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First-Line Targeted Therapies in NSCLC: What's New?

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FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

Sequencing Therapy in EGFR-Mutated NSCLC is an issue now

Why?

EGFR Pathway

Exon19del & Exon21 L858R

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

***EGFR* exon 19 deletion or exon 21 L858R mutations**

***EGFR* mutation discovered prior to first-line systemic therapy**

FIRST-LINE THERAPY[rr]

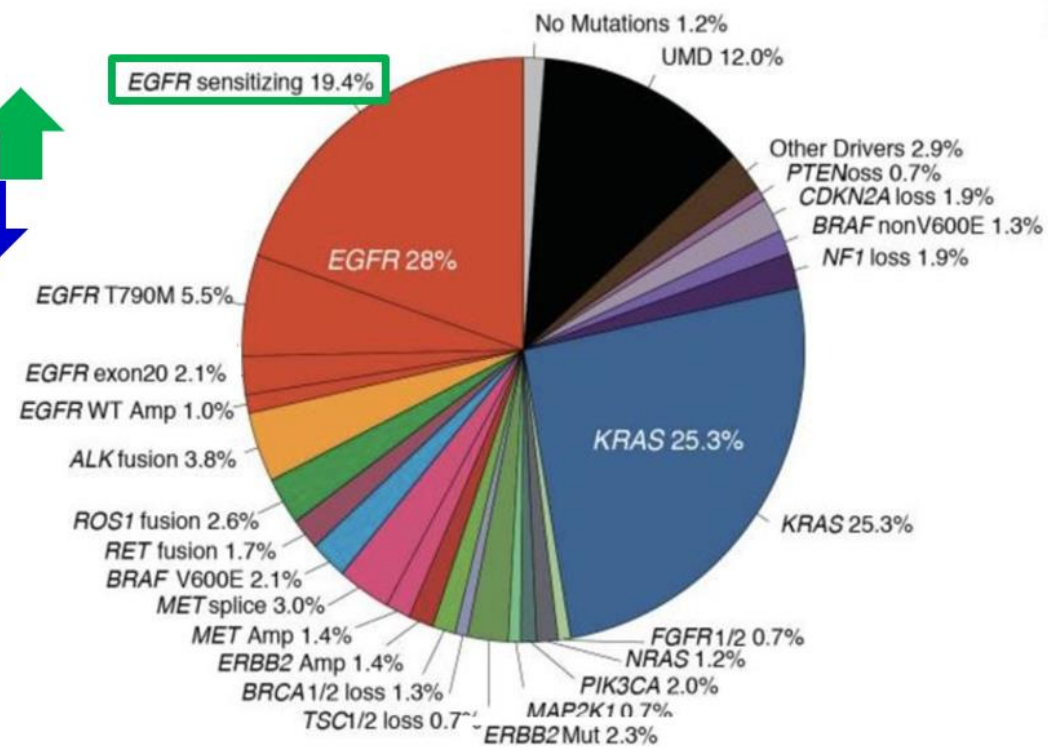
Preferred
Osimertinib[ss] (category 1)

Other Recommended
Amivantamab-vmjw + lazertinib (category 1)
or
Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous) (category 1)

Useful in Certain Circumstances
Afatinib[ss] (category 1)
or Dacomitinib[ss] (category 1)
or Erlotinib[ss] (category 1)
or Erlotinib + bevacizumab[uu,vv]
or Erlotinib + ramucirumab
or Gefitinib[ss] (category 1)

***EGFR* mutation discovered during first-line systemic therapy**

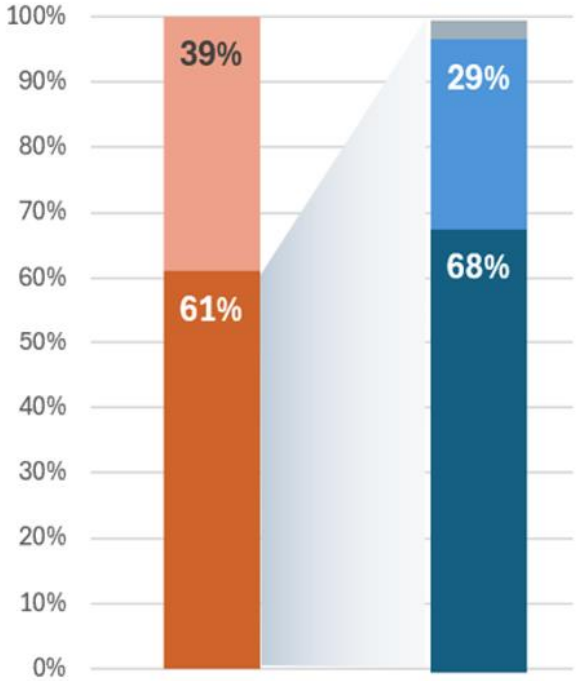
Add osimertinib to pemetrexed + (cisplatin or carboplatin) (nonsquamous)
or
Interrupt current therapy[ww,xx] and start Osimertinib or Amivantamab-vmjw + lazertinib[tt]
or
Afatinib or Dacomitinib or Erlotinib
or Erlotinib + bevacizumab[uu,vv]
or Erlotinib + ramucirumab or Gefitinib



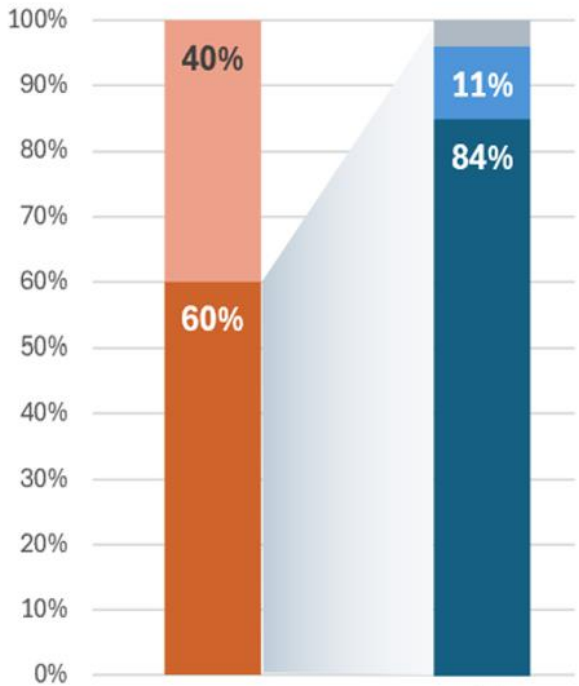
NCCN Version 3.2025, 1/14/25

What 2L Regimen Did Patients Receive? "Crossover" on the Control Arm

FLAURA
Osimertinib Arm

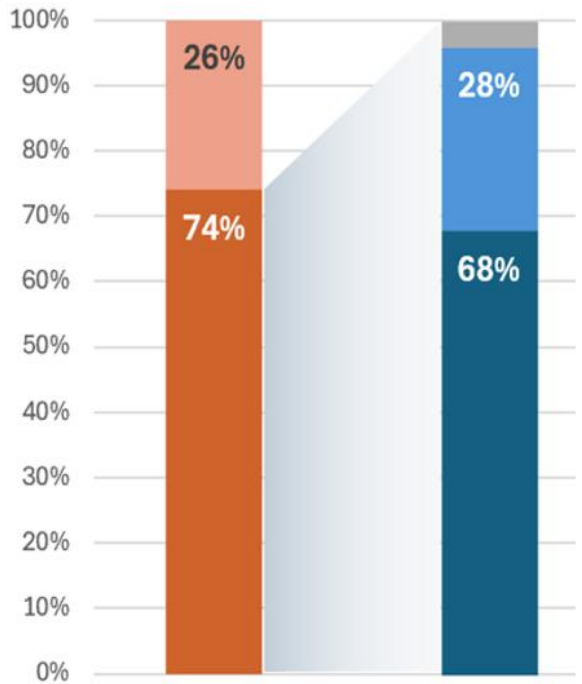


FLAURA2
Osimertinib Arm

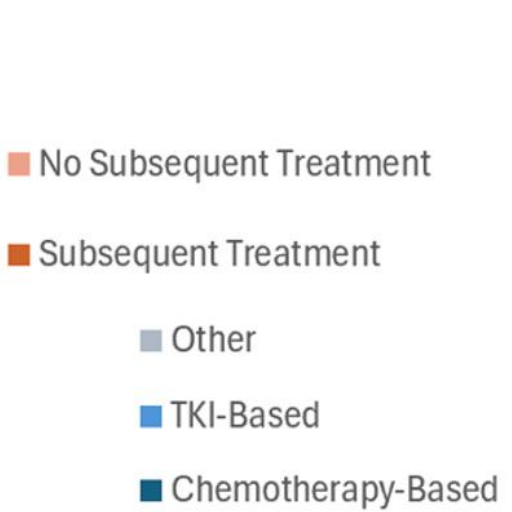


~81% Platinum Doublet

MARIPOSA
Osimertinib Arm

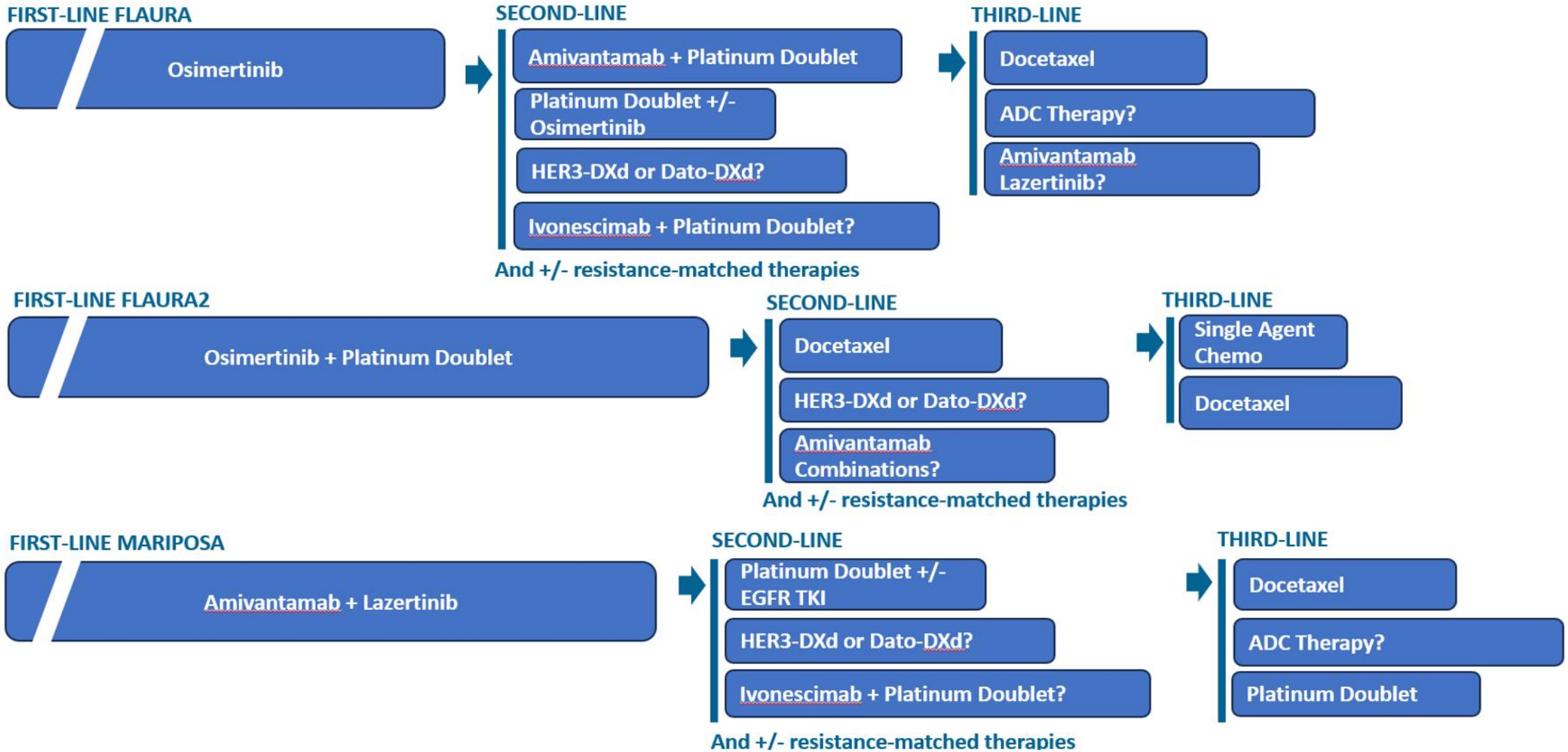


~1% Amivantamab



Ramalingam et al NEJM 2019; Valdiviezo et al ELCC 2024; Gadgeel et al. IASLC WCLC 2024. OA02.02

