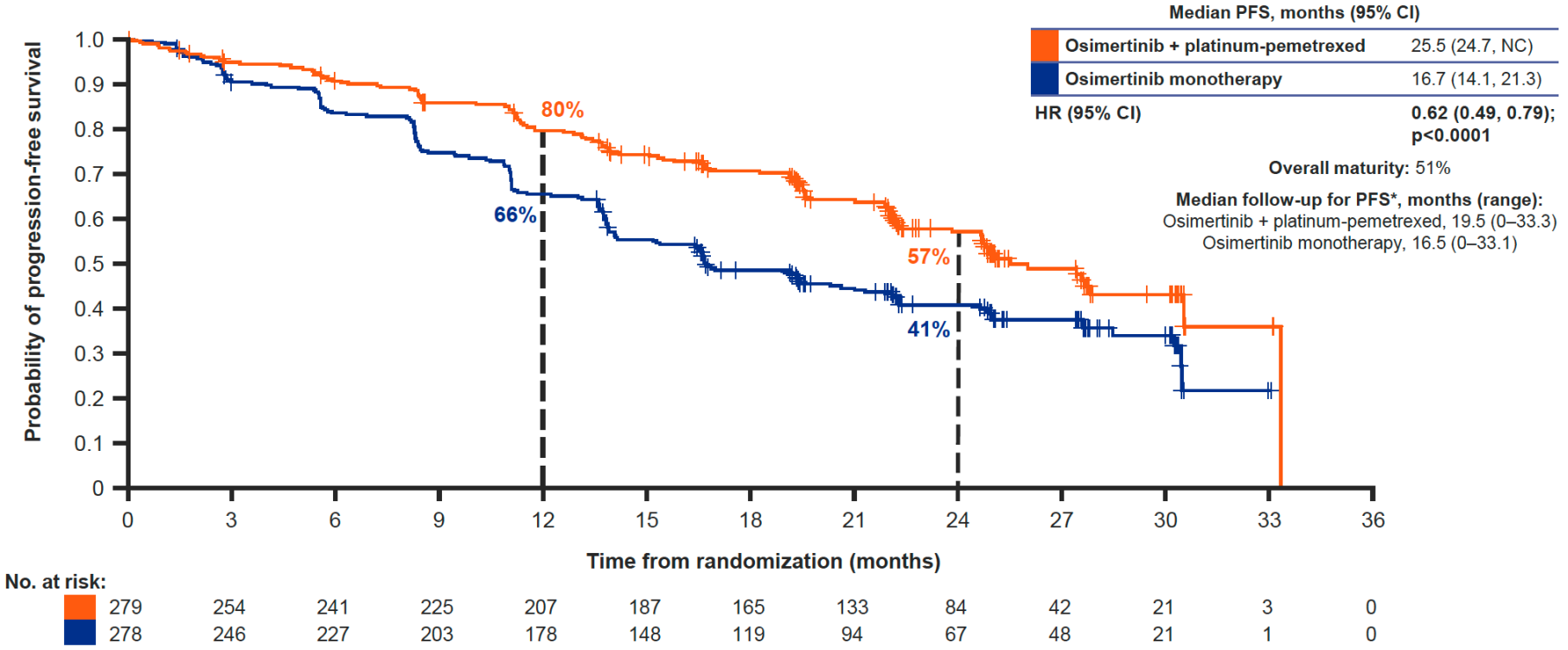
FLAURA2 Phase III study design



PL.03.13 Jänne et al.

Progression-free survival per investigator

- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



PL.03.13 Jänne et al.

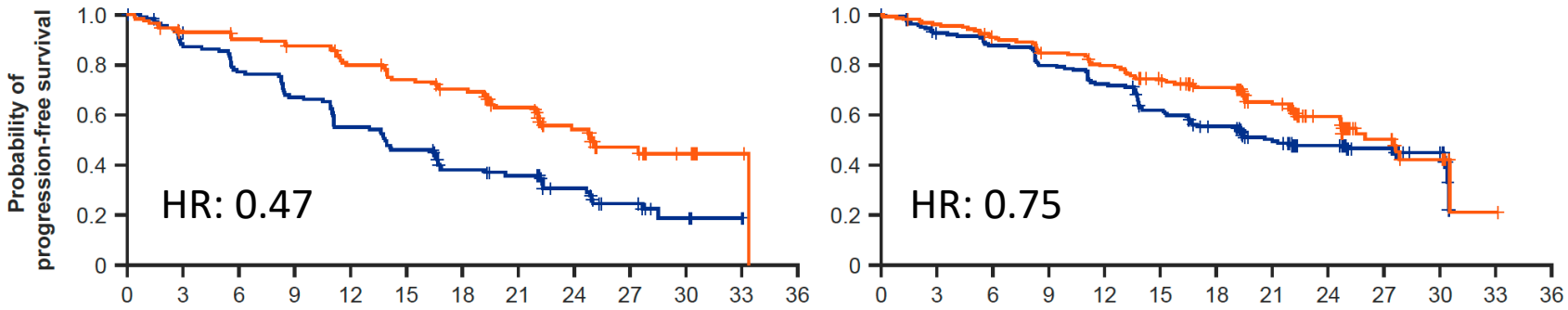
PFS per investigator in patients with / without CNS metastases at baseline*

With CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	24.9 (22.0, NC)
Osimertinib monotherapy	13.8 (11.0, 16.7)
HR (95% CI)	0.47 (0.33, 0.66)

Without CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	27.6 (24.7, NC)
Osimertinib monotherapy	21.0 (16.7, 30.5)
HR (95% CI)	0.75 (0.55, 1.03)



No. at risk:

Osimertinib + platinum-pemetrexed	116	101	98	93	84	77	70	58	34	19	8	2	0
Osimertinib monotherapy	110	95	84	73	60	50	37	32	21	13	5	1	0

Osimertinib + platinum-pemetrexed	163	153	143	132	123	110	95	75	50	23	13	1	0
Osimertinib monotherapy	168	151	143	130	118	98	82	62	46	35	16	0	0

PL.03.13 Jänne et al.

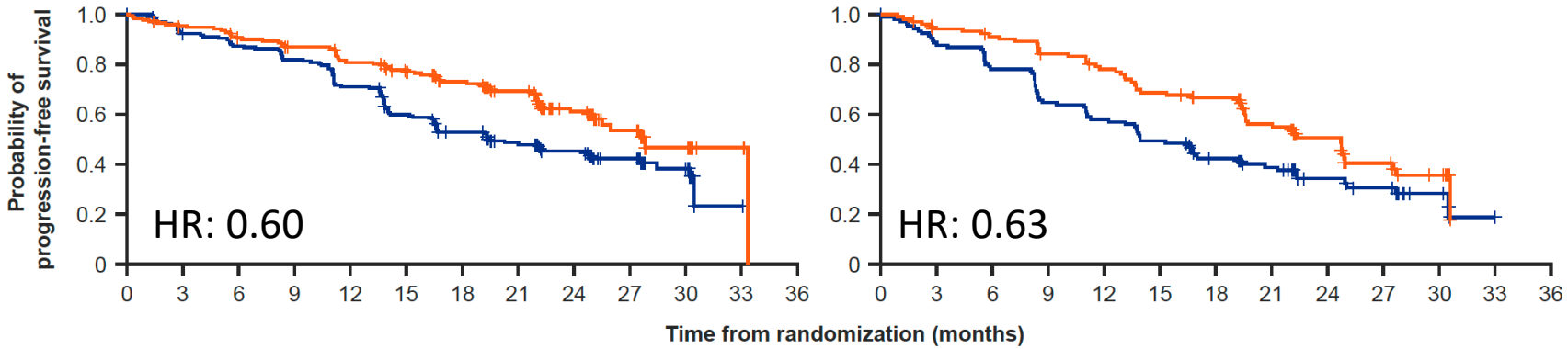
PFS per investigator by EGFR mutation type at baseline*

