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LUNG CANCER SYMPOSIUM

Updates in EGFR Mutated NSCLC

Suresh Ramalingam, MD, FACP, FASCO

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Disclosures

Honoraria*

- N/A

Research Support (to Institution)

- Amgen, Astra Zeneca, BMS, Merck, Pfizer

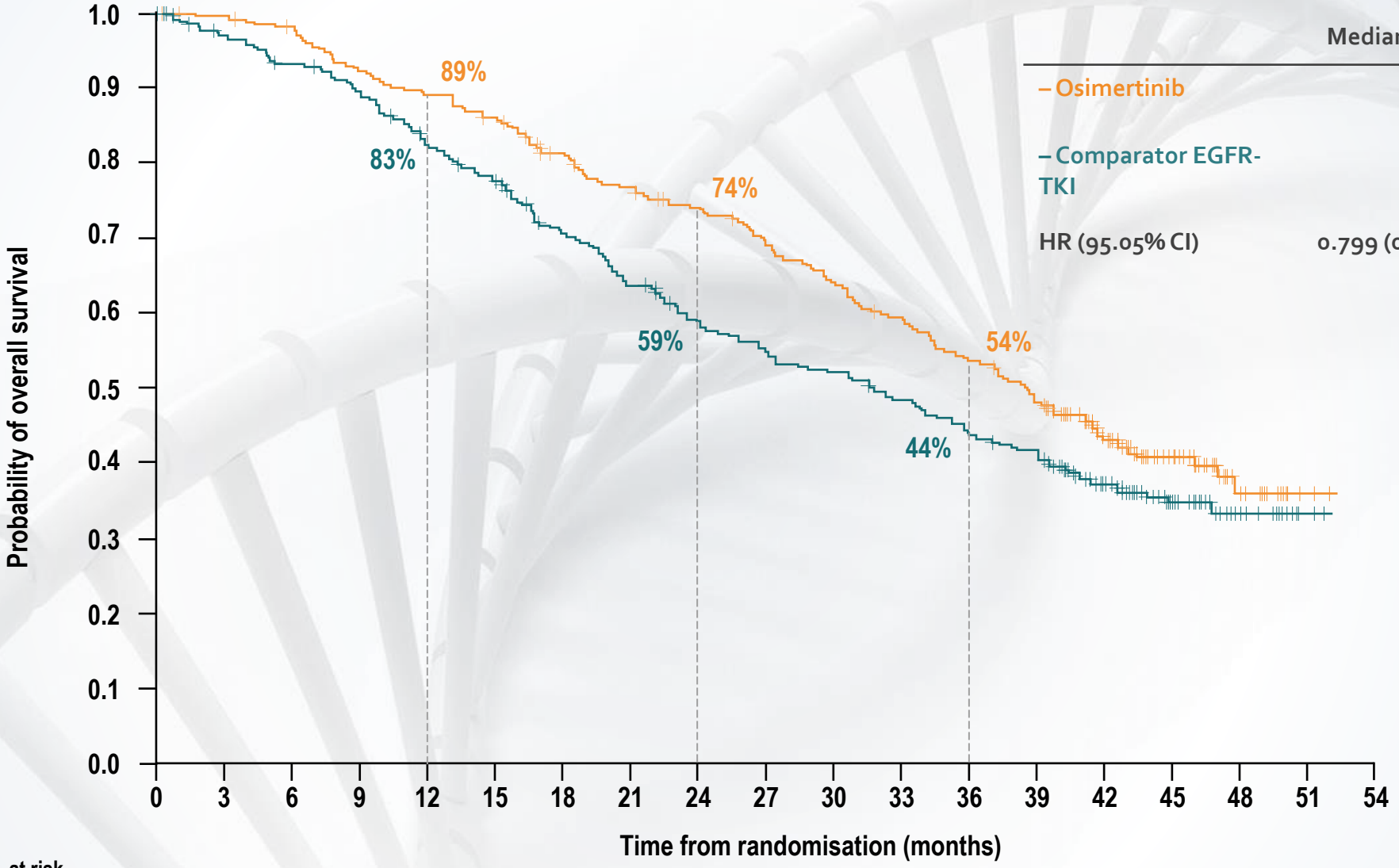
*2 year reporting period

Outline

- First line therapy
  - Monotherapy
  - Combination approaches

- Mechanisms of acquired resistance
- Salvage therapy

Osimertinib as 1st line Therapy: FLAURA Study



	Median OS, months (95% CI)
– Osimertinib	38.6 (34.5, 41.8)
– Comparator EGFR-TKI	31.8 (26.6, 36.0)
HR (95.05% CI)	0.799 (0.641, 0.997); p=0.0462

Ramalingam et al, N Engl J Med, 2020.

Third Generation EGFR TKIs: 1st Line Therapy

Agent	Median PFS	Response Rate
Osimertinib	18.9 m	80%
Furmomertinib	20.8 m	89%
Aumolertinib	19.3 m	74%

Ramalingam et al, NEJM, 2020; Shi et al, Lancet Resp Med 2022; Lu et al, J Clin Oncol, 2022.

Osimertinib + Chemo: FLAURA2

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

Stratification by:

- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

Randomization 1:1 (N=557)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†

Osimertinib 80 mg (QD)

Follow-up:

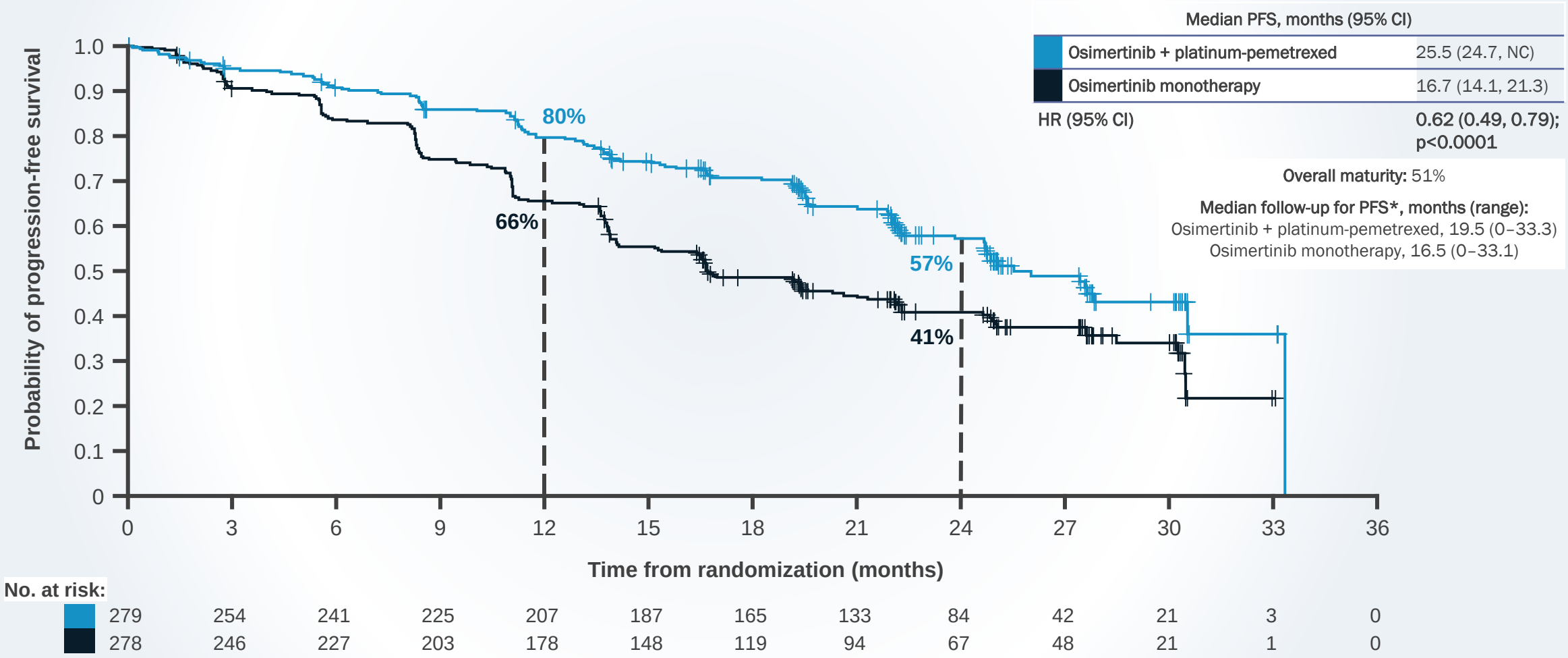
- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

Janne P et al, WCLC, 2023.