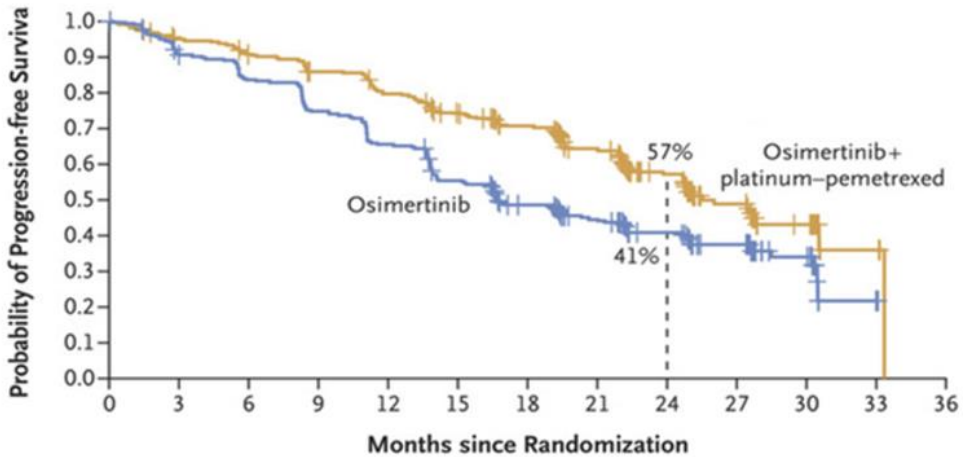
What would you choose as 1L will impact your 2L or 3L:



Julia Rotow, MD. IASLC Targeted Therapy in Lung Cancer 2025. Huntington Beach, CA. February 19-22, 2025

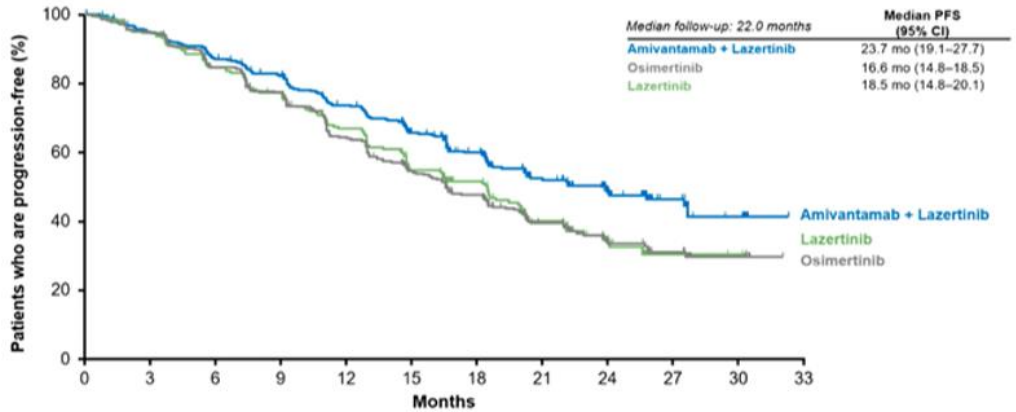
Upfront combination therapy improves PFS and may improve OS in EGFRm NSCLC

FLAURA2:
Osimertinib + Platinum Doublet vs Osimertinib



Median PFS 16.7 → 25.5 months
HR 0.62; 95% CI, 0.49 to 0.79

MARIPOSA:
Amivantamab + Lazertinib vs Osimertinib



Median PFS 16.6 → 23.7 months
HR 0.70; 95% CI, 0.58 to 0.85

But the potential benefit is not the same for all patients.
What does it mean to have “higher-risk” EGFR lung cancer?

Julia Rotow, MD. IASLC Targeted Therapy in Lung Cancer 2025. Huntington Beach, CA. February 19-22, 2025

NEWS RELEASE

Amivantamab-vmjw plus lazertinib show statistically significant and clinically meaningful improvement in overall survival versus osimertinib

2025-01-07

Median overall survival improvement expected to exceed one year

First and only regimen with a survival benefit over current standard of care in first-line treatment of EGFR-mutated lung cancer

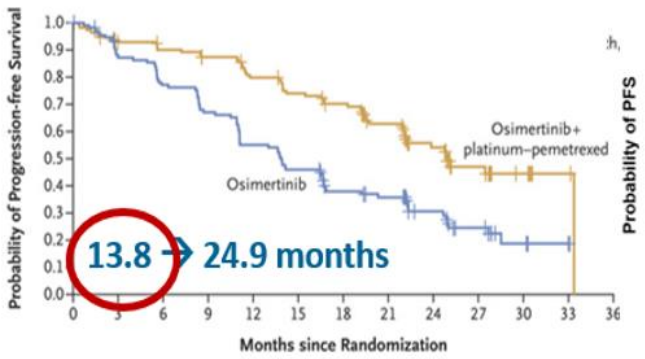
RARITAN, N.J., Jan. 7, 2025 /PRNewswire/ - Positive topline results were announced today for the gold standard endpoint in cancer treatment of overall survival (OS) from the Phase 3 MARIPOSA study, evaluating Amivantamab-vmjw plus lazertinib as a first-line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions (ex19del) or L858R substitution mutations. The chemotherapy-free combination regimen met the final pre-specified secondary endpoint of OS and demonstrated clinically meaningful and statistically significant improvement in OS versus the current standard of care osimertinib. Improvement in median OS is expected to exceed one year.

Unlike progression-free survival (PFS), which tracks the time a treatment keeps a patient's cancer from progressing, OS helps patients understand the impact therapy could have on the ability to live longer from the start of treatment. Extending life expectancy is the most meaningful indicator of a treatment's impact.