Ex19del

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	27.9 (25.1, NC)
Osimertinib monotherapy	19.4 (16.5, 27.6)
HR (95% CI)	0.60 (0.44, 0.83)

L858R

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	24.7 (19.5, 27.4)
Osimertinib monotherapy	13.9 (11.1, 19.4)
HR (95% CI)	0.63 (0.44, 0.90)



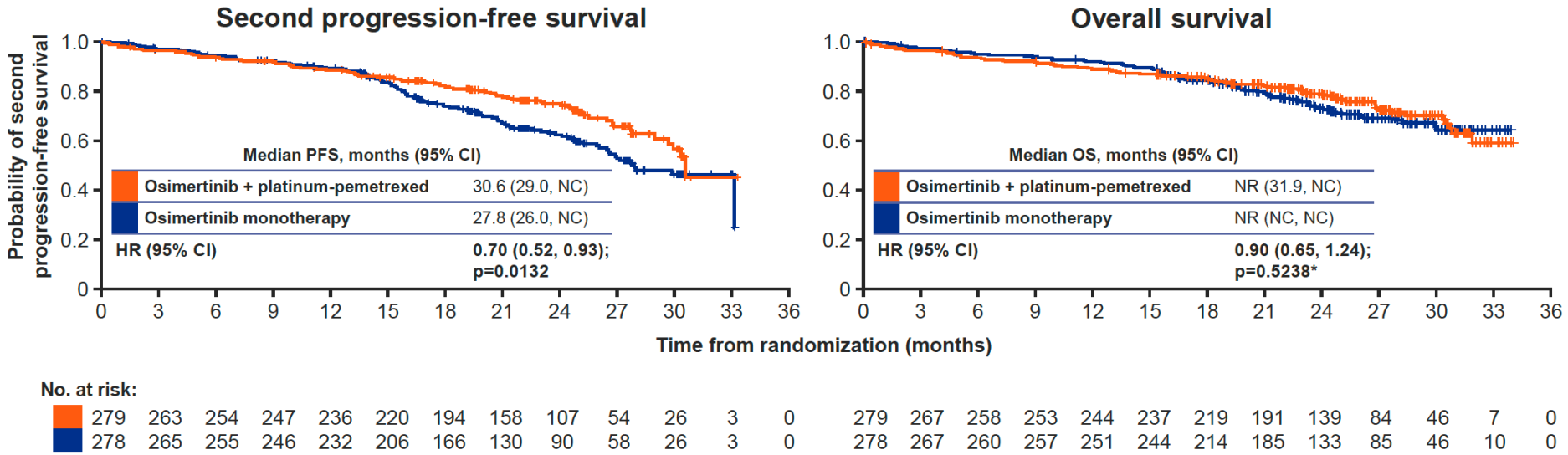
No. at risk:

Osimertinib + platinum-pemetrexed	172	159	150	142	131	120	103	86	53	23	9	3	0
Osimertinib monotherapy	169	152	144	135	117	96	79	63	48	33	16	1	0

Osimertinib + platinum-pemetrexed	106	95	91	83	76	67	62	47	31	19	12	0	0
Osimertinib monotherapy	107	92	82	68	61	52	40	31	19	15	5	0	0

PL.03.13 Jänne et al.

PFS2 and interim analysis of OS



No. at risk:

	279	263	254	247	236	220	194	158	107	54	26	3	0		279	267	258	253	244	237	219	191	139	84	46	7	0
	278	265	255	246	232	206	166	130	90	58	26	3	0		278	267	260	257	251	244	214	185	133	85	46	10	0

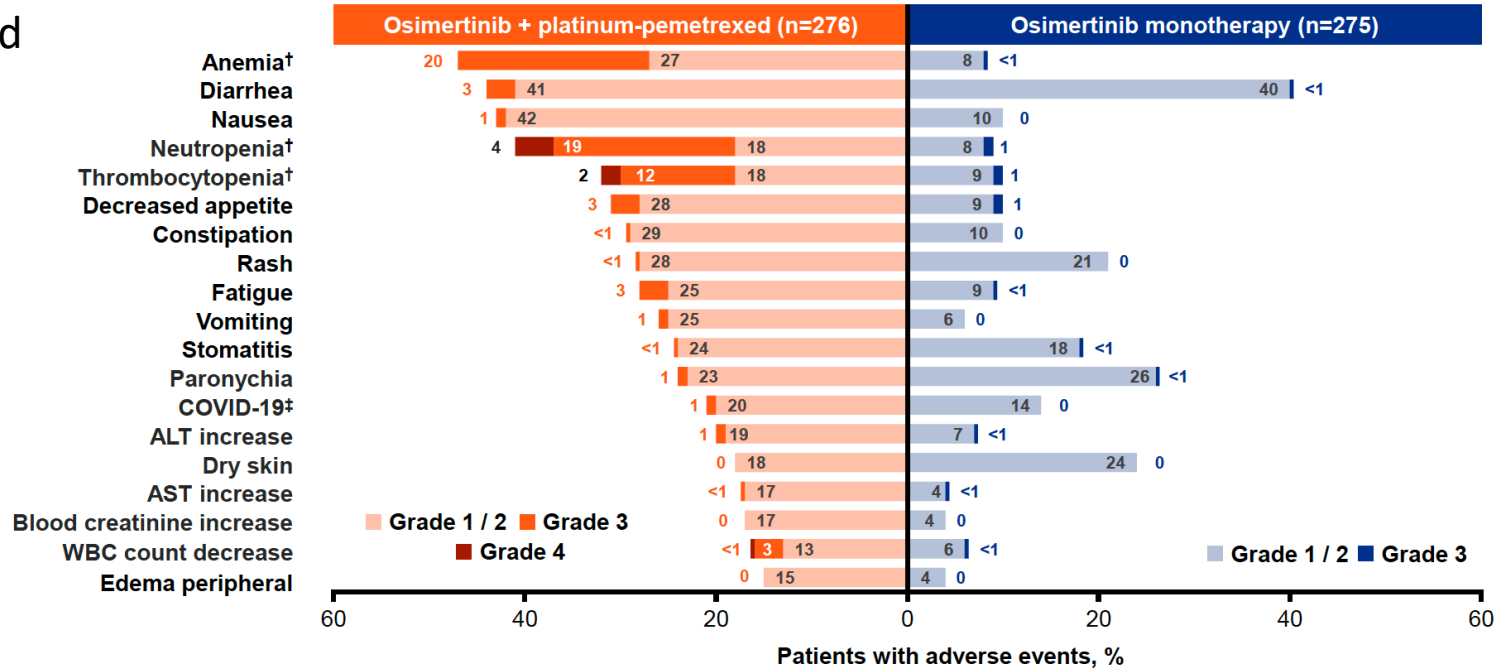
- PFS2 and OS were immature at this interim analysis (34% and 27% data maturity, respectively)
- At DCO, 57 / 123 patients (46%) in the osimertinib plus platinum-pemetrexed arm and 91 / 151 patients (60%) in the osimertinib monotherapy arm received any subsequent anti-cancer treatment†
  - In both arms, cytotoxic chemotherapy was the most common subsequent anti-cancer treatment (33% and 54% in the combination and monotherapy arms, respectively)†

PL.03.13 Jänne et al.