Progression-free survival per investigator

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



Janne P et al, WCLC, 2023.

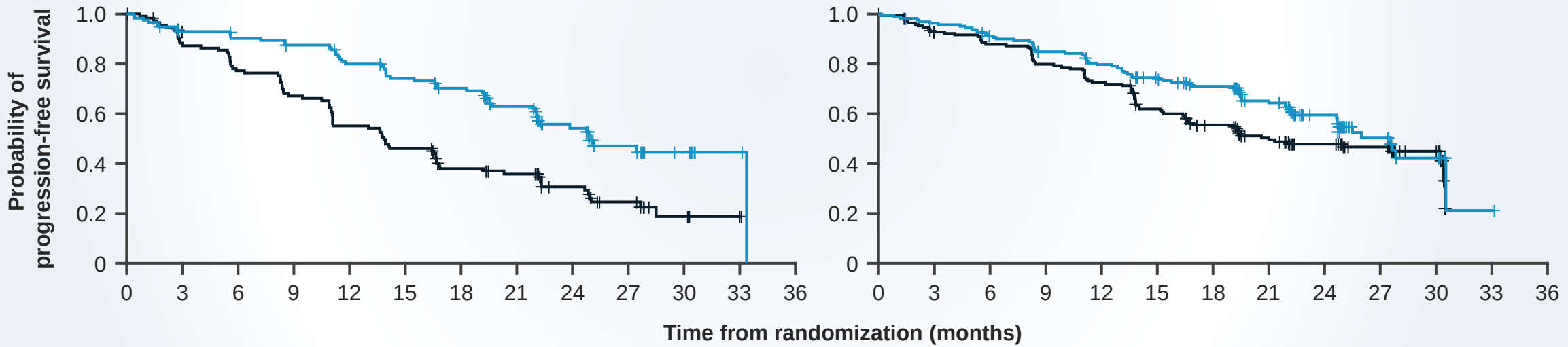
PFS per investigator in patients with / without CNS metastases at baseline*

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)



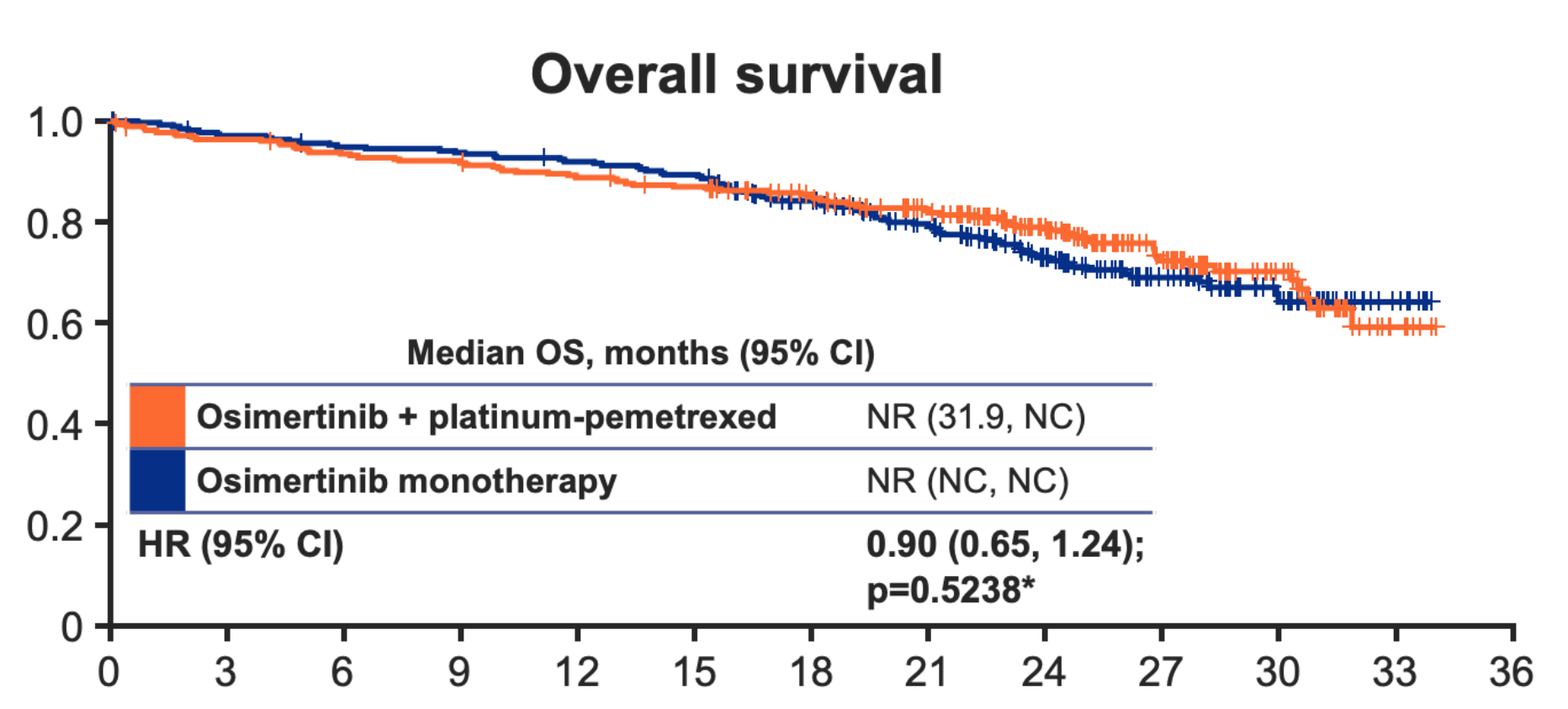
No. at risk:

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

163	153	143	132	123	110	95	75	50	23	13	1	0	
168	151	143	130	118	98	82	62	46	35	16	0	0	

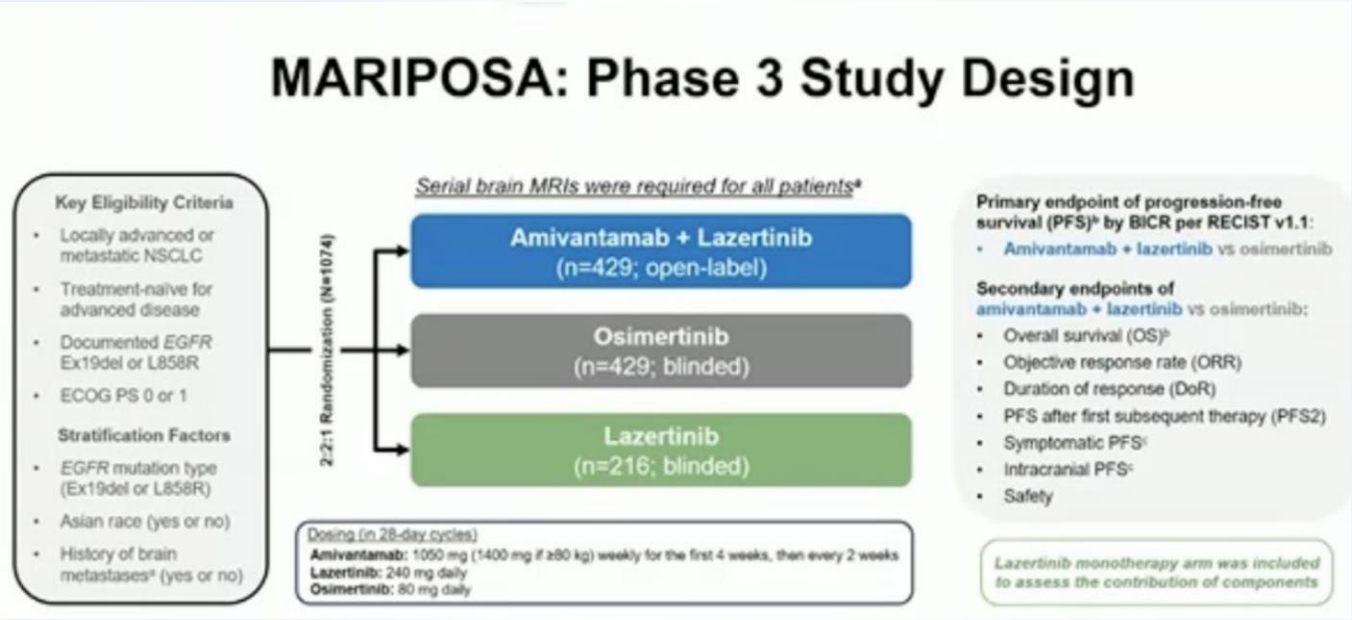
Janne P et al, WCLC, 2023.