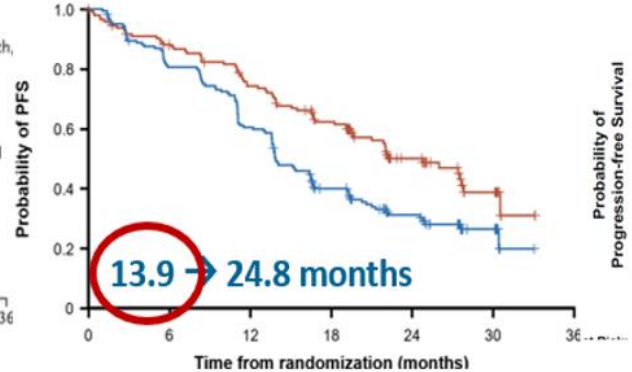
mOS is expected to exceed one year

FLAURA2 Subgroup Analysis

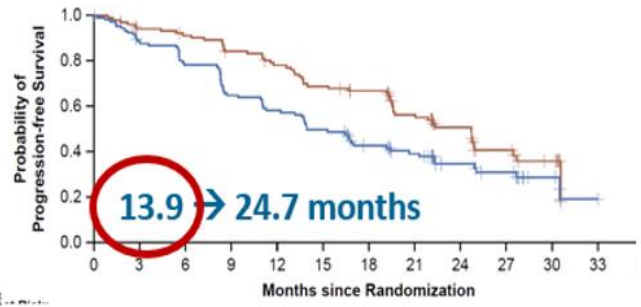
With Brain Metastases



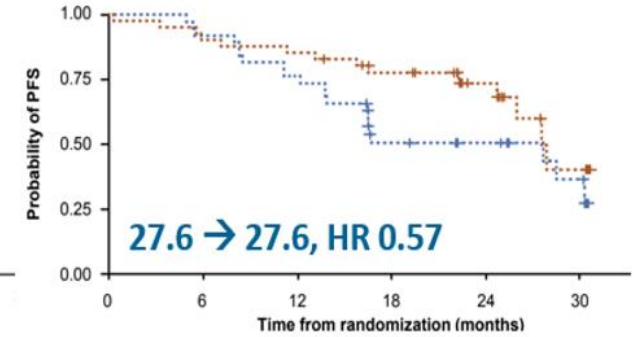
Plasma EGFR Detectable



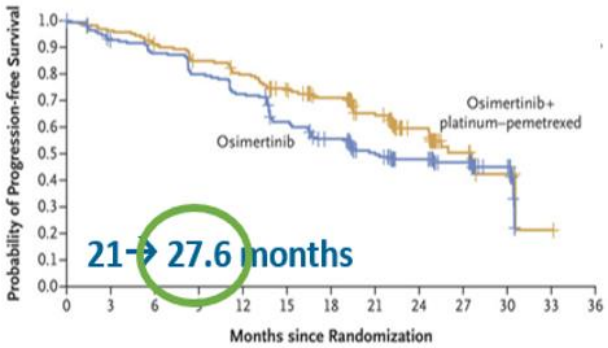
EGFR L858R



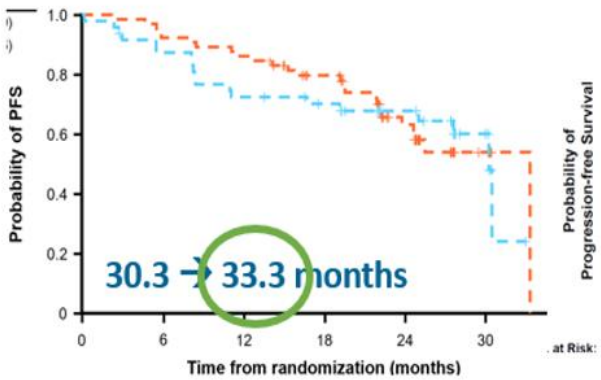
TP53 Mutated



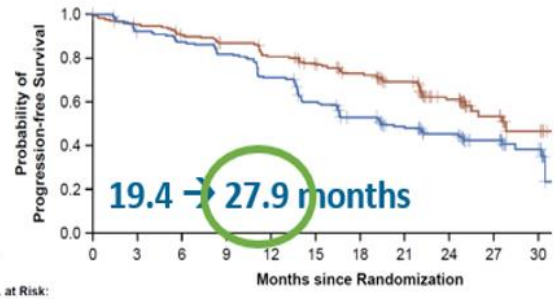
Without Brain Metastases



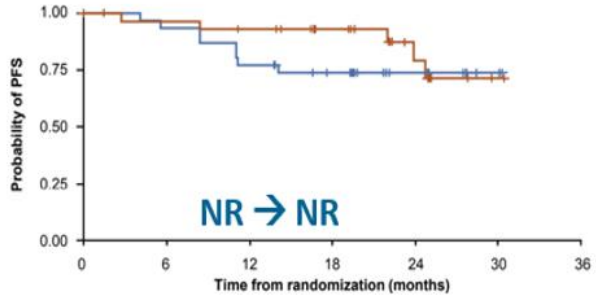
Plasma EGFR Undetectable



EGFR Exon 19 Deletions



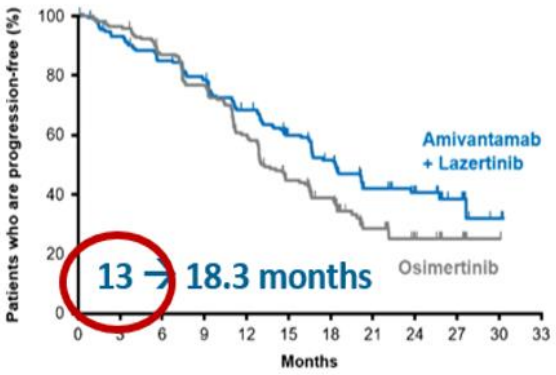
TP53 Wild Type



Planchard et al. *N Engl J Med*. 2023;389(21):1935-1948; Janne, AACR 2024

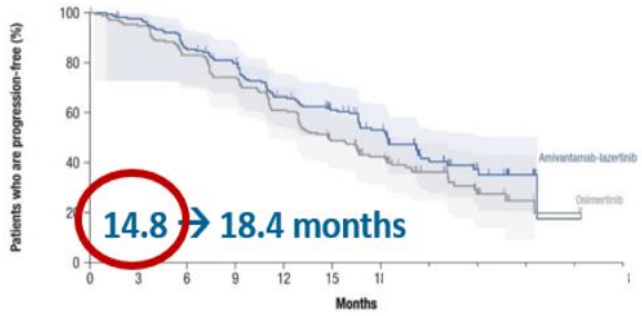
MARIPOSA Subgroup Analysis

With Brain Metastases

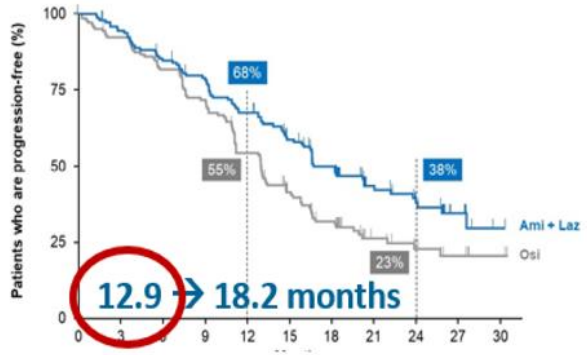


Plasma EGFR Detectable

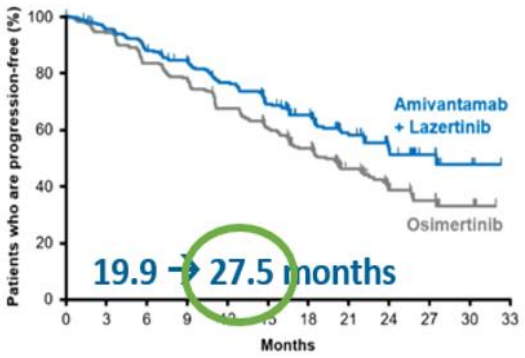
EGFR L858R



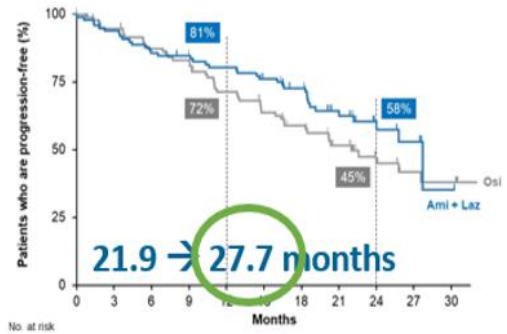
TP53 Mutated



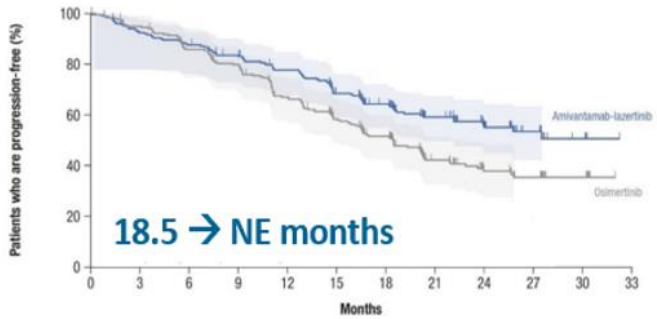
Without Brain Metastases



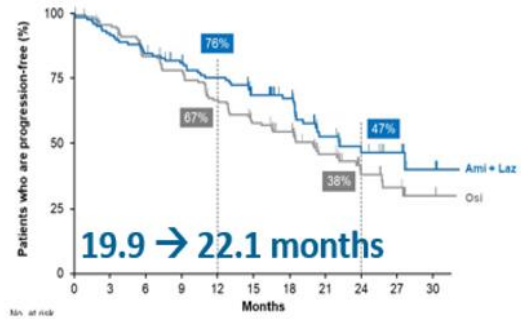
Plasma EGFR Undetectable



EGFR Exon 19 Deletions



TP53 Wild Type



Cho et al. ESMO 2023. LBA14; Felip et al ASCO 2024; Cho et al NEJM 2024

Toxicity Profiles- FLAURA2 & MARIPOSA

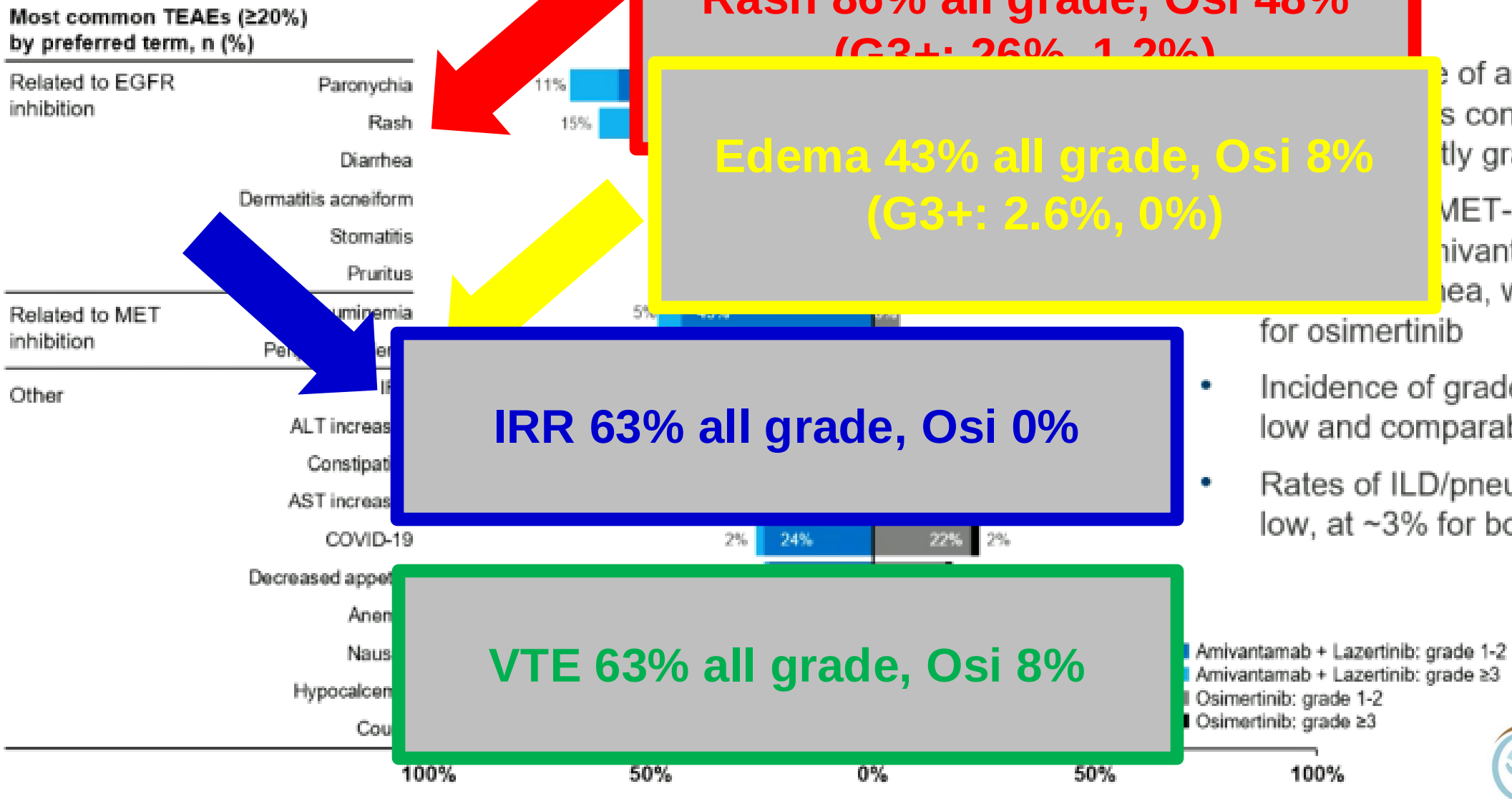
Amivantamab/Laz

Rash 86% all grade, Osi 48%
(G3+: 26%, 1.2%)

Edema 43% all grade, Osi 8%
(G3+: 2.6%, 0%)

IRR 63% all grade, Osi 0%

VTE 63% all grade, Osi 8%



- of amivantamab + s consistent with prior tly grades 1-2
- MET-related AEs were nivantamab + lazertinib ea, which was higher for osimertinib
- Incidence of grade 4-5 AEs was low and comparable between arms
- Rates of ILD/pneumonitis remained low, at ~3% for both arms

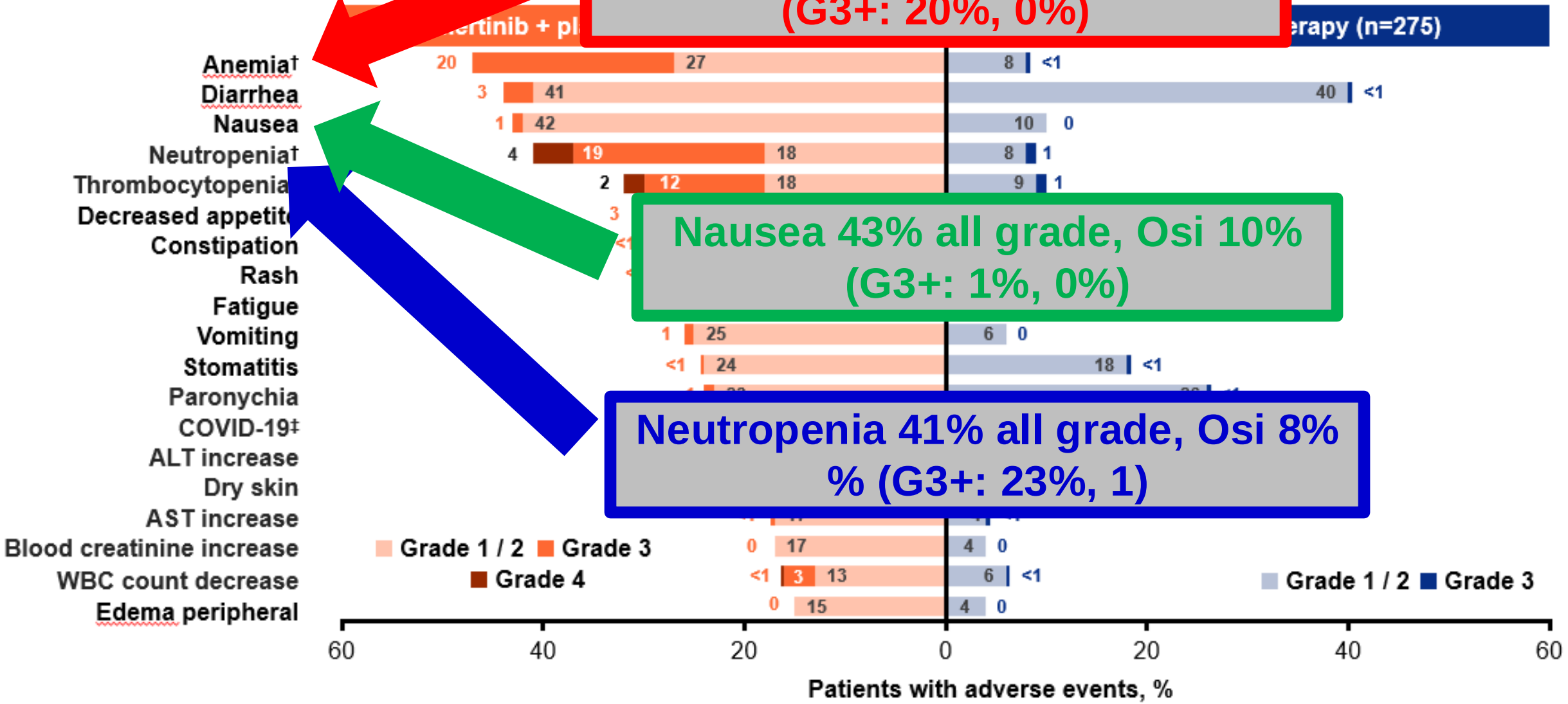
The Oncology Institute of Hope & Innovation

Chemo/Osimerti

Anemia 47% all grade, Osi 8%
(G3+: 20%, 0%)

Nausea 43% all grade, Osi 10%
(G3+: 1%, 0%)

Neutropenia 41% all grade, Osi 8%
% (G3+: 23%, 1)



PALOMA-3
Ami + Laz in
3L *EGFR*+ NSCLC

PALOMA-3: Phase 3 Study Design

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Disease had progressed on or after osimertinib and platinum-based chemotherapy, irrespective of order
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0–1

Stratification factors

- Brain metastases (yes or no)
- *EGFR* mutation type (Ex19del vs L858R)
- Race (Asian vs non-Asian)
- Type of last therapy (osimertinib vs chemotherapy)

1:1 randomization (N=418)

SC Amivantamab + Lazertinib (n=206)

IV Amivantamab + Lazertinib (n=212)

Dosing (in 28-day cycles)

SC Amivantamab[a,b] (co-formulated wit
administered by manual injection): 160
≥80 kg) weekly for the first 4 weeks, the
thereafter

IV Amivantamab[b]: 1050 mg weekly (1
for the first 4 weeks, then every 2 weeks thereafter

Lazertinib: 240 mg PO daily

PALOMA-3
Ami + Laz in
3L *EGFR*+ NSCLC

Prophylactic anticoagulation recommended for the first 4 months of treatment

Co-primary endpoints[c]**:**

- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

Secondary endpoints:

- ORR (noninferiority)
- PFS (superiority)
- DoR
- Patient satisfaction[f]
- Safety

Exploratory endpoints:

- OS

ASCO 2024 Updates

PALOMA-3 (ClinicalTrials.gov Identifier: NCT05388669) enrollment period: August 2022 to October 2023; data cutoff: 03-Jan-2024.