Common adverse events (≥15% of patients)*

Any treatment related AE ≥ grade 3: 53%

Any AE leading to treatment discontinuation: 48%



Any treatment related AE ≥ grade 3: 11%

Any AE leading to treatment discontinuation: 6%

- Of most common AEs (occurring in ≥15% of patients in either arm), all Grade 4 AEs in the osimertinib plus platinum-pemetrexed arm were hematological toxicities, known to be associated with chemotherapy; there were no common Grade 4 AEs in the monotherapy arm

PL.03.13 Jänne et al.

Summary

1. The addition of platinum + pemetrexed to 1st line osimertinib improves PFS from 16.7 to 25.5 months, but also significantly increases toxicity.

2. While data are immature, OS is not improved by the addition of platinum + pemetrexed to 1st line osimertinib.

3. Improvement in PFS is most pronounced in patients with CNS metastases or L858R mutations.

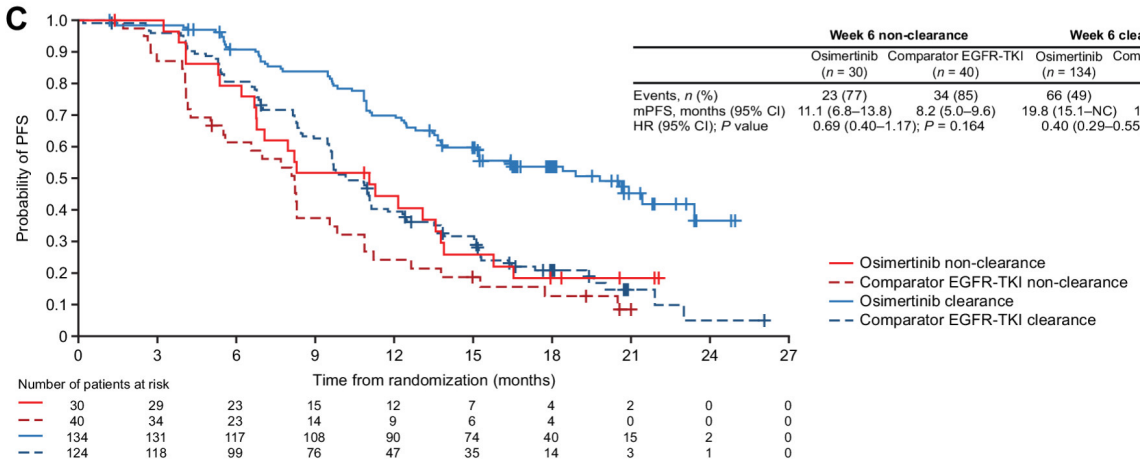
Conclusions

1. Osimertinib + platinum/pemetrexed **should not** be the new standard of care 1st line therapy for **all** advanced EGFRmt lung cancer patients.

2. Osimertinib + platinum/pemetrexed **should be** considered as first line therapy for patients with **CNS metastases** or with **EGFR L858R** mutations.

3. Other high-risk features (absence of ctDNA clearance, TP53 or RBM10 mutations) should be studied and considered for combination treatment.

Lack of ctDNA clearance correlates with decreased PFS



	Week 6 non-clearance		Week 6 clearance	
	Osimertinib (n = 30)	Comparator EGFR-TKI (n = 40)	Osimertinib (n = 134)	Comparator EGFR-TKI (n = 124)
Events, n (%)	23 (77)	34 (85)	66 (49)	99 (80)
mPFS, months (95% CI)	11.1 (6.8–13.8)	8.2 (5.0–9.6)	19.8 (15.1–NC)	10.2 (9.5–11.1)
HR (95% CI); P value	0.69 (0.40–1.17); P = 0.164		0.40 (0.29–0.55); P < 0.0001	

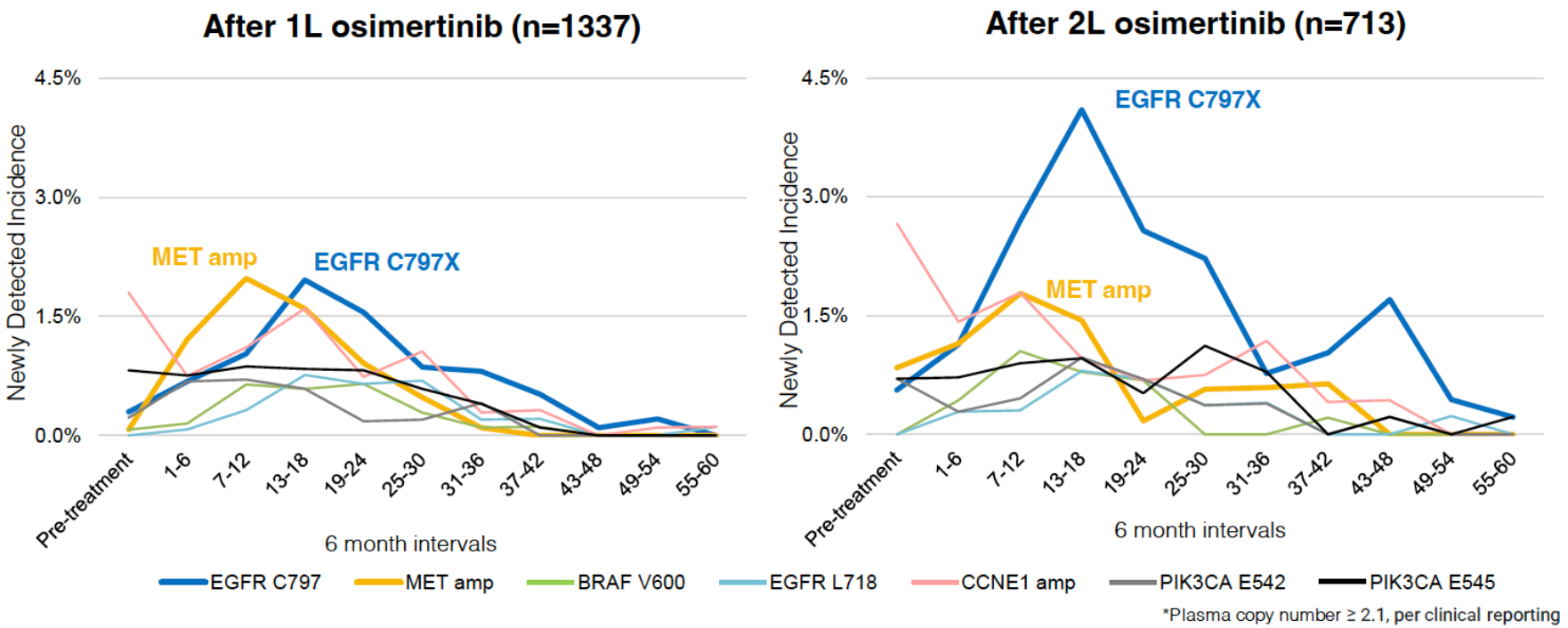
Clin Cancer Res. 2023;29(17):3340-3351. doi:10.1158/1078-0432.CCR-22-3146