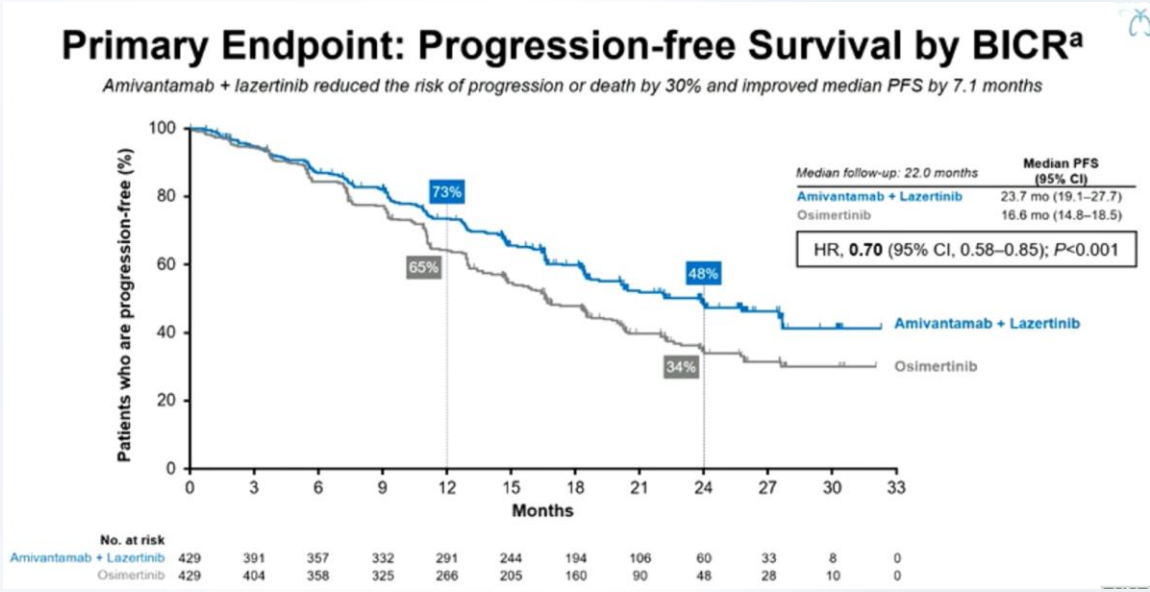
FLAURA2: Preliminary Overall Survival



Janne P et al, WCLC, 2023.

Amivantamab + Lazertinib: 1st Line Therapy

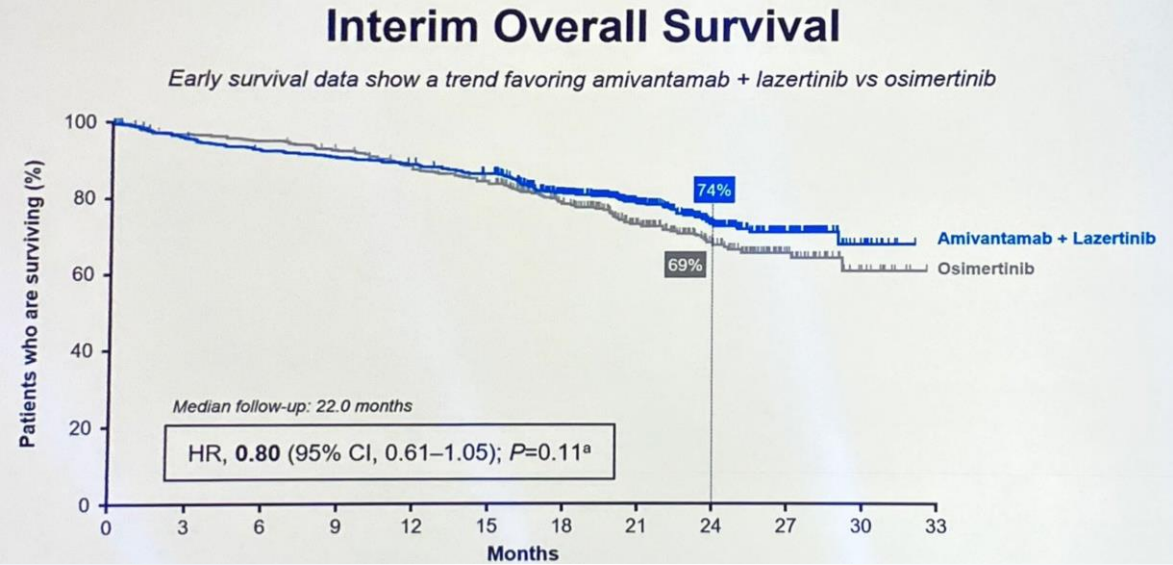


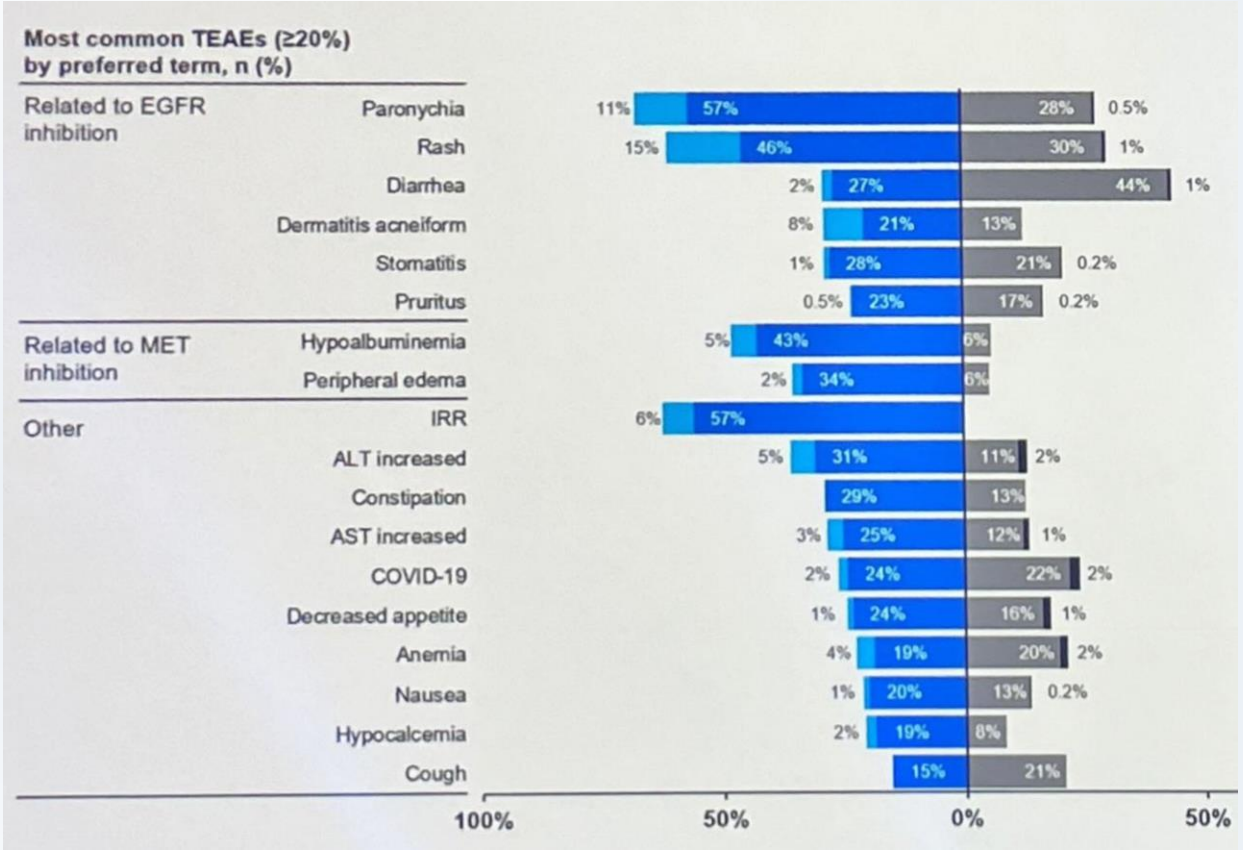


Study met its primary endpoint

Cho B et al, ESMO 2023.