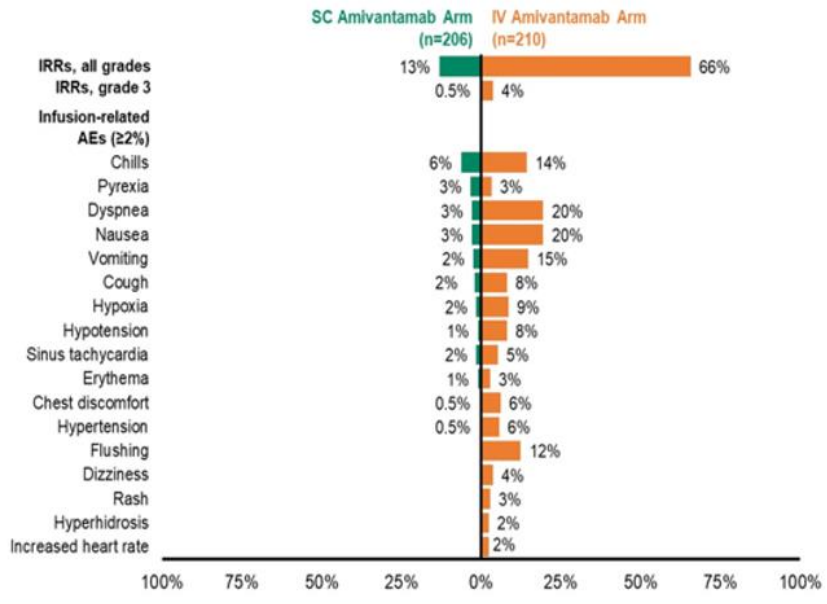
[a]SC amivantamab was co-formulated with rHuPH20 at a concentration of 160 mg/mL. [b]C1 for IV: Days 1 to 2 (Day 2 applies to IV split dose only [350 mg on Day 1 and the remainder on Day 2]), 8, 15, and 22; C1 for SC: Days 1, 8 , 15, and 22; after C1 for all: Days 1 and 15 (28-day cycles). [c]For calculating primary and key secondary outcomes, we estimated that a sample size of 400 patients would provide >95% power for a 1-sided alpha of 0.05 allocated to each of the co-primary endpoints and 80% power with a 1-sided alpha of 0.025 allocated to ORR. A hierarchical testing approach at a 2-sided alpha of 0.05 was used for the co-primary endpoints (noninferiority), followed by ORR (noninferiority) and PFS (superiority), with a combined 2-sided alpha of 0.05. [d]Two definitions of the same endpoint were used as per regional health authority guidance. [e]Measured between C2D1 and C2D15. [f]Assessed by modified TASQ.

AUC, area under the concentration-time curve; C, Cycle; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; rHuPH20, hyaluronidase; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

Leighl N et al. 2024 ASCO

PALOMA-3

Incidence of IRR-related Symptoms



- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
  - There were no grade 4 or 5 IRRs
  - Most IRRs occurred during Cycle 1
- IRRs leading to hospitalization were not observed in the SC arm vs 2 events in the IV arm
- No IRR-related discontinuations occurred in the SC arm vs 4 events in the IV arm

SC amivantamab + lazertinib demonstrated noninferior efficacy, lower rates of IRRs and VTE, and is more convenient for patients and providers vs IV amivantamab + lazertinib

FDA approves lazertinib with amivantamab-vmjw for non-small lung cancer

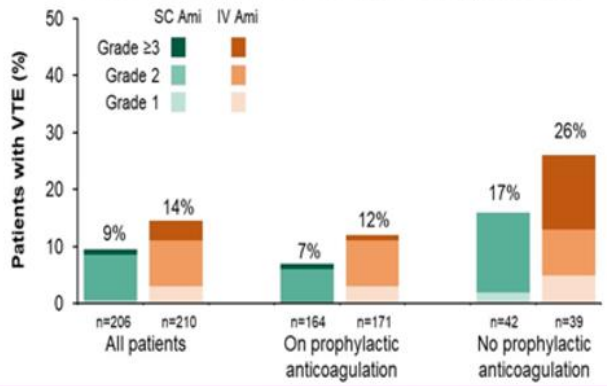
Approved on August 19, 2024

On August 19, 2024, the Food and Drug Administration approved lazertinib , in combination with amivantamab-vmjw , for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test.

Adverse Event of Special Interest: VTE[a]

- Prophylactic anticoagulation[b] was administered to 80% (164/206) of patients in the SC arm and 81% (171/210) for IV
- Among all patients in the study, VTE was reported in 10% (32/335) of those receiving prophylactic anticoagulation vs 21% (17/81) who did not
- Rates of grade ≥3 bleeding events were uncommon in the SC (2%) and IV (1%) arms for those receiving prophylactic anticoagulation

Rates of VTE by Treatment Arm and Prophylaxis Status



- Between study arms, incidence of VTE was less frequent in the SC amivantamab arm compared to the IV arm, regardless of prophylactic anticoagulation status

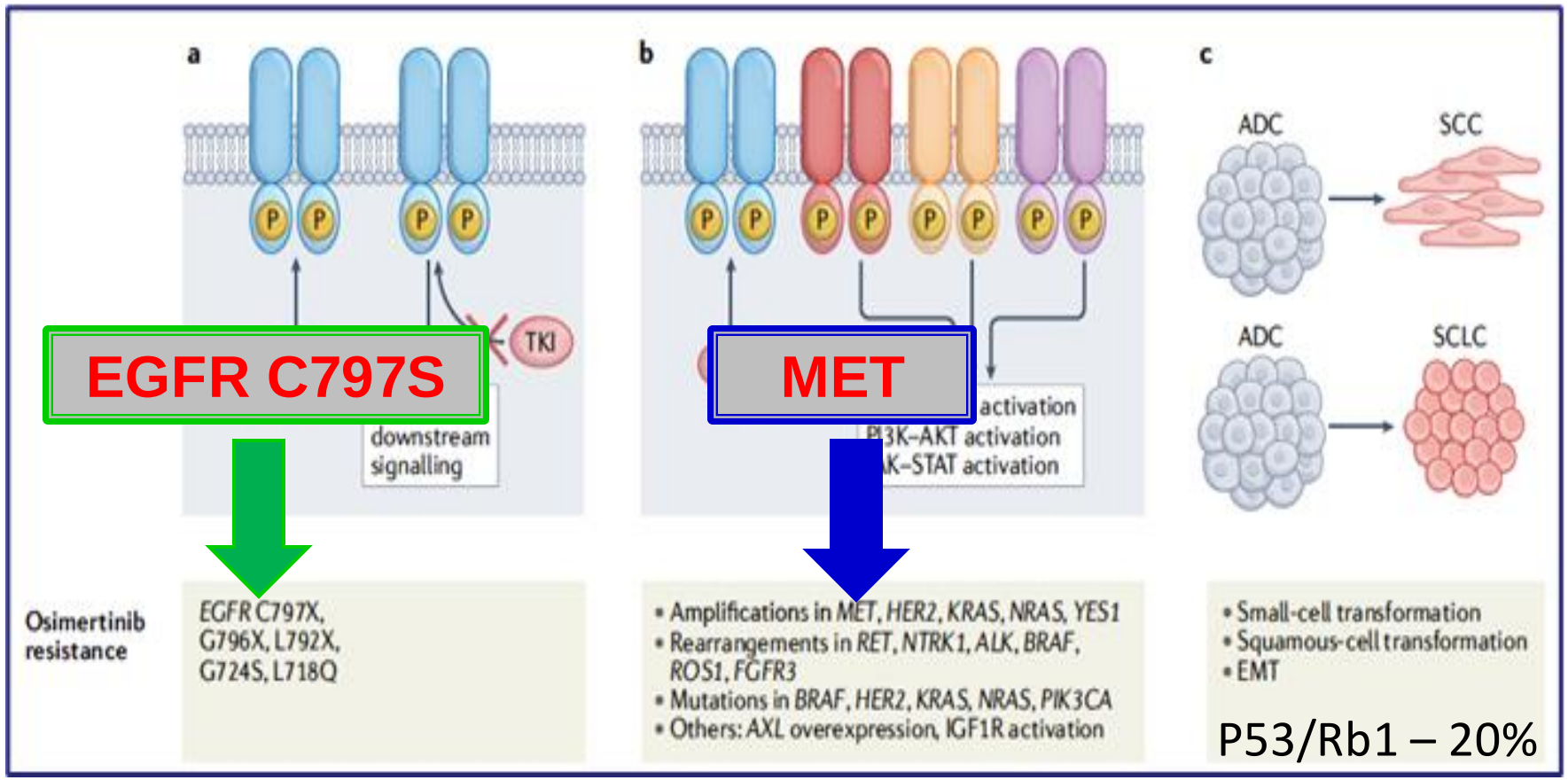
Combination therapy may prevent acquired resistance to EGFR TKI monotherapy