Open at UCSF

A Phase 2 Randomized Study of Osimertinib Versus Osimertinib Plus Chemotherapy for Patients With Metastatic EGFR-Mutant Lung Cancers That Have **Detectable EGFR-Mutant cfDNA in Plasma After Initiation of Osimertinib**:
NCT: NCT04410796 (PI: Helena Yu)

MET amp is most common acquired resistance mechanism in 1st year of 1L osimertinib, while EGFR C797X is most common after the 1st year

6-month Incidence of Common Acquired Resistance Mutations after osimertinib



Ramalingam, IASLC 2022

INSIGHT 2: an Open-label, Two-arm Phase II Study[1]

- *MET*amp is a common driver of secondary resistance in patients with *EGFR*m NSCLC following treatment with 1L osimertinib,[2,3] that may be responsive to MET inhibition
- TBx FISH is the gold standard for *MET*amp detection, with rates of ~50% compared with ~15% by LBx NGS testing[4,5]

Key inclusion criteria

- Locally advanced/metastatic *EGFR*m NSCLC
- Acquired resistance to 1L osimertinib
- ***MET*amp** by:
  - **TBx FISH** (GCN ≥5 and/or *MET*:*CEP7* ≥2) and/or **LBx NGS** (≥2.3 Archer®)
- ECOG PS of 0 or 1

Tepotinib 500 mg QD
+
Osimertinib 80 mg QD

Tepotinib monotherapy
500 mg QD*

Endpoints

Primary endpoint
- **Objective response by IRC** in patients with **TBx FISH** *MET*amp

Selected secondary endpoints
- Objective response in patients with LBx NGS *MET*amp
- DOR
- PFS
- OS
- HRQoL
- Safety
- Biomarkers

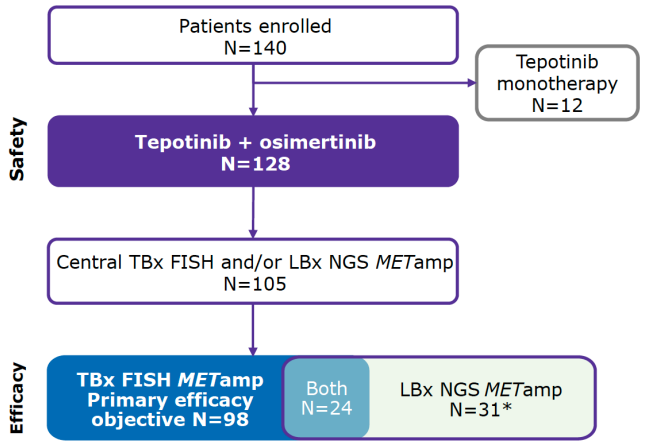
Selected tertiary endpoints
- RANO-BM

- The trial aims for an ORR in the range of ~50% with a lower limit of the corresponding exact 2-sided 95% CI (according to Clopper–Pearson) to exceed an ORR of 35%
- Subgroup analysis of Asian patients† was preplanned
- Data cut-off: March 28, 2023
- Efficacy population has ≥9 months follow-up

OA21.05, Kim et al.

INSIGHT 2 Primary Analysis: Objective Response by IRC

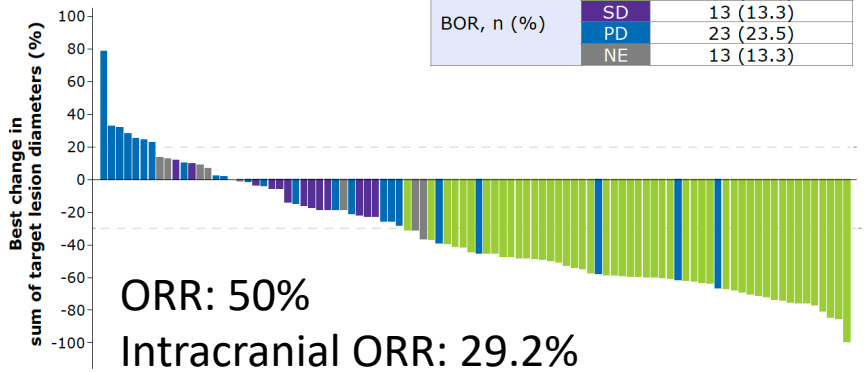
- Of 481 patients prescreened, METamp detected by TBx FISH in 35.1% and by LBx NGS in 10.8%



TRAEs of any grade in >10% of all patients	Tepotinib + osimertinib (N=128)	
	Any grade n (%)	Grade ≥3 n (%)
Any	**113 (88.3)**	**44 (34.4)**
Diarrhea	63 (49.2)	1 (0.8)
Peripheral edema	52 (40.6)	6 (4.7)
Paronychia	29 (22.7)	1 (0.8)
Nausea	27 (21.1)	3 (2.3)
Decreased appetite	26 (20.3)	5 (3.9)
Hypoalbuminemia	23 (18.0)	1 (0.8)
AST increased	16 (12.5)	0
Anemia	15 (11.7)	2 (1.6)
Vomiting	15 (11.7)	1 (0.8)
Blood creatinine increased	15 (11.7)	0
Lipase increased	14 (10.9)	3 (2.3)
ALT increased	14 (10.9)	2 (1.6)
Rash	14 (10.9)	0 (0.0)

- **The INSIGHT 2 primary analysis showed an ORR of 50% in patients with *EGFR*m NSCLC who have progressed on 1L osimertinib and had *MET*amp (central TBx FISH)**

Tumor shrinkage (n=98*)



ORR, % (95% CI)		50.0 (39.7, 60.3)
BOR, n (%)	PR	49 (50.0)
	SD	13 (13.3)
	PD	23 (23.5)
	NE	13 (13.3)

ORR: 50%
Intracranial ORR: 29.2%

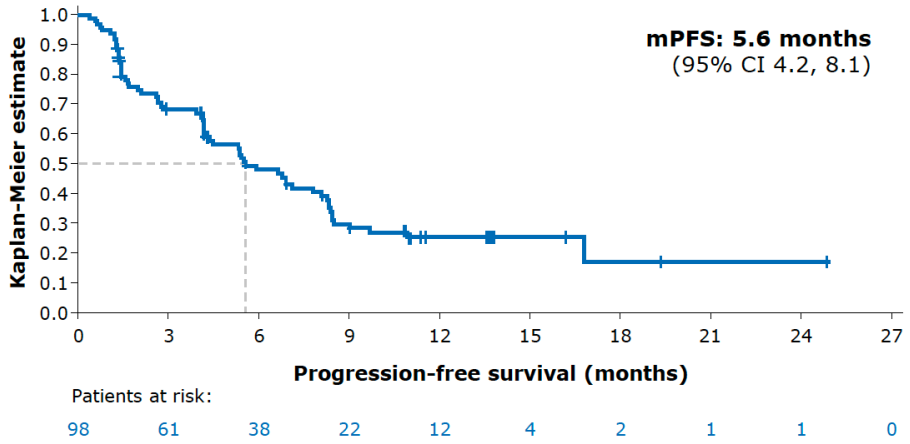
- Patients in the monotherapy arm (n=12) showed an ORR of 8.3% (95% CI 0.2, 38.5), which has been reported previously[1]