Overall Survival and Safety





37% incidence of venous thromboembolism (DVT/PE) with Ami-Lazertinib- requires prophylactic anticoagulation

Cho B et al, ESMO 2023.

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Salvage Therapy

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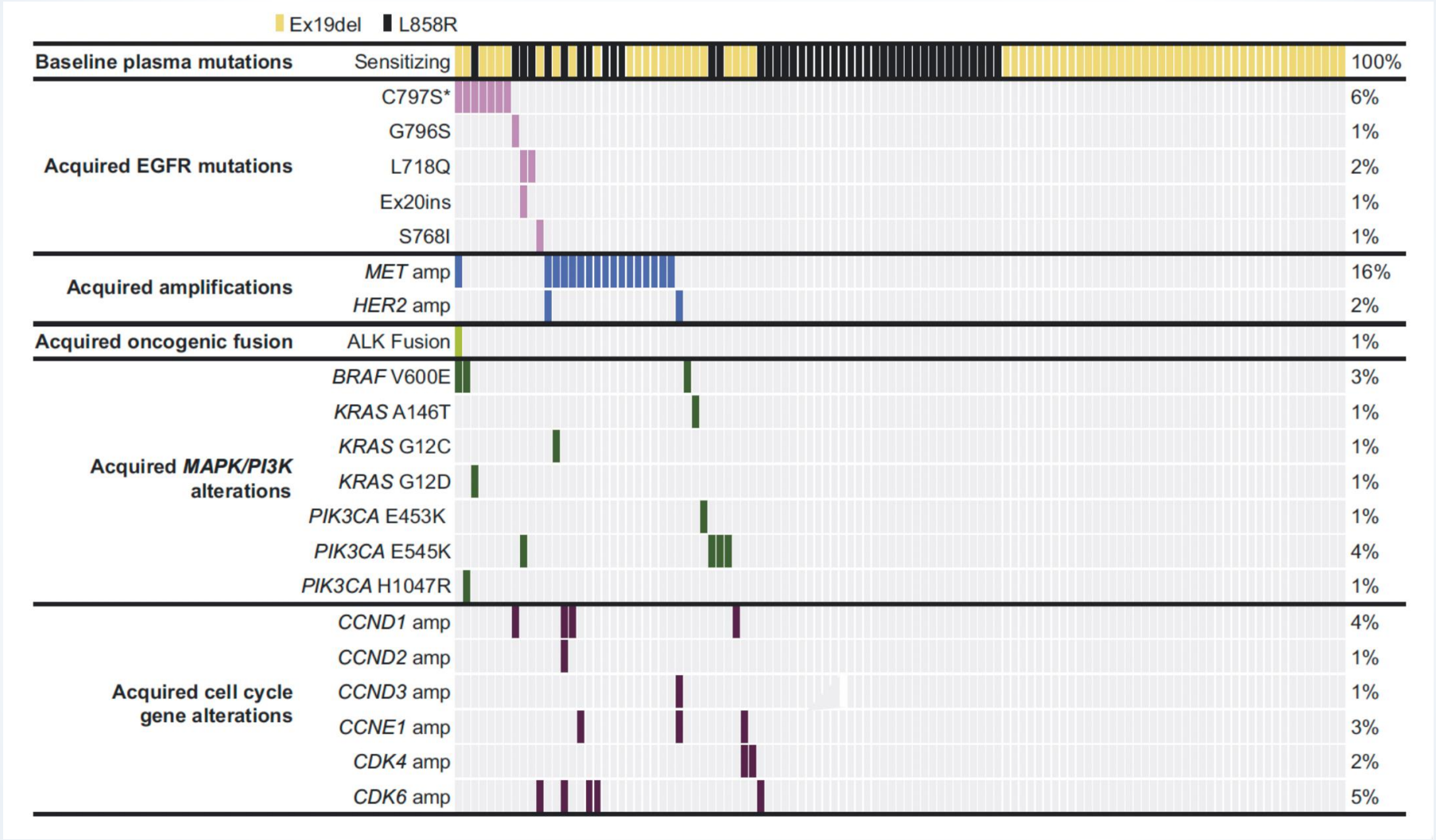
Osimertinib: Acquired Resistance Mechanisms (Plasma)



Chmielecki J et al, Nat Comm, 2023.

BLU 945: 4th Generation EGFR TKI

Key eligibility criteria

- **Adults with metastatic *EGFR*m NSCLC**
- **No other known oncogenic tumor drivers**
- **ECOG status 0-1**
- **Prior treatment with ≥1 EGFR TKI with activity against T790M; progression on osimertinib as last therapy (part 1B only)**

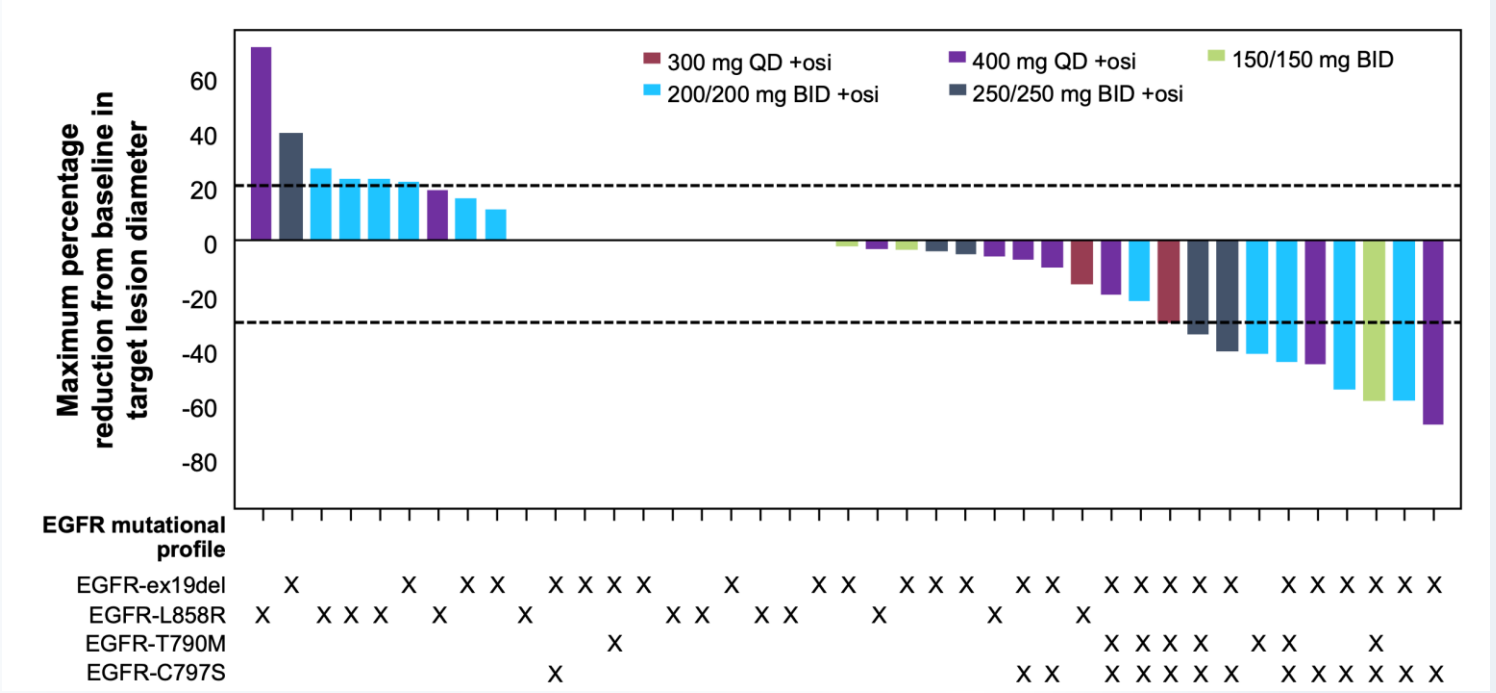
Phase 1 (dose escalation)