Mechanisms of Osimertinib Resistance

On-Target: EGFR resistance mt

Off-Target: Diverse Bypass MOR

Histologic transformation

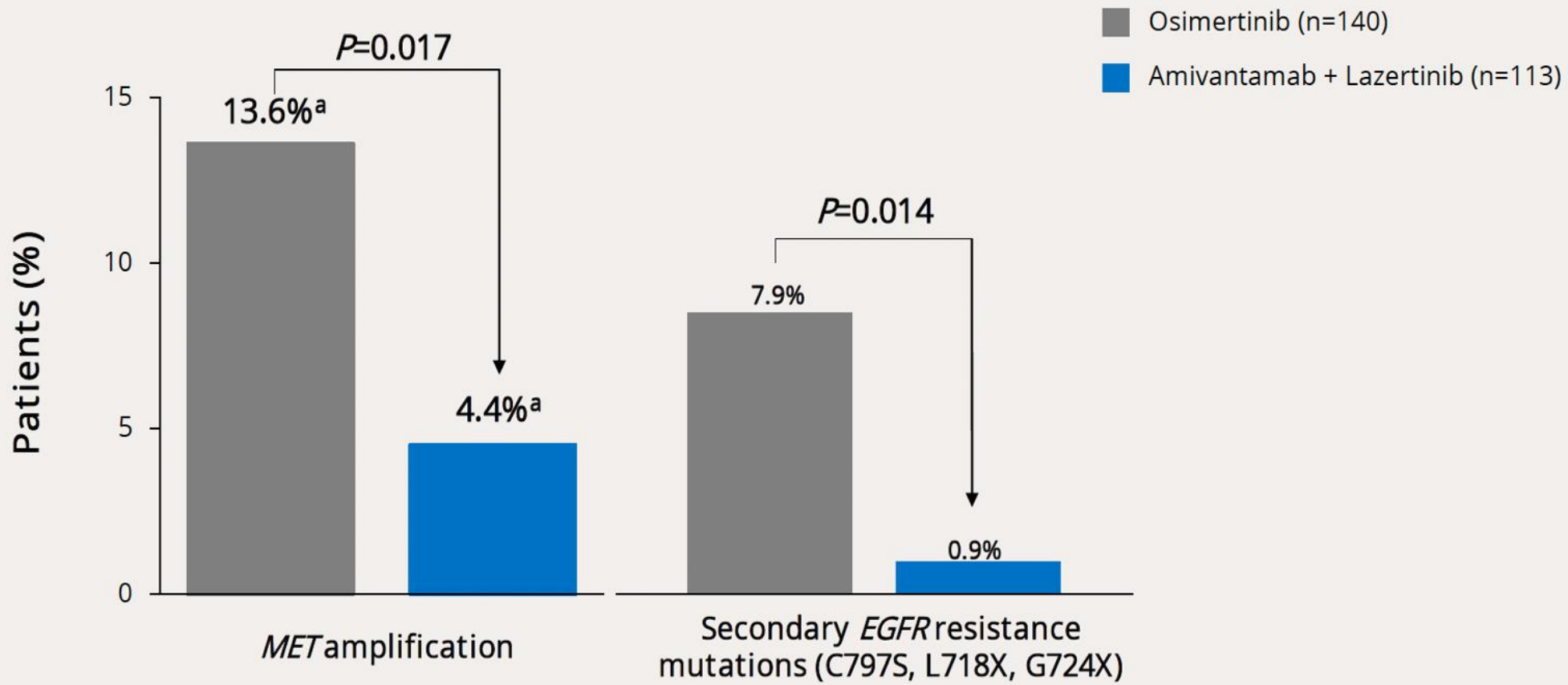


Cooper AS, et al, Nat Rev Clin Oncol 2022

MET and *EGFR*-based Resistance Mechanisms

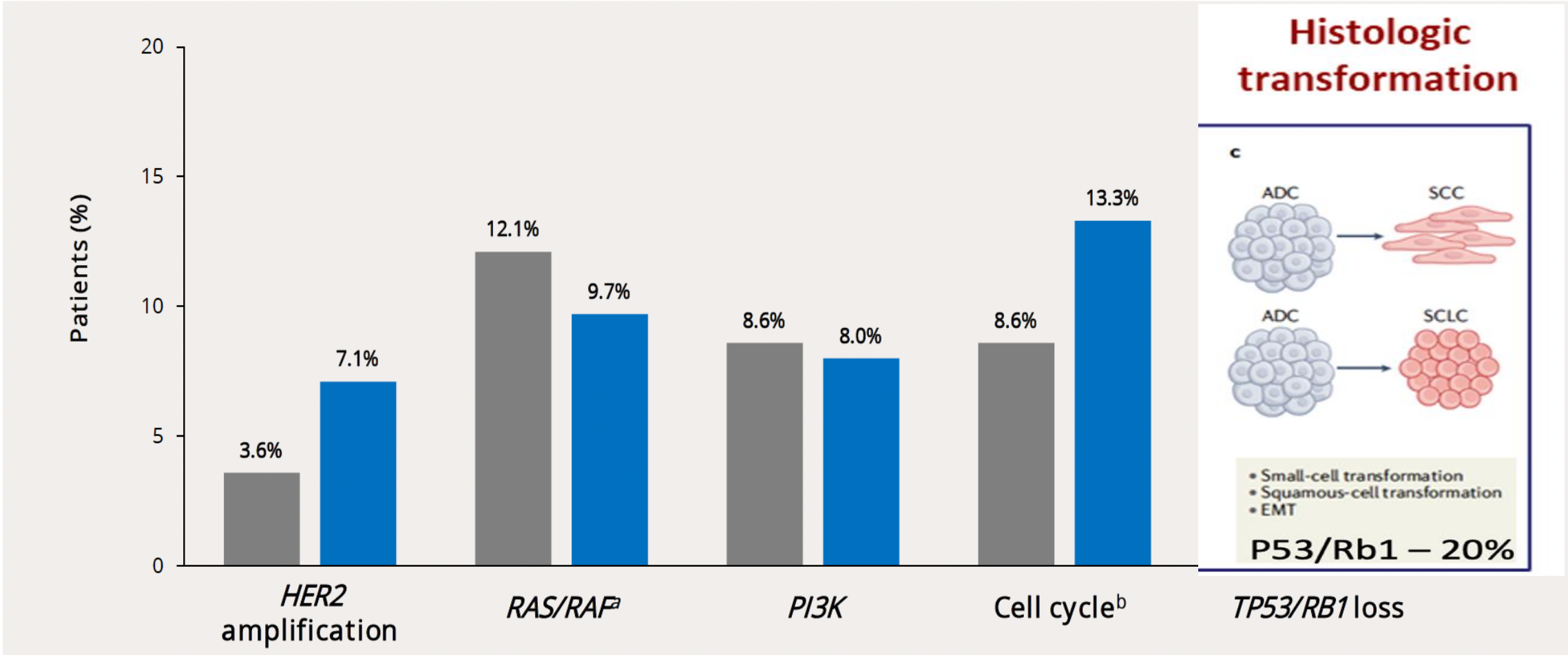
MARIPOSA
Ami + Laz in
1L *EGFR*+ NSCLC

Amivantamab + lazertinib significantly reduced the incidence of acquired MET amplifications and EGFR resistance mutations vs osimertinib



MET and *EGFR* Independent Resistance Mechanisms

No statistically significant differences were seen between arms for other resistance mechanisms



Unanswered questions

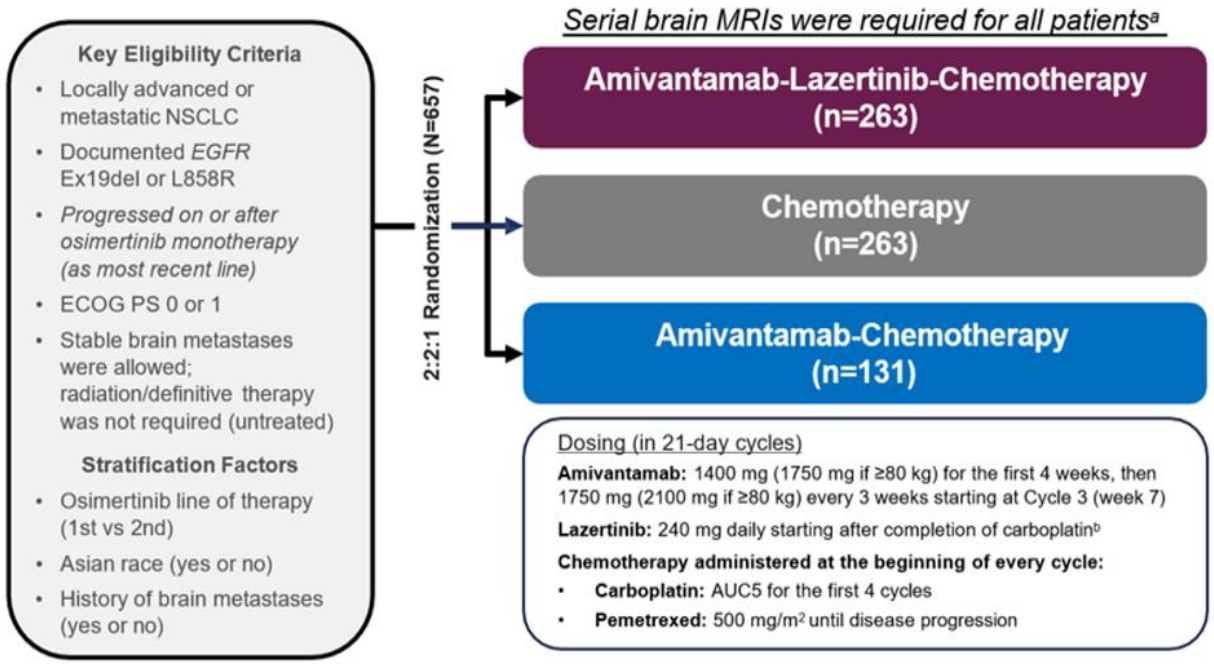
First-Line Therapy	MRD	Second-Line Therapy	Third-Line and Later
• **Do all patients need upfront combination therapy?**		• **Is there a biomarker to select among current and/or emerging 2L options?**	• How can we address the challenges of increasing tumor heterogeneity and histologic transformation?
• **To what extent will intensify up-front therapy translate to survival benefit?**		• Is an 'all-comers' strategy the best approach?	• How to prevent emergence of resistance in the CNS?
• How will perioperative therapy change options at disease relapse?		• When is an EGFR TKI needed post-progression?	• Will ADC sequencing be feasible?
• How to apply novel regimens to uncommon EGFR mutations?			

Can targeting residual disease pharmacologically or with local ablative therapy improve survival?

Julia Rotow, MD. IASLC Targeted Therapy in Lung Cancer 2025. Huntington Beach, CA. February 19-22, 2025

Only Regimen Approved After Osimertinib Progression:

MARIPOSA-2: Phase 3 Study Design



Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:

- **Amivantamab-Lazertinib-Chemotherapy** vs **Chemotherapy**
- **Amivantamab-Chemotherapy** vs **Chemotherapy**

Secondary endpoints:

- Objective response rate (ORR)[c]
- Duration of response (DoR)
- Overall survival (OS)[c]
- Intracranial PFS
- Time to subsequent therapy[d]
- PFS after first subsequent therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

MARIPOSA-2 (ClinicalTrials.gov Identifier: NCT04988295) enrollment period: December 2021 to April 2023; data cut-off: 10-Jul-2023

[a]Patients who could not have MRI were allowed to have CT scans.
[b]All patients randomized before 7Nov2022 initiated lazertinib on the first day of Cycle 1 (see next slide).
[c]Key statistical assumptions: 600 patients with 350 events across all 3 arms would provide approximately 83% and 93% power for amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy, respectively, vs chemotherapy to detect a HR of 0.65 using a log-rank test, with an overall two-sided alpha of 0.05 (median PFS of 8.5 months for amivantamab-containing arms vs 5.5 for chemotherapy). Statistical hypothesis testing included PFS, ORR, and then OS.
[d]These secondary endpoints (time to subsequent therapy, PFS2, and symptomatic PFS) will be presented at a future congress.

AUC, area under the curve; BICR, blinded independent central review; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletions; HR, hazard ratio; IDMC, independent data monitoring committee; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

BREAKING NEWS

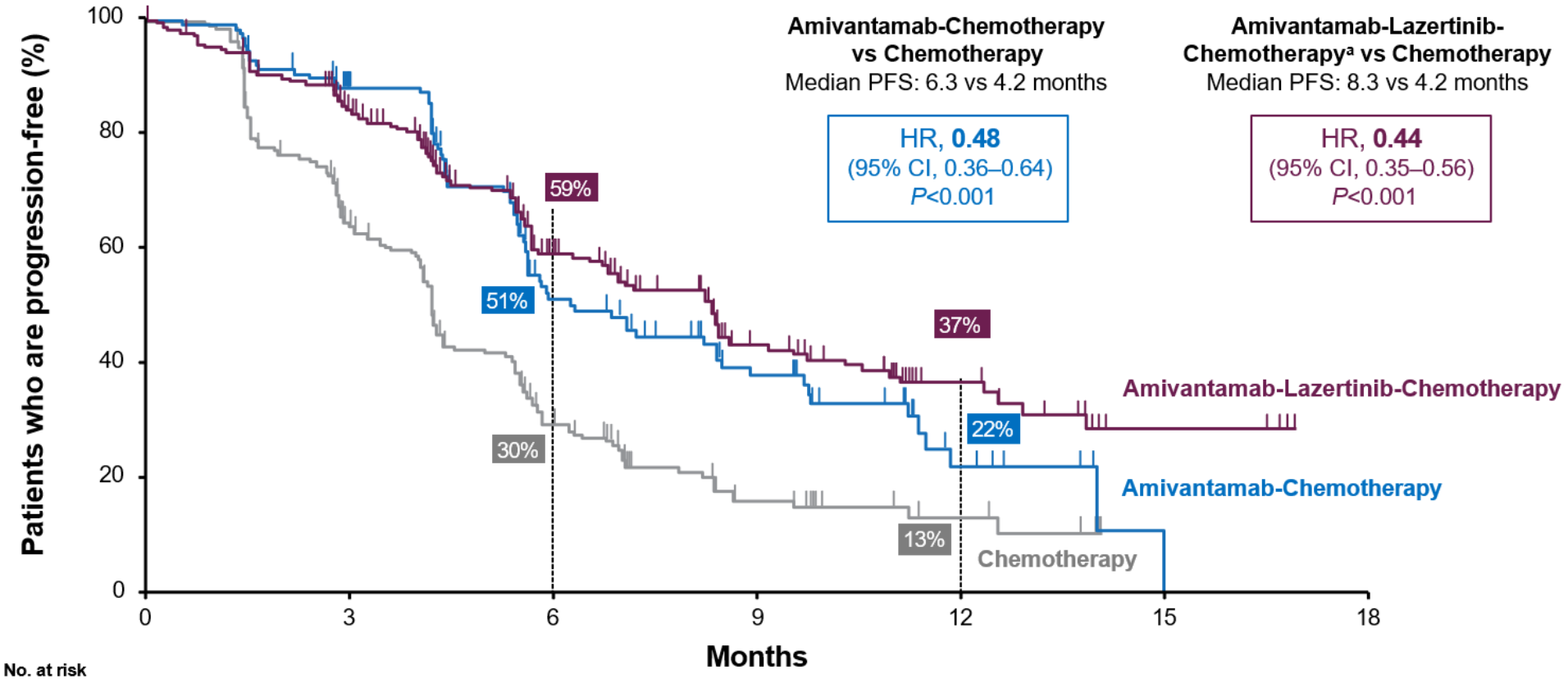
Approved on September 19, 2024

Amivantamab Plus Chemo Approved by FDA in EGFR-Mutated NSCLC

Results from the MARIPOSA-2 trial led to the approval of amivantamab plus chemotherapy in patients with *EGFR*-mutated NSCLC.