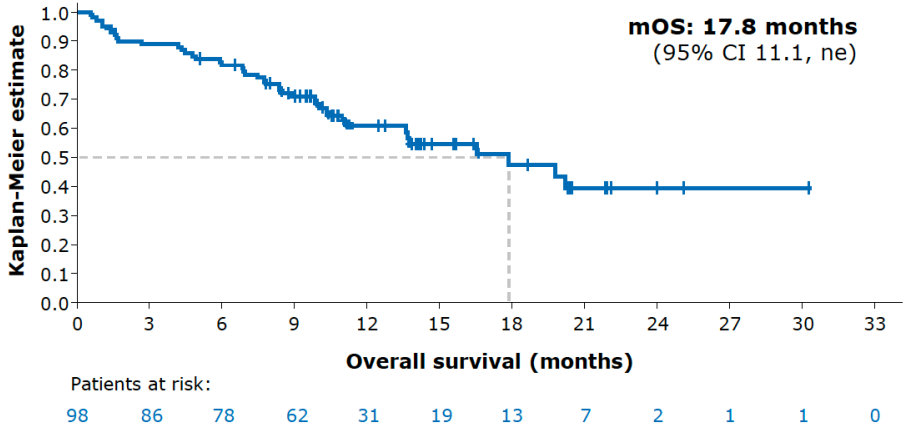
*Four patients were excluded due to baseline/post-baseline measurement not being available.
†Only patients with a response were included in Kaplan-Meier analyses.
Abbreviations defined on last slide.
1. Mazieres J, et al. *Ann Oncol.* 2022;33:S808–S869.

OA21.05, Kim et al.

INSIGHT 2 Secondary Objectives: PFS, OS, and LBx NGS Efficacy

- PFS and OS were clinically meaningful in patients with *EGFR*m NSCLC who have progressed on 1L osimertinib and had *MET*amp (central TBx FISH)





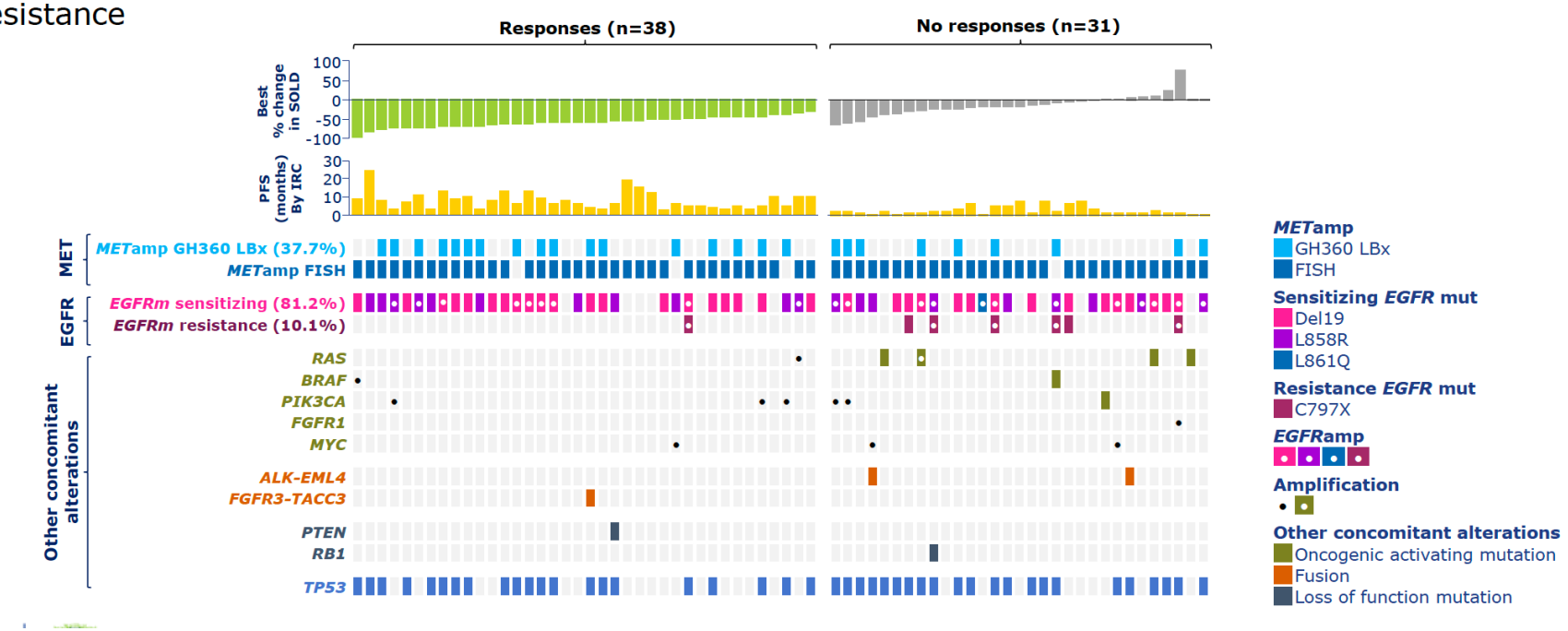
In patients with LBx NGS *MET*amp (n=31)

- ORR: 54.8% (95% CI 36.0, 72.7)
- mDOR: 5.7 months (95% CI 2.9, 15.4)
- mPFS: 5.5 months (95% CI 2.7, 7.2)
- mOS: 13.7 months (95% CI 9.6, ne)

OA21.05, Kim et al.

Baseline Biomarker Profiles

- Baseline biomarker profiles by NGS Guardant360® LBx were available for 69 patients
- Better outcomes were reported in patients without other concomitant biomarkers for osimertinib resistance



OA21.05, Kim et al.

Summary

1. 50% ORR and PFS of 5.6 months with Tepotinib + Osimertinib in patients with MET AMP (FISH) resistance.

2. Toxicity profile appears to be manageable.

3. Patients with MET AMP detected by liquid biopsy respond similarly, but rate of detection is much lower.

4. Detection of other concurrent resistance mechanism correlates with decreased response.

Conclusions

1. Tepotinib + Osimertinib is a reasonable option in patients with MET AMP as only detectable resistance alteration.

2. FISH is better than LBx at detecting MET AMP and should be considered in all patients with available tissue at Osimertinib resistance.

CHRYSALIS-2: Amivantamab, Lazertinib + Platinum Chemotherapy in Post-TKI Advanced EGFR mutated NSCLC

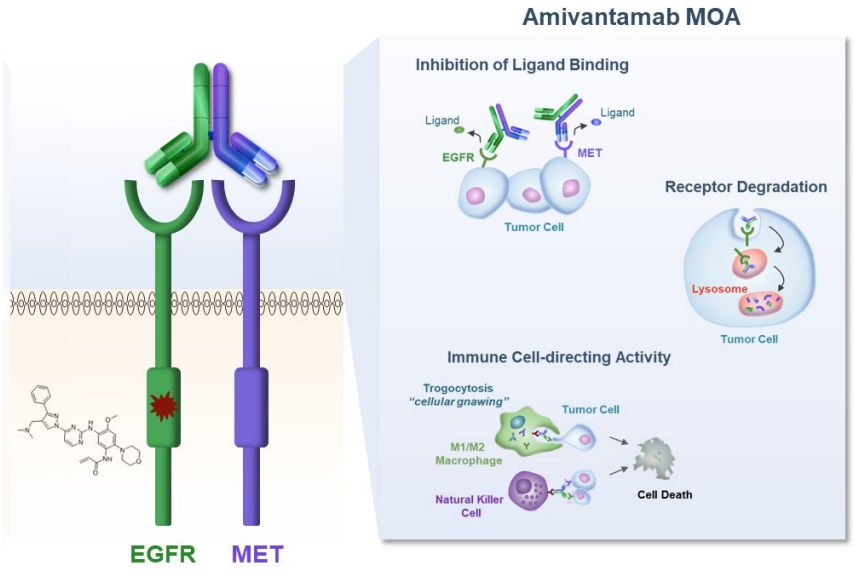
CHRYSALIS-2 (NCT04077463)