Part 1A (N=112)
BLU-945 monotherapy
BOIN design
Starting dose: 25 mg QD[a]
Initiated May 2021

Part 1B (N=55)
BLU-945 + osimertinib (80 mg)
Starting dose:
BLU-945 200 mg QD[a]
Initiated June 2022

All combination patients received osimertinib as last line of therapy without a washout period

Primary endpoints
MTD, RP2D, safety



Efficacy with Osi + BLU 945

Elamin Y et al, ASCO 2023.

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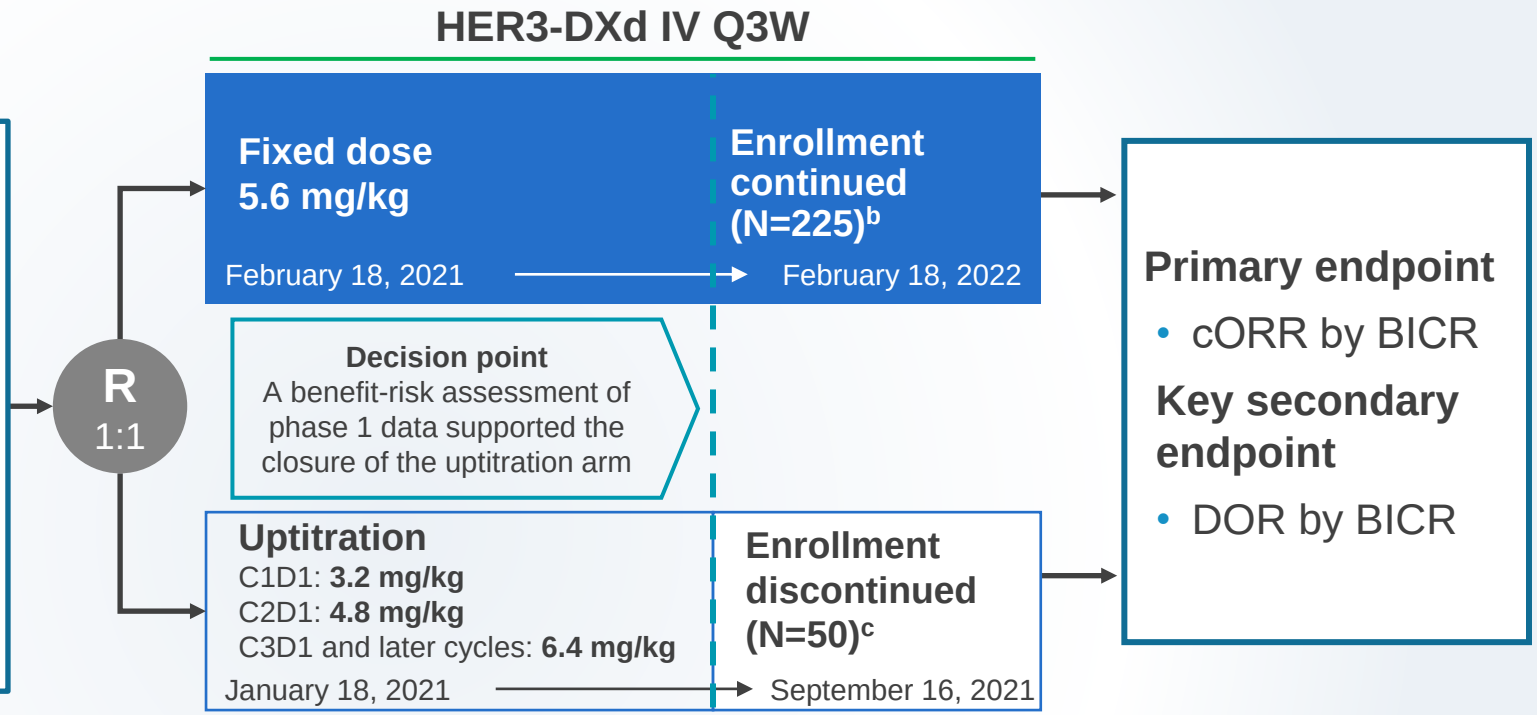
Patritumab Deruxtecan: HERTHENA-Lung01 Study

Patient population

- Advanced *EGFR*-mutated NSCLC
- Progression on most recent systemic therapy
- Prior EGFR TKI and prior platinum-based chemotherapy (amended protocol required prior osimertinib)
- Inactive or previously treated asymptomatic brain metastases allowed
- Pretreatment tumor tissue required[a]



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

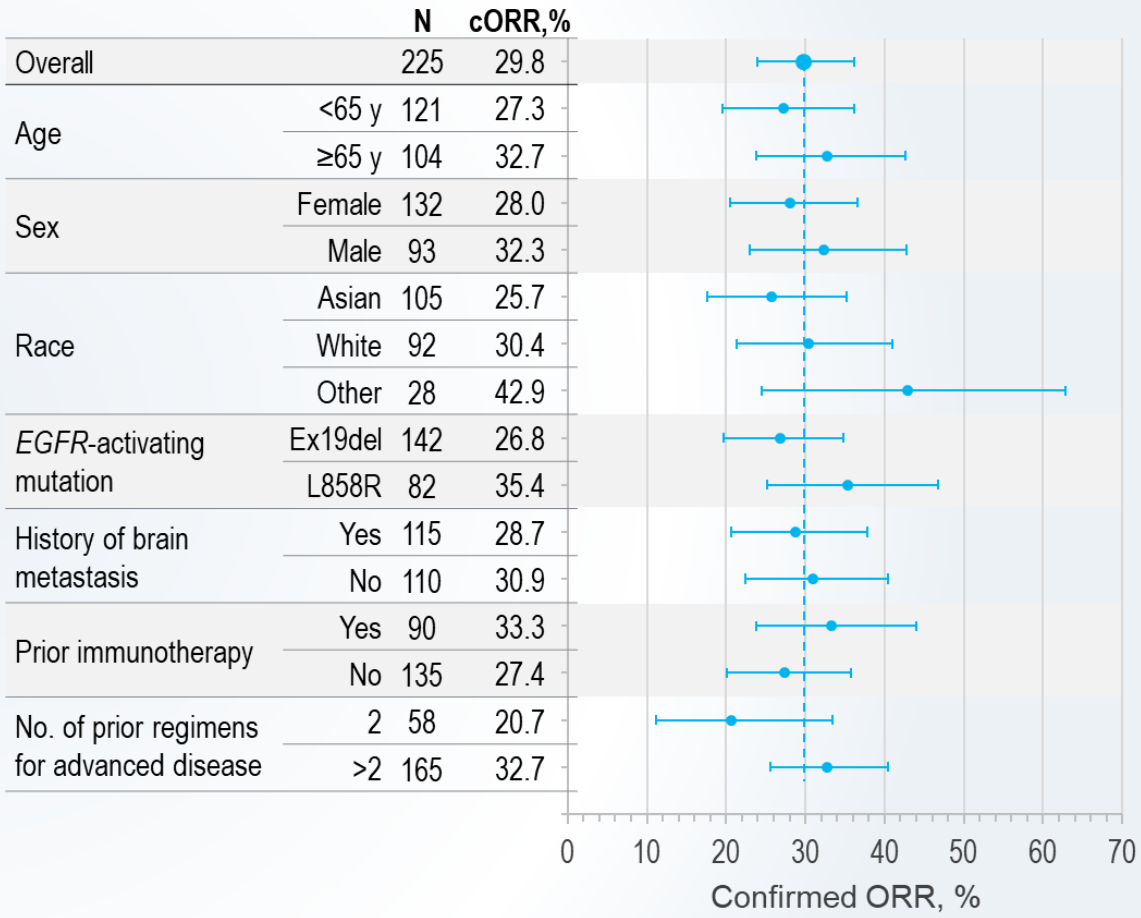
- Efficacy from snapshot data cutoff—median study follow-up, 18.9 (range, 14.9-27.5) months
- Safety from primary data cutoff—median treatment duration, 5.5 (range, 0.7-18.2) months

Yu H et al, WCLC, 2023.