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



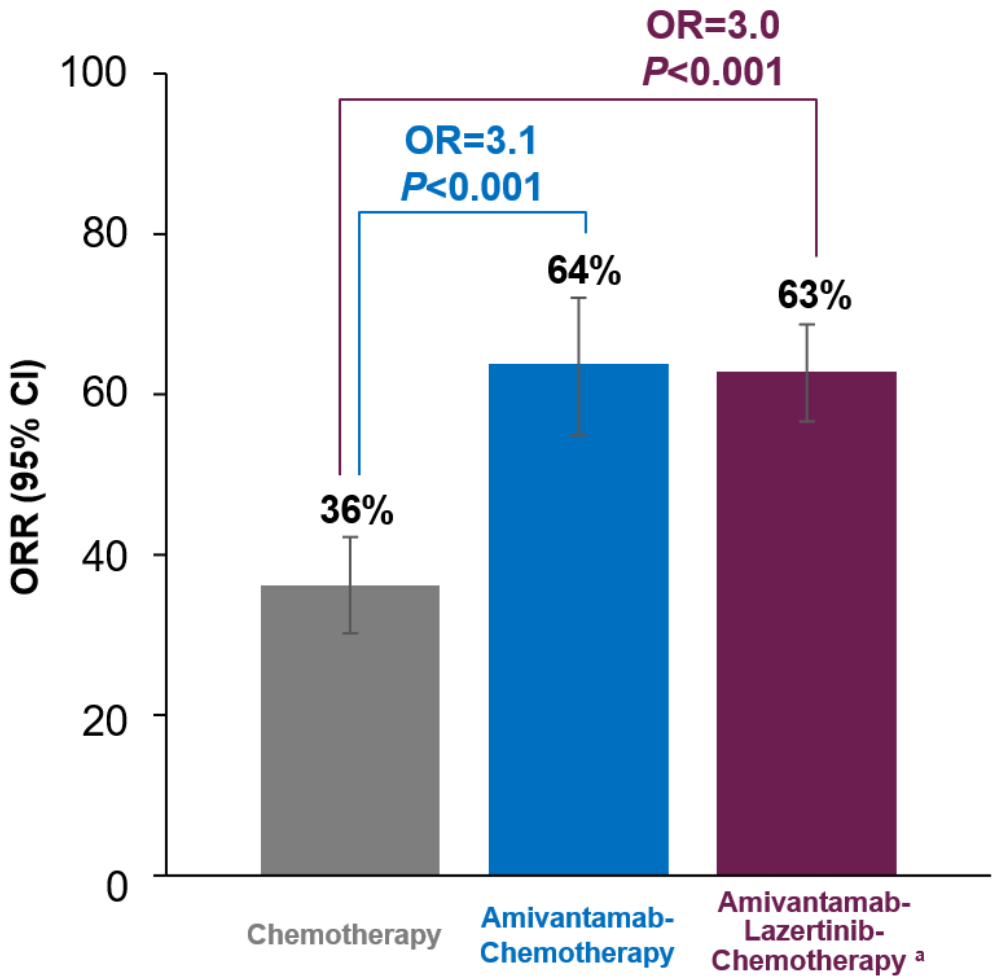
No. at risk						
Amivantamab-Chemotherapy	131	99	49	27	7	0	0
Amivantamab-Lazertinib-Chemotherapy	263	194	104	52	21	4	0
Chemotherapy	263	135	49	17	6	0	0

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])

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

ORR and DoR by BICR



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)

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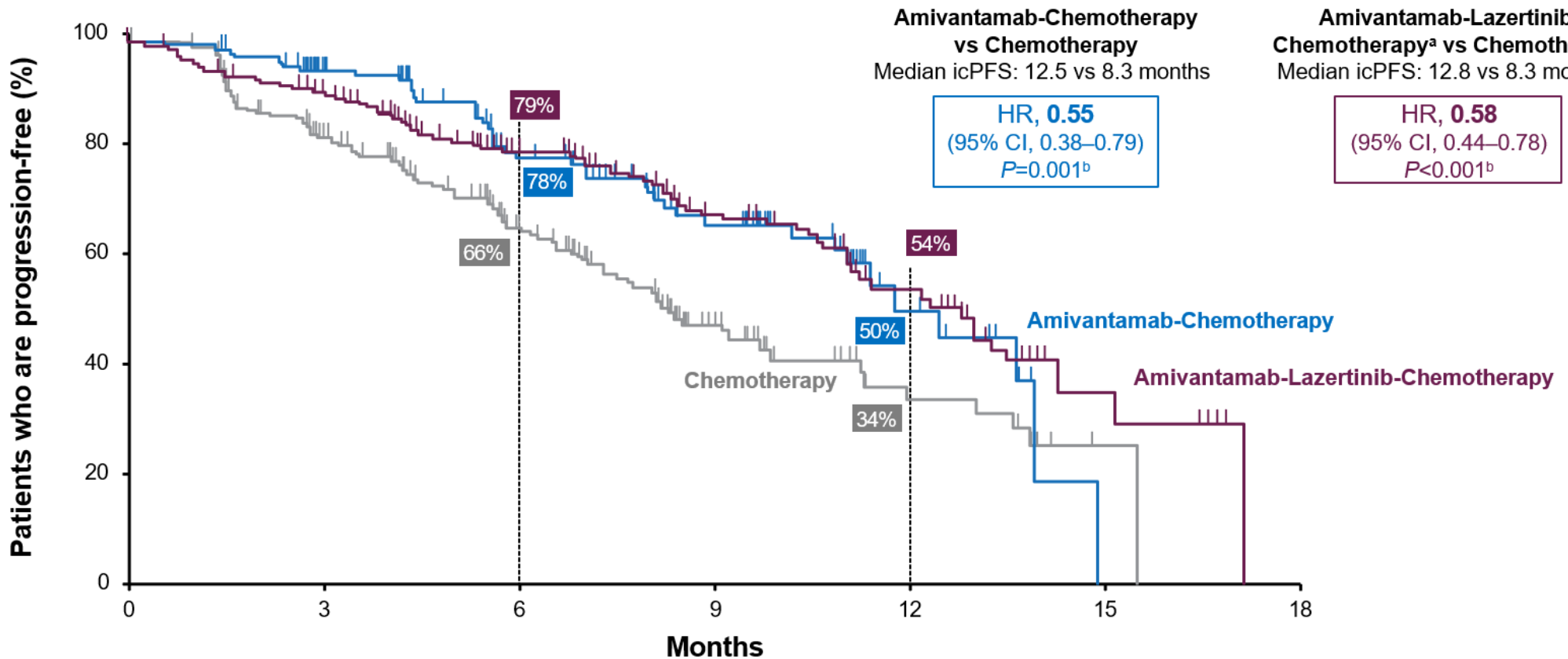
[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]No. of patients with measurable disease at baseline by BICR was 260 for chemotherapy, 130 for amivantamab-chemotherapy, and 259 for amivantamab-lazertinib-chemotherapy. [c]Among confirmed responders.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; mo, months; NE, not estimable; NE/UNK, not evaluable/unknown; OR, odds ratio; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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



No. at risk							
Amivantamab-Chemotherapy	131	103	72	40	11	0	0
Amivantamab-Lazertinib-Chemotherapy	263	211	135	74	32	6	0
Chemotherapy	263	167	89	37	13	1	0

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[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; icPFS, intracranial progression-free survival.

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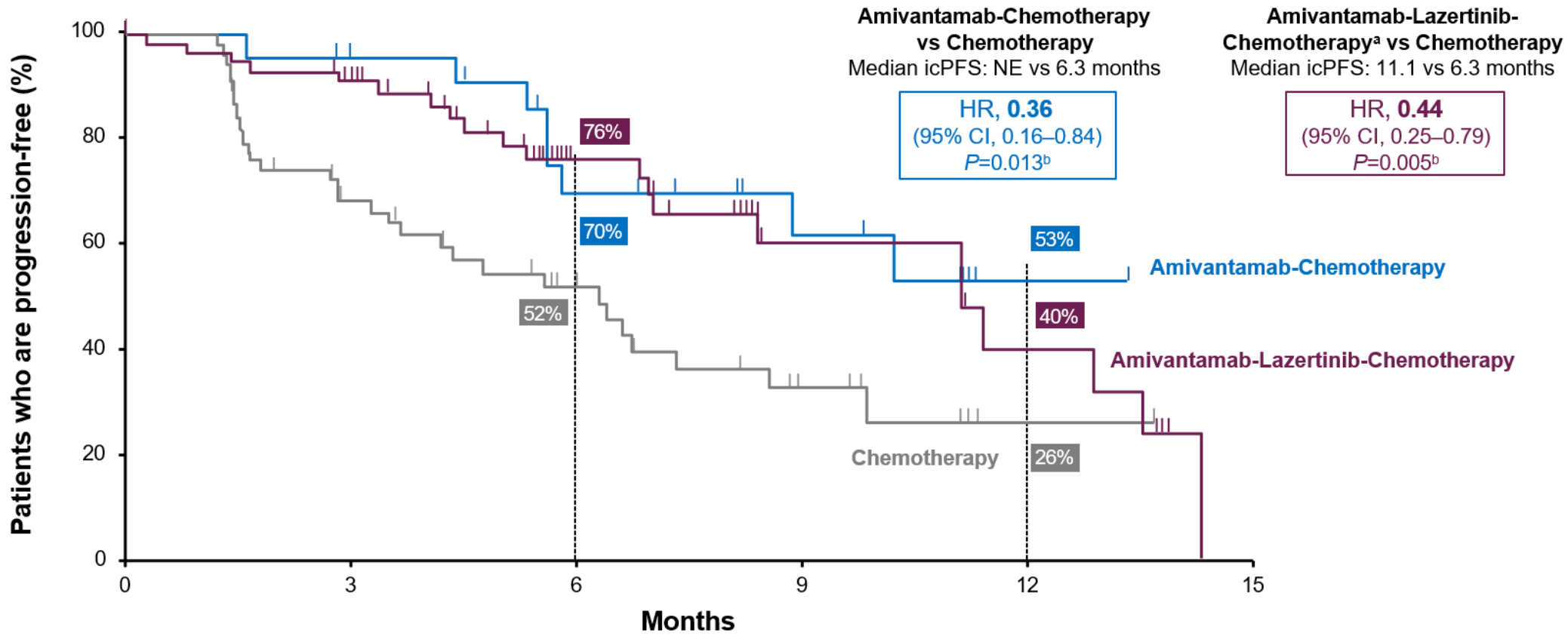
Intracranial Progression-free Survival by BICR Among Patients With a History of Brain Metastases and No Prior Brain Radiotherapy



No. at risk						
Amivantamab-Chemotherapy	24	20	13	8	1	0
Amivantamab-Lazertinib-Chemotherapy	56	42	22	10	5	0
Chemotherapy	61	32	17	7	1	0

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[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; icPFS, intracranial progression-free survival; NE, not estimable.