Eligibility
EGFR-mutated, advanced NSCLC post-TKI (max of 3 prior lines)

Dosing (21-day cycle)	
Lazertinib	240 mg daily
Amivantamab	1400/1750[b] mg on C1 D1/D2, C1D8, C1D15, C2D1; 1750/2100[b] mg C3+ Q3W
Chemotherapy	Carboplatin (AUC5; stopped after 4 cycles)
	Pemetrexed (500 mg/m^2) until disease progression

Endpoints

- Adverse events (primary)
- Objective response rate
- Duration of response
- Clinical benefit rate[c]
- Progression-free survival
- Overall survival

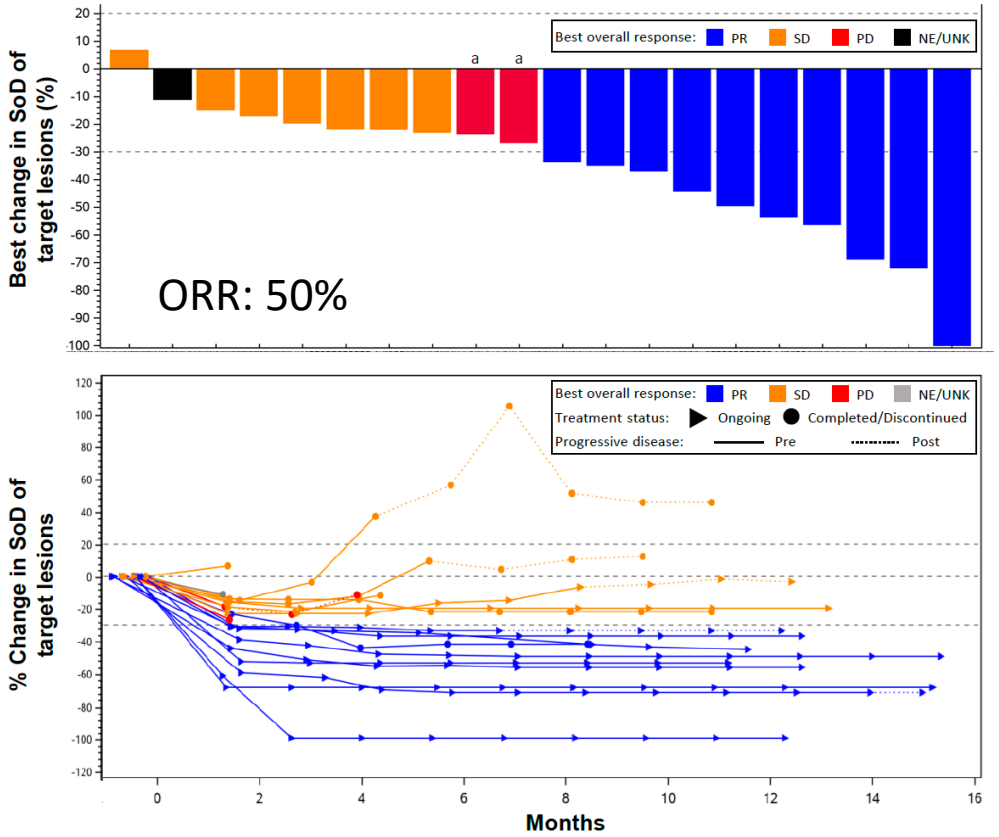


MA13.06, Lee et al.

Safety Profile

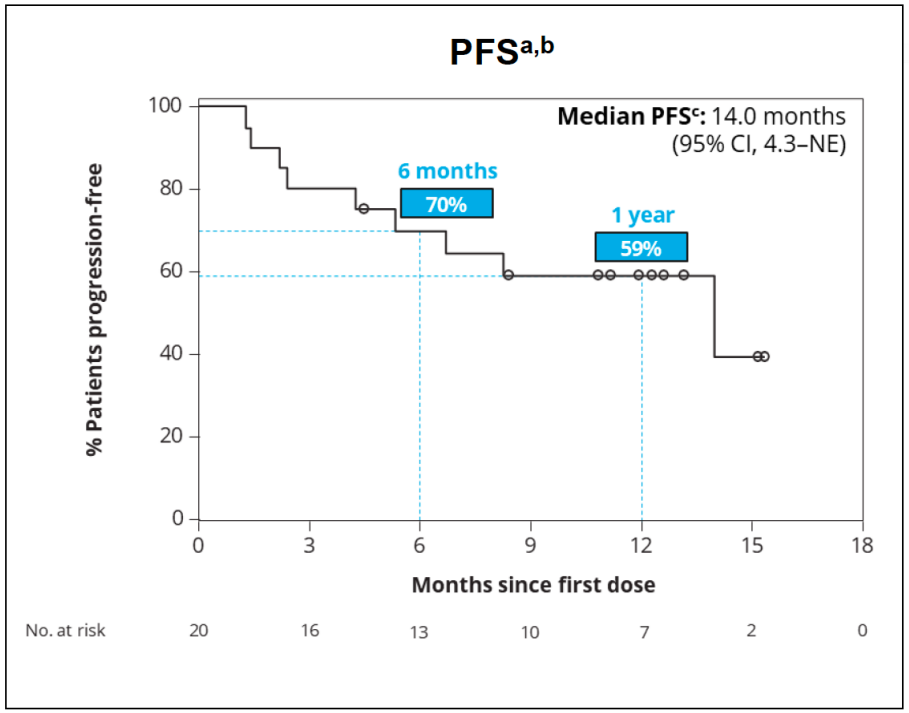
AEs (≥20%) by preferred term, n (%)	Total[a]	Grade ≥3
Associated with EGFR inhibition		
Rash	15 (75)	1 (5)
Paronychia	12 (60)	0
Stomatitis	12 (60)	0
Dermatitis acneiform	8 (40)	2 (10)
Diarrhea	6 (30)	1 (5)
Associated with MET inhibition		
Hypoalbuminemia	8 (40)	2 (10)
Other		
Neutropenia	18 (90)	14 (70)
IRR	13 (65)	0
Fatigue	10 (50)	5 (25)
Nausea	10 (50)	0
COVID-19	8 (40)	0
Thrombocytopenia	8 (40)	5 (25)
Constipation	7 (35)	0
Decreased appetite	7 (35)	1 (5)
Leukopenia	7 (35)	4 (20)
Alanine aminotransferase increased	6 (30)	0
Anemia	6 (30)	2 (10)
Pulmonary embolism	6 (30)	1 (5)
Aspartate aminotransferase increased	5 (25)	0
Back pain	5 (25)	0
Epistaxis	5 (25)	0
Hemorrhoids	5 (25)	0
Peripheral sensory neuropathy	5 (25)	0