ADC targeting HER-3: Patritumab Deruxtecan in EGFR^{MT} NSCLC

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)

cORR by Patient and Disease Characteristics at Study Entry

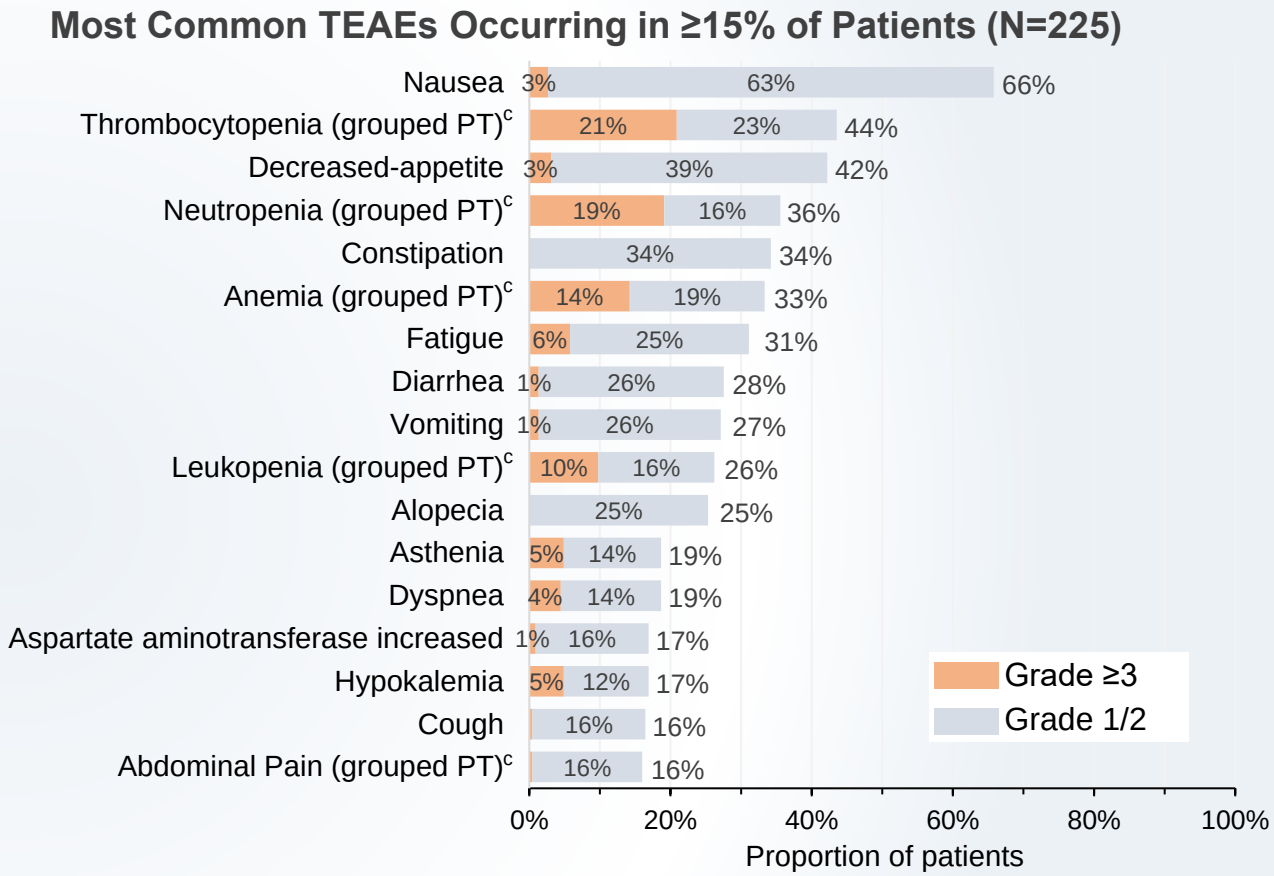


Yu H et al, WCLC, 2023.

Patritumab: Safety Profile

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.



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

Yu H et al, WCLC, 2023.

ADC Targeting Trop2: Datopotamab Deruxtecan

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

- 137 patients (100%) experienced **TEAEs** (grade ≥3, 47%)
  - 129 (94%) experienced **treatment-related TEAEs** (grade ≥3, 29%)
  - 34 (25%) experienced **serious AEs** (grade ≥3, 5%)
- 30 (22%), 13 (10%), and 2 (2%) patients experienced TEAEs associated with **dose reduction, dose withdrawal, and death**,[c] respectively

AESI Incidence by Grade[d]

n (%)	Total	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis	90 (66)	45 (33)	30 (22)	15 (11)
Ocular surface toxicity[e]	36 (26)	26 (19)	7 (5)	3 (2)[f]
IRR	22 (16)	15 (11)	7 (5)	0
Adjudicated drug-related ILD	5 (4)	1 (1)	3 (2)	1 (1)[g]

Paz Ares L et al, ESMO 2023

MARIPOSA 2: Phase 3 Study

A phase 3, global, randomized, controlled trial

2:2:1 Randomization (N=657)

Serial brain MRIs were required for all patients[a]

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Documented *EGFR* Ex19del or L858R
- *Progressed on or after osimertinib monotherapy (as most recent line)*
- ECOG PS 0 or 1
- Stable brain metastases were allowed; radiation/definitive therapy was not required (untreated)

Amivantamab-Lazertinib-Chemotherapy (n=263)

Chemotherapy (n=263)

Amivantamab-Chemotherapy (n=131)

Stratification Factors

- Osimertinib line of therapy (1st vs 2nd)
- Asian race (yes or no)
- History of brain metastases (yes or no)

Dosing (in 21-day cycles)

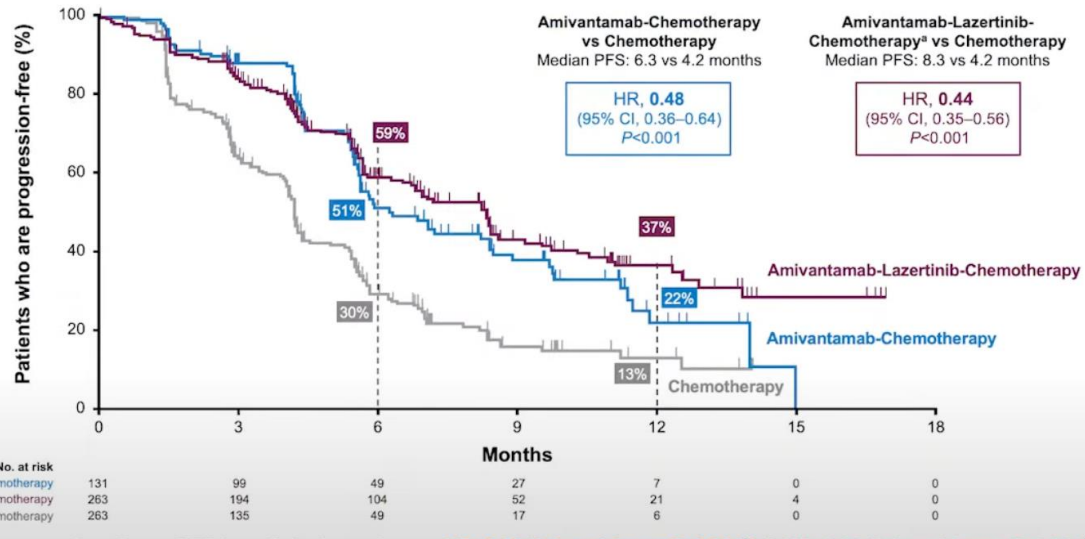
Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at Cycle 3 (week 7)

Lazertinib: 240 mg daily starting after completion of carboplatin[b]

Chemotherapy administered at the beginning of every cycle:

- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² until disease progression

Primary endpoint
Progression-free survival by BICR



Consistent PFS benefit by investigator: HR, 0.41 (8.2 vs 4.2 mo; *P*<0.001[b]) & HR, 0.38 (8.3 vs 4.2 mo; *P*<0.001[b])

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Passaro A et al, ESMO 2023.