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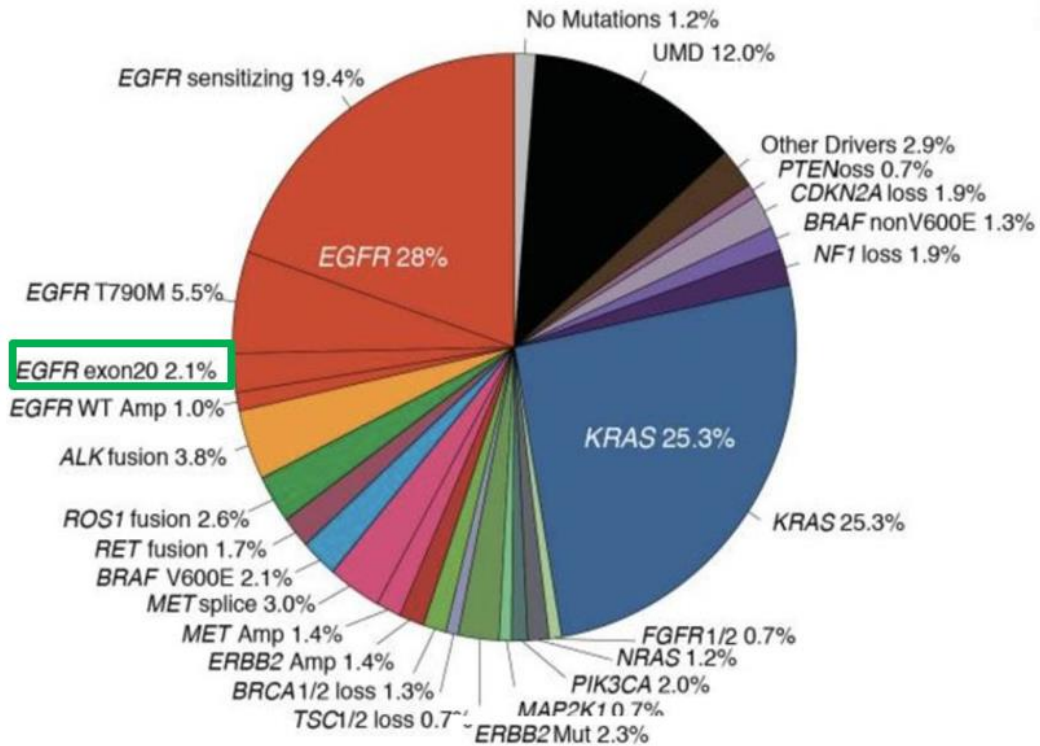
EGFR Pathway
Exon 20 Insertion

FIRST-LINE THERAPY[iii]

***EGFR* exon 20 insertion mutation** →

- **Amivantamab-vmjw + carboplatin/ pemetrexed[rr] (nonsquamous) (category 1) (preferred)**
- **or**
- **Systemic Therapy[s] Adenocarcinoma (NSCL-K 1 of 5)**
- **or**
- **Squamous Cell Carcinoma (NSCL-K 2 of 5)**



NCCN Version 3.2025, 1/14/25

What is coming?

Sunvozertinib
Zipalertinib
Firmonertinib
YK-029A

Sunvozertinib

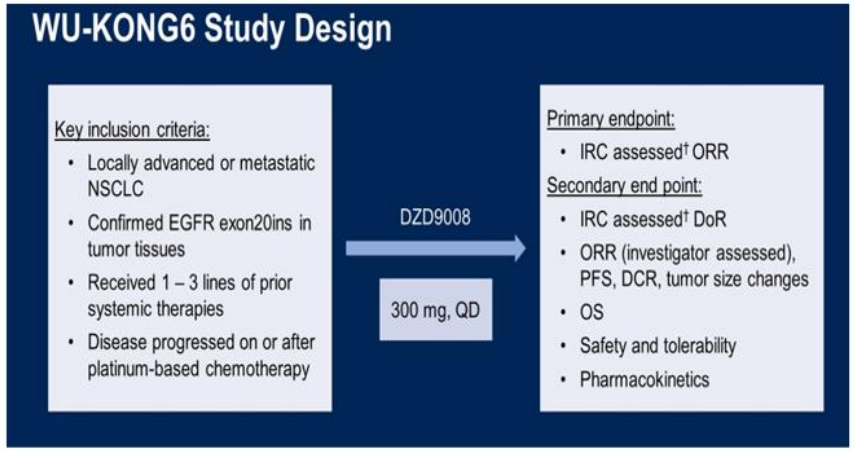
WU-KONG6

2023 ASCO ANNUAL MEETING

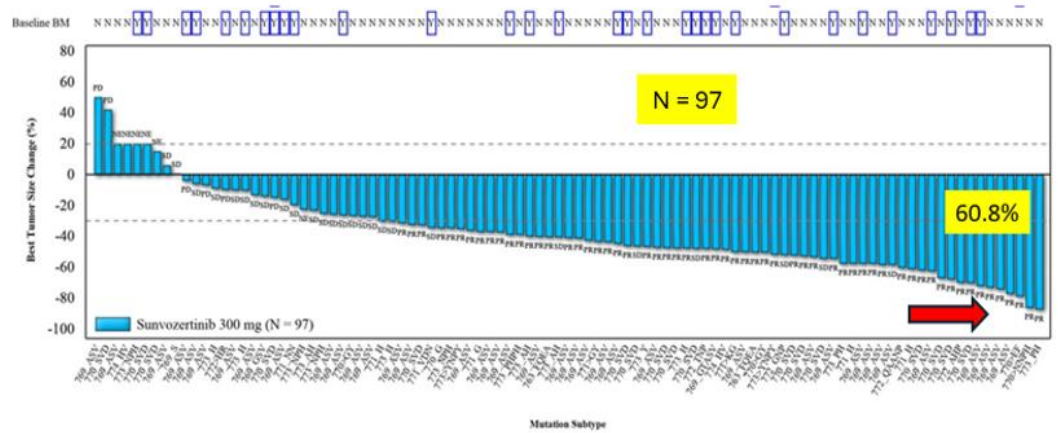
Sunvozertinib for the Treatment of NSCLC with *EGFR* Exon20 Insertion Mutations: the First Pivotal Study Results

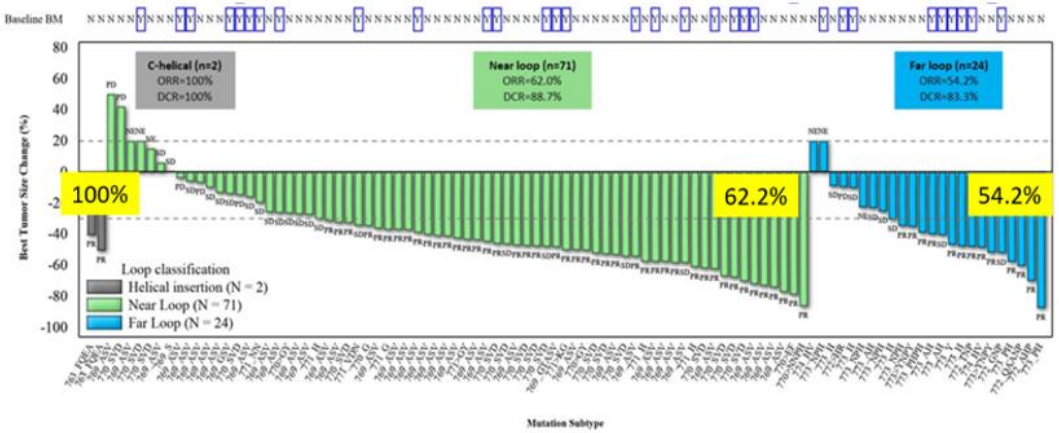
Mengzhao Wang[1], Yun Fan[2], Meili Sun[3], Yongsheng Wang[4], Yanqiu Zhao[5], Bo Jin[6] Ying Hu[7], Zhigang Han[8], Xia Song[9], Anwen Liu[10], Kejing Tang[11], Cuimin Ding[12], Li Liang[13], Lin Wu[14], Junzhen Gao[15], Jianghong Wang[16], Ying Cheng[17], Jianying Zhou[18] Yong He[19], Li Zheng[20]

WU-KONG6 Study Design



Wang. M et al ASCO 2023





Wang. M et al ASCO 2023

Update ESMO 2024
N=107
ORR 53.3%
CR 3 pts (4.8%)

WU-KONG28

A phase III, multinational, randomized study WU-KONG28
Sunvozertinib vs chemotherapy as first line treatment
for *EGFR* exon20ins NSCLC ongoing

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Zipalertinib

Zipalertinib: REZILIENT1 Phase 1/2a cohorts: 100 mg bid

	<65 mg (N=23)	100 mg (N=39)	150 mg (N=11)	Total (N=73)
ORR	8 (35%)	16 (41%) ★	4 (36%)	28 (38%)
Median PFS	8 mo	12 mo ★	8 mo	10 mo
Gr3+ Rash	0	0	1 (9%)	1 (1%)
Gr3+ Diarrhea	0	0	2 (18%)	2 (3%)
Dose Reductions	2 (9%)	5 (13%)	3 (27%)	10 (14%)
Dose Discontinuations	2 (9%)	2 (5%)	2 (18%)	6 (8%)

BARCELONA 2024 ESMO congress

REZILIENT1

Pivotal Phase 2b cohorts

Prior chemo only

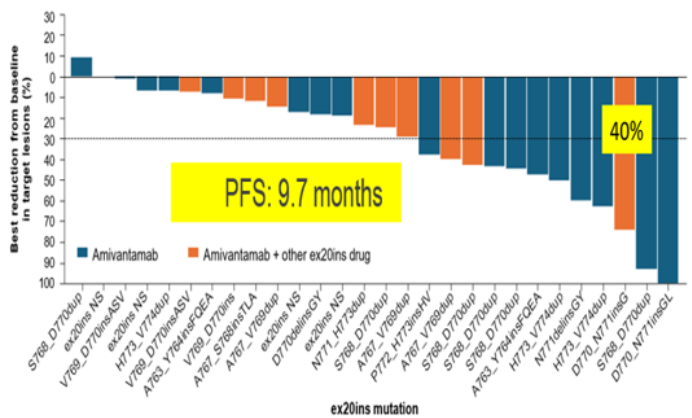
Prior chemo + approved ex20 treatment

Prior chemo + amivantamab

Primary endpoint: ORR

Ongoing Phase 3:
Zipalertinib + chemo vs chemo

Zipalertinib in NSCLC Patients With EGFR Exon 20 Insertion Mutations Who Received Prior Amivantamab



Putting it all together→Summary:

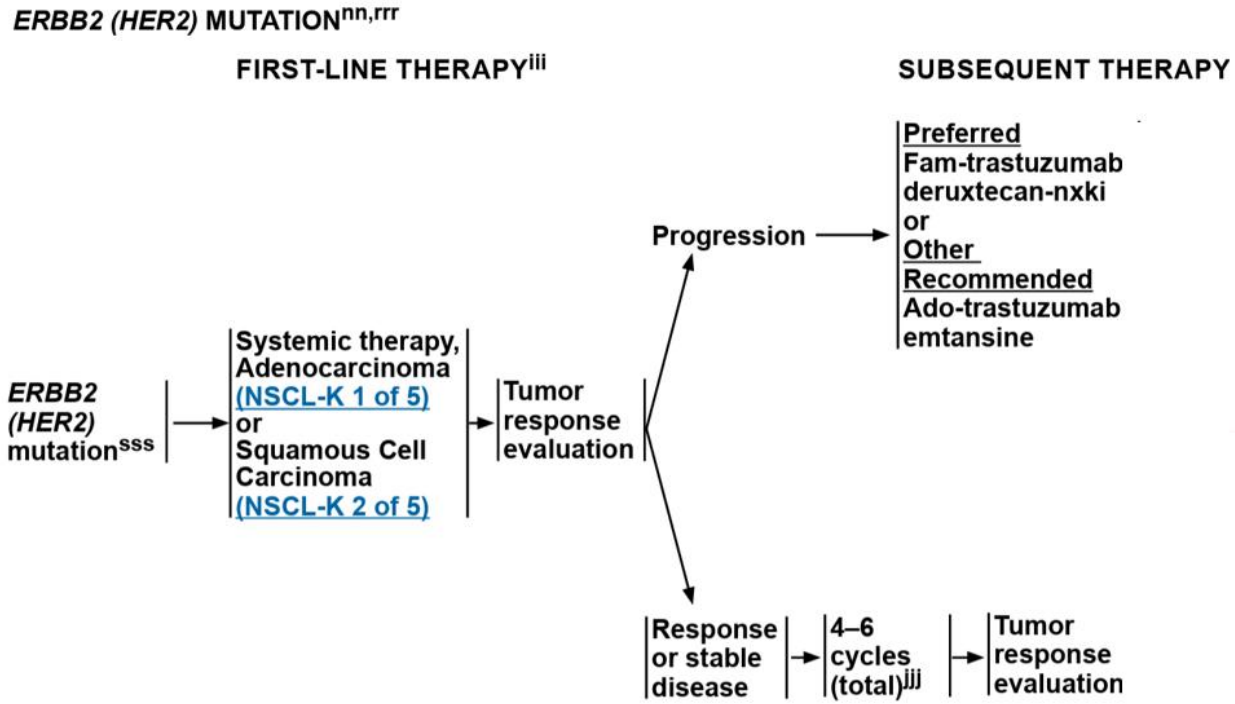
Drug Name	Trial Phase	N	ORR%	ORR% T Naive	CR	PFS	Toxicity	Toxicity Grade 3
Amivantamab + Chemotherapy	III	153 All TN	73	73	4	11.4 months	Neutropenia 59% Rash 54%	75%
Sunvozertinib	I/II	97	60.8	0	3 ✦	> 4 months	Diarrhea 53.9% Rash 40.2%	33.3%
Zipalalertinib	I/II	73	40	0	1 ✦	10 months	Diarrhea 53.9% Rash 80%	0%
Firmonertinib	I	80 30 TN	54.4	78.6	0	63% at 6 months	Diarrhea26.4%, Rash 26.4% Anemia 43%	0%
YK-029A	I	28 All TN	73.1	73.21	0	9.3 months	Diarrhea 49.1% Rash 34.3% Anemia 50.9%	38%