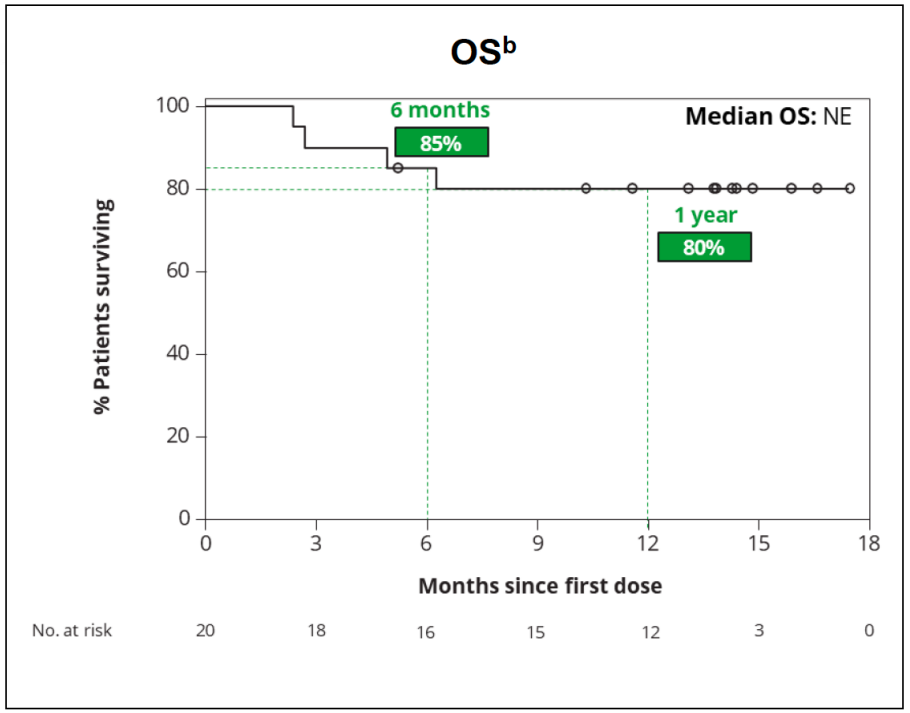
ORR and Durability



MA13.06, Lee et al.

PFS and OS





MA13.06, Lee et al.

Summary

1. Phase II trial (n = 20) shows 50% ORR and mPFS or 14 months with amivantamab + lazertinib + carbo/pemetrexed after progression on EGFR TKI.

2. Grade 3 neutropenia and thrombocytopenia are common.

3. Awaiting results of larger randomized MARIPOSA-2 Trial.

Conclusions

1. Activity of amivantamab + lazertinib + carbo/pemetrexed at TKI resistance appears promising, but trial is too small to make recommendations.

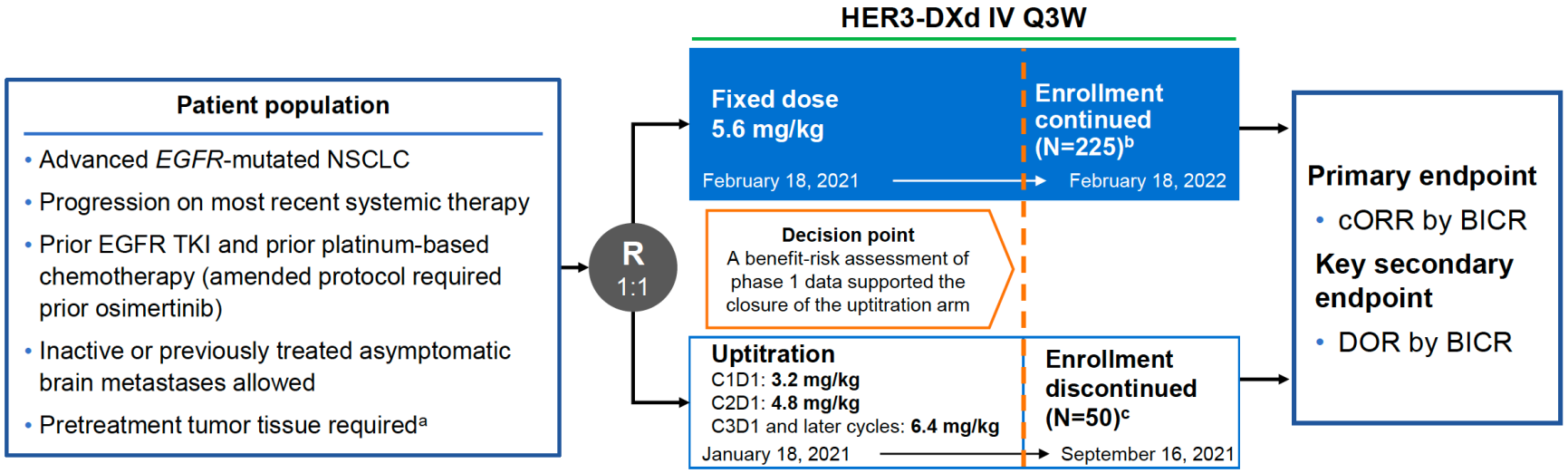
2. Wait for MARIPOSA-2 results before considering this as a treatment option.

3. Toxicity is a significant concern (rash, cytopenias).

4. Need biomarker testing to determine who is most likely to benefit.

Patritumab Deruxtecan
HERTHENA-Lung01

HERTHENA-Lung01 Study Design[1]



Primary data cutoff, 21 Nov 2022[d]
Snapshot data cutoff, 18 May 2023 (additional 6 months follow-up)
Data are presented for the 5.6-mg/kg fixed-dose arm

- Efficacy from snapshot data cutoff—median study follow-up, 18.9 (range, 14.9-27.5) months
- Safety from primary data cutoff—median treatment duration, 5.5 (range, 0.7-18.2) months

BICR, blinded independent central review; C, cycle; cORR, confirmed objective response rate (complete or partial response confirmed ≥4 weeks after initial response [RECIST version 1.1]); D, day; DOR, duration of response; HER, human epidermal growth factor receptor; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.
[a] Inclusion not based on detection of HER3 expression. [b] 226 patients were enrolled; 225 received ≥1 dose. [c] 51 patients were enrolled; 50 received ≥1 dose. [d] Data cutoff for the primary analysis occurred when all enrolled patients had either ≥9 months of follow-up or had discontinued from the study earlier.
1. Yu HA, et al. *Future Oncol*. 2023;19:1319-1329.

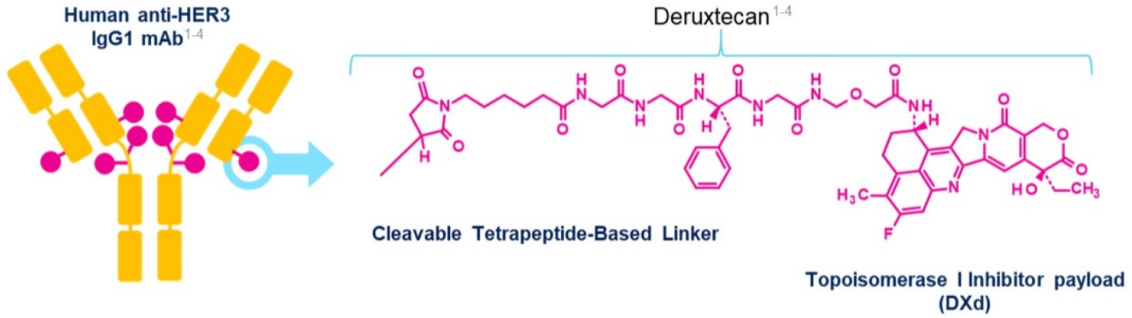
OA05.03, Yu et at.