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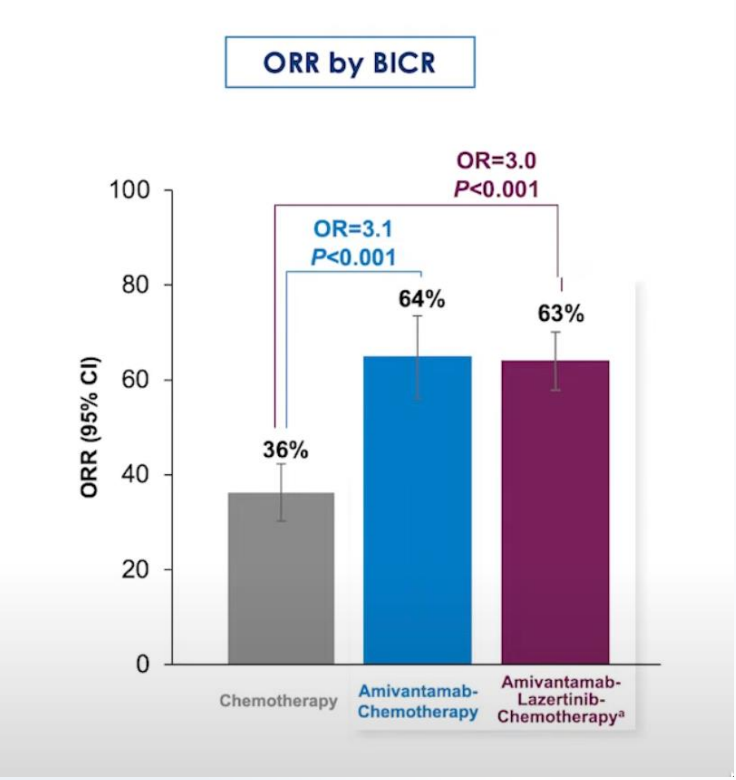
MARIPOSA 2: Response Rate and Safety



Most common TEAEs (≥25%) by preferred term, n (%)	Chemotherapy (n=243)		Amivantamab-Chemotherapy (n=130)		Amivantamab-Lazertinib-Chemotherapy[a] (n=263)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition						
Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
Stomatitis	21 (9)	0	41 (32)	1 (1)	120 (46)	24 (9)
Diarrhea	16 (7)	1 (0.4)	18 (14)	1 (1)	68 (26)	10 (4)
Associated with MET inhibition						
Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Associated with Chemotherapy						
Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Anemia	97 (40)	23 (9)	51 (39)	15 (12)	141 (54)	48 (18)
Leukopenia	68 (28)	23 (9)	37 (28)	26 (20)	106 (40)	71 (27)
Other						
Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)
Nausea	90 (37)	2 (1)	58 (45)	1 (1)	131 (50)	16 (6)
Constipation	72 (30)	0	50 (38)	1 (1)	96 (37)	3 (1)
Decreased appetite	51 (21)	3 (1)	40 (31)	0	85 (32)	7 (3)
Vomiting	42 (17)	1 (0.4)	32 (25)	1 (1)	76 (29)	10 (4)
Fatigue	47 (19)	4 (2)	36 (28)	4 (3)	69 (26)	15 (6)
Asthenia	40 (16)	5 (2)	34 (26)	1 (1)	67 (25)	14 (5)
Alanine aminotransferase increased	67 (28)	10 (4)	26 (20)	7 (5)	55 (21)	14 (5)
AESIs by grouped term, n (%)						
Rash[b]	30 (12)	0	92 (71)	13 (10)	197 (75)	40 (15)
VTE[c]	11 (5)	7 (3)	13 (10)	3 (2)	58 (22)	17 (6)
ILD	0	0	2 (2)	1 (1)	7 (3)	5 (2)

Passaro A et al, ESMO 2023.

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Role of IO in EGFR^{MT} NSCLC

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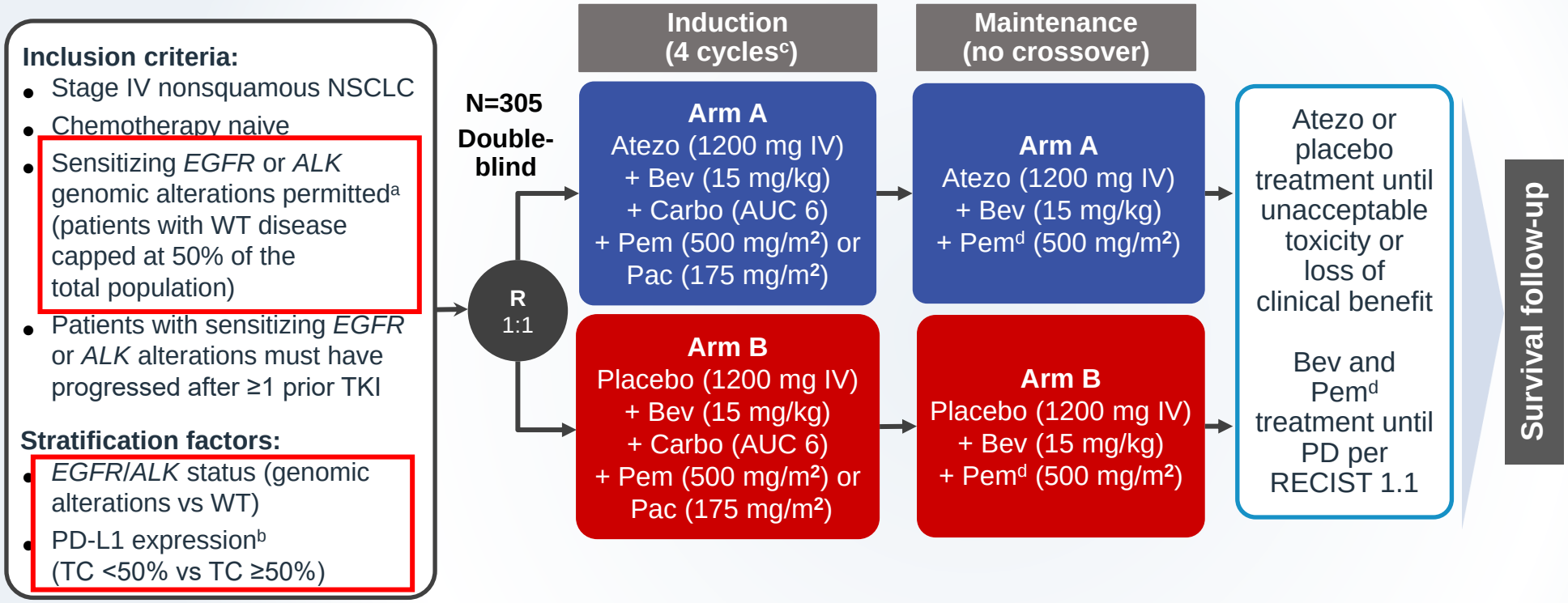
IMpower151 (Phase 3): 1L atezolizumab + bevacizumab + chemotherapy for metastatic NSQ-NSCLC



Study objectives

Primary efficacy
- INV-PFS in ITT

Secondary efficacy
- OS in ITT
- INV-PFS in *EGFR/ALK*+
- INV-PFS in PD-L1+
- IRF-PFS in ITT
- ORR
- DOR

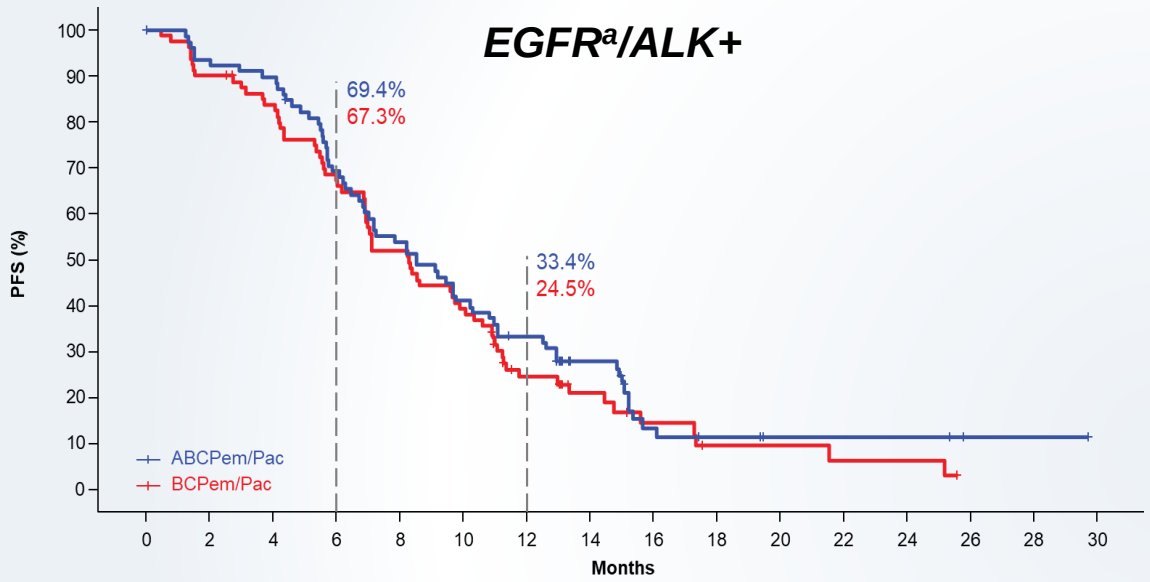
Safety

Other
- Biomarker analysis

- A target sample size of 306 patients allowed for 90% power to detect a HR of 0.65, corresponding to an improvement in median PFS from 6.8 to 10.5 months in the ITT population

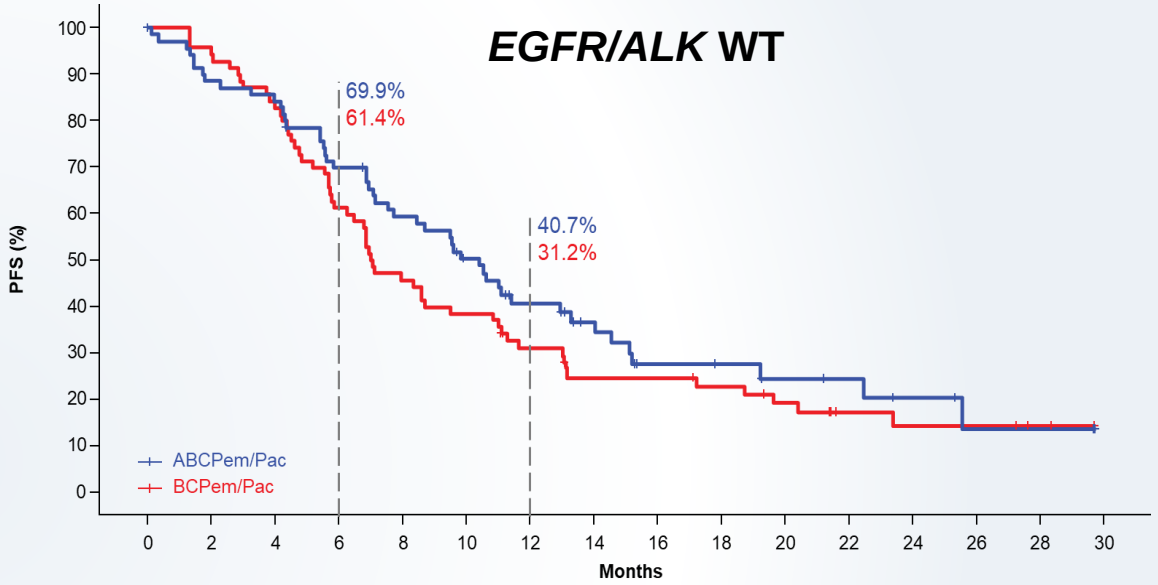
Zhou C, et al. WCLC 2023 Abstract OA09.06.

INV-PFS by *EGFR/ALK* genotype (non powered population)



No. at risk																
ABCPem/Pac	81	74	71	54	42	32	25	17	7	5	3	3	3	1	1	0
BCPem/Pac	82	73	66	53	41	31	16	10	8	3	3	2	2	0	0	0

	ABCPem/Pac (n=81)	BCPem/Pac (n=82)
Patients with an event, n (%)	65 (80.2)	68 (82.9)
Median, mo (95% CI)	8.5 (6.9, 10.3)	8.3 (6.9, 10.1)
Unstratified HR (95% CI)	**0.86 (0.61, 1.21)**	

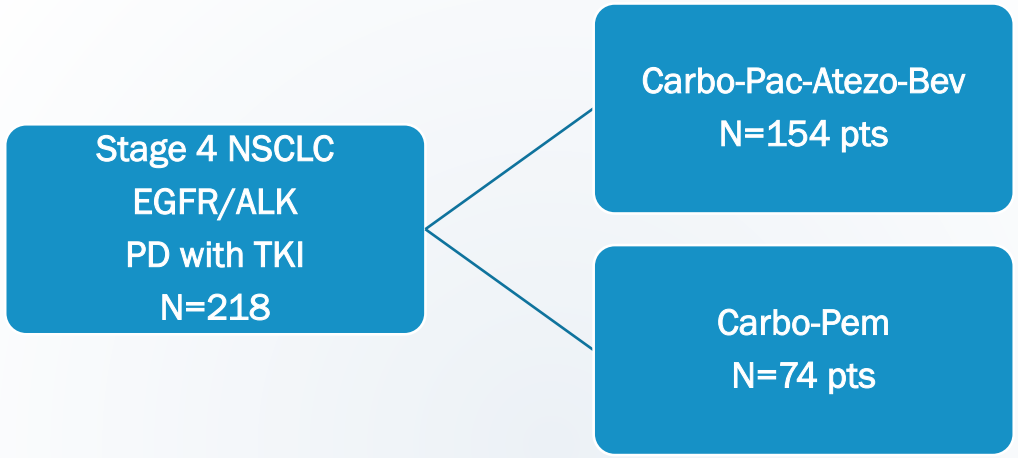


No. at risk																
ABCPem/Pac	71	62	59	48	40	32	22	16	10	9	7	6	4	2	2	0
BCPem/Pac	71	66	58	43	32	27	20	15	15	13	10	6	5	4	2	0

	ABCPem/Pac (n=71)	BCPem/Pac (n=71)
Patients with an event, n (%)	49 (69.0)	57 (80.3)
Median, mo (95% CI)	10.4 (7.6, 13.3)	7.0 (6.2, 9.5)
Unstratified HR (95% CI)	**0.81 (0.55, 1.19)**	

Zhou C, et al. WCLC 2023 Abstract OA09.06.

ATTLAS Study: Role of IO Combination



	Carbo-Pac-Atezo-Bev	Carbo=Pem
Response Rate	70%	42%
mPFS	8.5m (HR 0.62)	5.6m
m OS	20.6 m (HR 1.01)	20.3 m

Ahn M et al, ESMO 2023

EGFR^{MT} NSCLC: Conclusions

- Combination options show improved PFS in 1st line therapy
  - Impact on survival is yet to be demonstrated
  - No biomarkers to predict benefit from combination therapy
  - Toxicity considerations are not trivial
- Monotherapy with Osimertinib remains my ‘go-to’ approach
- New options for salvage therapy are emerging
- No evidence to support chemo-IO/Chemo-bevavizumab-IO in the salvage therapy setting