Patritumab Deruxtecan (HER3-DXd)—Targeting HER3 May Address Multiple EGFR TKI Resistance Mechanisms

- HER3-DXd is an ADC with 3 components:[1-6]
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to:
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker
- HER3-DXd is in clinical evaluation for NSCLC, metastatic breast cancer, and colorectal cancer

HER3 is expressed in 83% of NSCLC tumors[7,a]

HER3 alterations are not known to be a mechanism of resistance to EGFR TKI in *EGFR*m NSCLC



[a] HER3 overexpression is associated with metastatic progression and decreased relapse-free survival in patients with NSCLC.

1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046. 7. Scharpenseel H et al. *Sci Rep* 2019;9(1):7406.

Overall Response

Confirmed responses and survival		Prior EGFR TKI (any) and PBC (N=225)	Subset with prior 3G EGFR TKI and PBC (n=209)
cORR (95% CI), %		**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)

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

Intracranial Response

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)
DCR (95% CI), %	76.7 (57.7-90.1)
DOR, median (95% CI), mo	8.4 (5.8-9.2)

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

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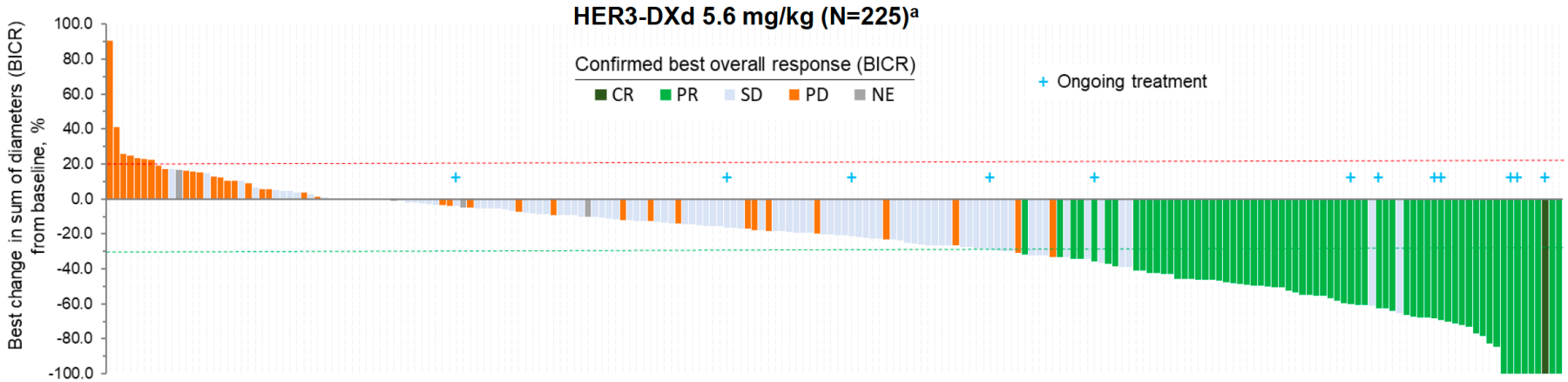
Patritumab Deruxtecan
HERTHENA-Lung01

Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance



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

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

BICR, blinded independent central review; CR, complete response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] 210 patients had evaluable target lesion measurements at both baseline and post baseline and are included.

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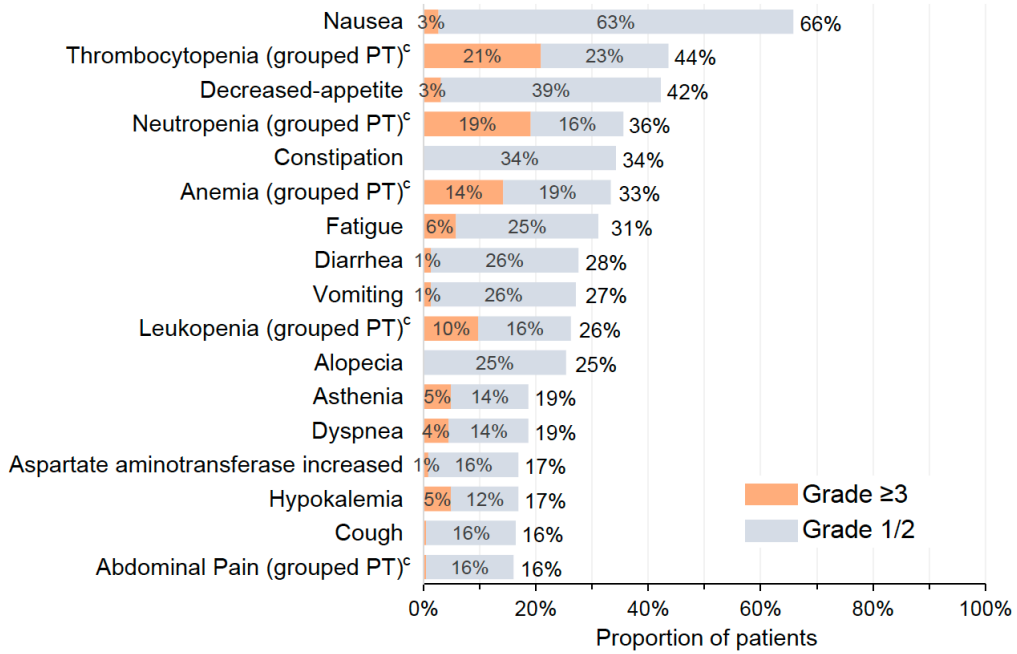
HERTHENA-Lung01

The Safety Profile of HER3-DXd Was Manageable and Tolerable

Safety summary	HER3-DXd 5.6 mg/kg (N=225)
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation[a]	16 (7.1)
Associated with treatment dose reduction	48 (21.3)
Associated with treatment dose interruption	91 (40.4)
Grade ≥3 TEAE, n (%)	146 (64.9)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[b]	4 (1.8)
Grade ≥3	102 (45.3)
Serious TEAE	34 (15.1)
Adjudicated interstitial lung disease, n (%) [All were adjudicated as treatment-related]	12 (5.3)
Grade 1	1 (0.4)
Grade 2	8 (3.6)
Grade 3	2 (0.9)
Grade 4	0
Grade 5	1 (0.4)

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

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



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

OA05.03, Yu et at.

Summary

1. HER3-DXd demonstrated 29% ORR and 5.5 month PFS as 3rd line+ therapy in EGFRmt NSCLC.
2. Chemo-related toxicities are common, ILD 5.3% .
3. Appears to be active regardless of TKI resistance mechanism.

Conclusions

1. HER3-DXd is a promising 3rd line option for EGFR-mutated NSCLC.
2. Biomarker testing not likely needed.
3. Combination therapies (TKI or IO) should be studied.

Proposed Treatment Paradigm for Advanced EGFR-mutated (Exon 19 del or L858R) NSCLC

1st line	2nd line	3rd line
Exon 19 del, no CNS mets	MET AMP (FISH or NGS)	Consider platinum doublet chemo +/- Bev (if not given in 1st/2nd line) or Lazertinib + amivantamab* +/- chemo (if not given in 2nd line)
Osimertinib	Consider Osimertinib + tepotinib (or other MET TKI)	
CNS mets or L858R	No MET AMP or multiple resistance mechanisms	Consider HER3-DXd* (if prior platinum doublet)
Consider Osimertinib + carboplatin/pemetrexed	Consider platinum doublet chemo +/- Bev(if not given in 1st line) or Lazertinib + amivantamab* +/- chemo	

* If FDA-approved