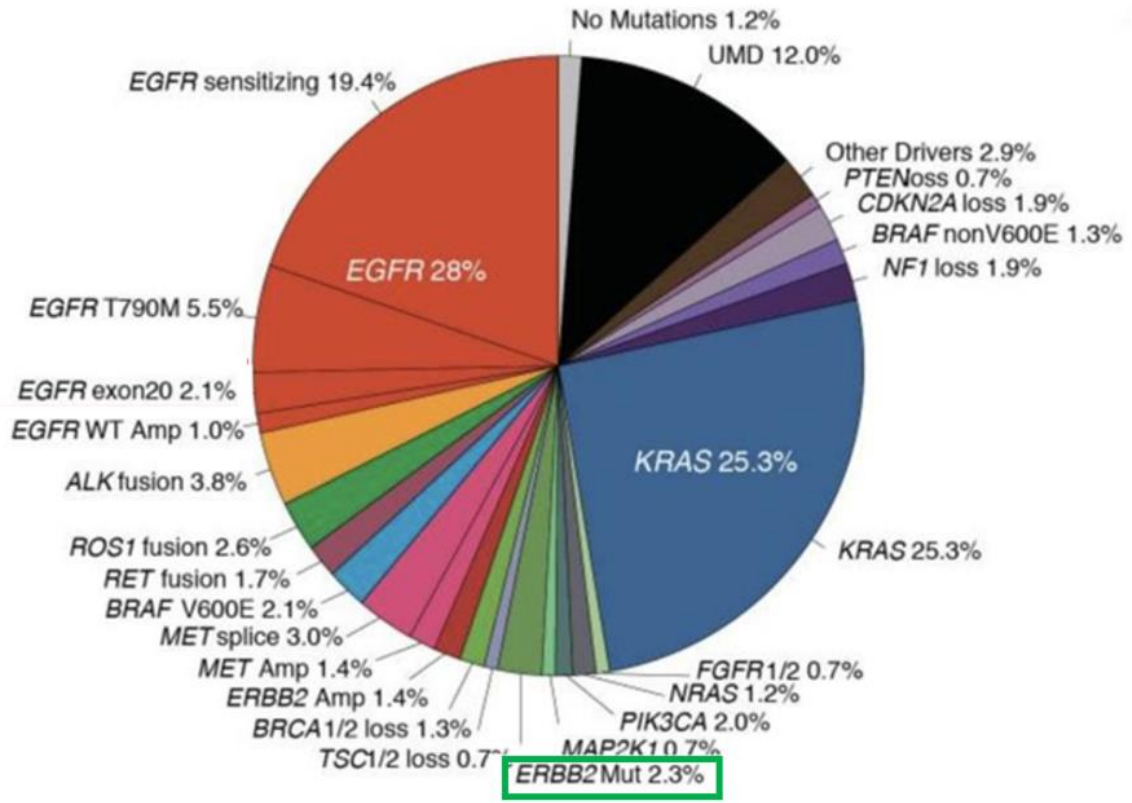
Barbara Melosky, MD. IASLC Targeted Therapy in Lung Cancer 2025. Huntington Beach, CA. February 19-22, 2025

ESMO 2024 ✦

EGFR Pathway

ERBB2 | HER-2 mutation





NCCN Version 3.2025, 1/14/25

Zongertinib (Beamion LUNG1)

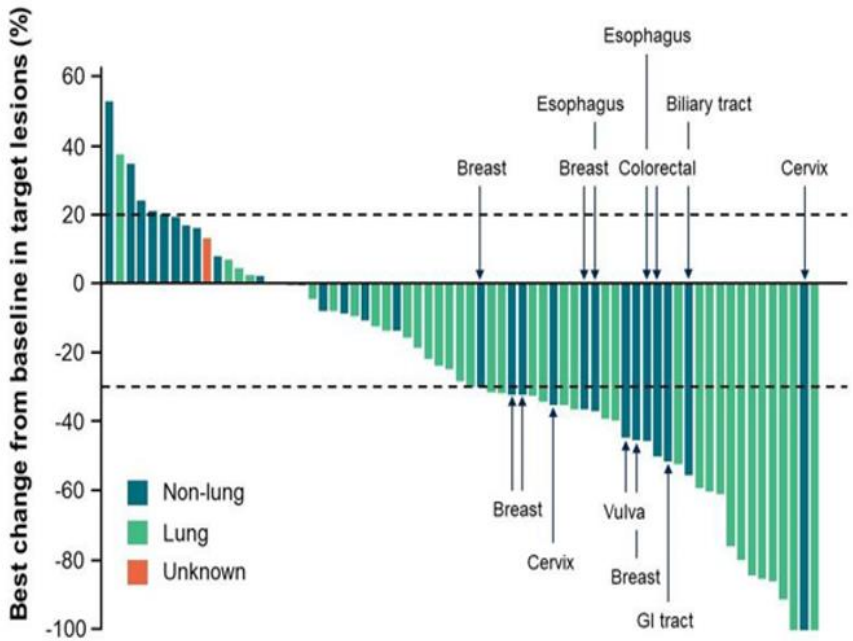
HER2 covalent, selective TKI ($EGFR_{wt}$-sparing)

Key inclusion criteria

HER2 aberration: overexpression, amplification, somatic mutation, or gene rearrangement involving *HER2* or *NRG1*

Ph 1a: Dose-escalation in solid tumors

NSCLC cohort – ORR 44%



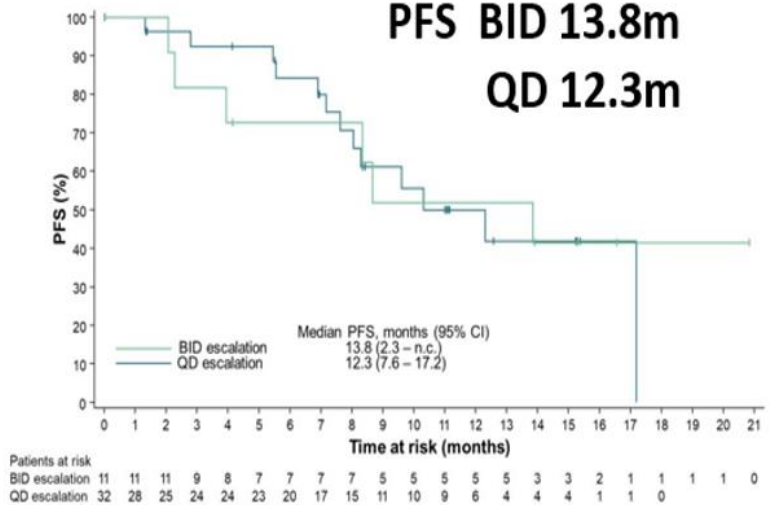
Ph 1a: Safety

TRAEs (%)	Total (N=83)	
	All grades	G≥3
Any TRAE*	**75.9**	**9.6**
Diarrhea	42.2	1.2
Rash†	12.0	0.0
Decreased appetite	9.6	0.0
ALT increased	8.4	3.6
AST increased	8.4	1.2
Anemia	8.4	0.0
Fatigue	8.4	0.0
Dysgeusia	7.2	0.0
Paronychia	7.2	0.0
Dry skin	6.0	0.0
Nausea	6.0	0.0

Ph 1a: Efficacy

PFS BID 13.8m

QD 12.3m



Zongertinib (Beamion LUNG1)

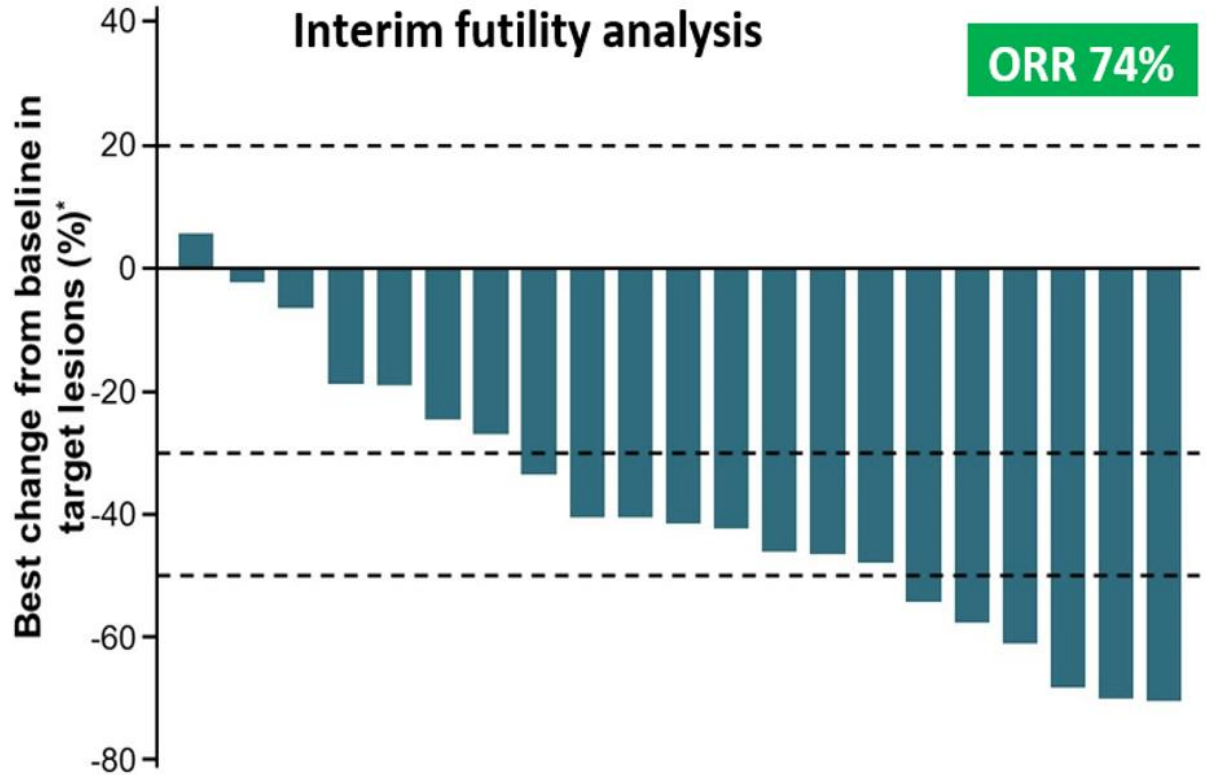
HER2 covalent, selective TKI ($EGFR_{wt}$-sparing)

Ph 1b: Dose-expansion in NSCLC

Cohort 1:	Pre-treated NSCLC‡ with a *HER2* TKD mutation
Cohort 2:	Treatment-naïve NSCLC with a *HER2* TKD mutation
Cohort 3:	NSCLC with a non-TKD *HER2* mutation or *HER2* TKD mutation-positive squamous NSCLC, pre-treated
Cohort 4:	NSCLC with active brain metastases with a *HER2* TKD mutation
Cohort 5:	NSCLC with a *HER2* TKD mutation and prior treatment with HER2 directed ADCs

Ph 1b: Cohort 1 (no prior ADC)
Interim futility analysis

ORR 74%



Beamion LUNG-2 (1st line) zongertinib vs SOC TBD

Zongertinib receives Priority Review from U.S. FDA for the treatment of HER2 (ERBB2)-mutant advanced NSCLC.

Ridgefield, Conn., U.S., and Ingelheim, Germany, **Wed, 02/19/2025.**

- Zongertinib would be the **first orally administered**, targeted therapy for previously treated patients with HER2 (*ERBB2*)-mutant advanced non-small cell lung cancer (NSCLC), if approved.

- The application for this investigational treatment is based on positive results from the **Phase Ib Beamion LUNG-1**, Cohort 1 trial that demonstrated an objective **response rate of 71% in 75 previously treated patients** with advanced NSCLC.

- HER2 (*ERBB2*)-mutant advanced NSCLC is linked to poor prognosis and currently has limited treatment options·

HER2 NSCLC: Several novel agents under clinical investigation

HER2-selective TKI/small molecule	
ELVN-002	NCT05650879
NVL-330	NCT06521554
IAM1363	NCT06253871

EGFR and HER2 targeting TKI	
Furmonertinib	NCT05364073
BH-30643	NCT06706076
ORIC-114	NCT05315700
STX-721	NCT06043817
FWD1509	NCT05068024

HER2 ADC (solid tumors)	
DT-1303/BNT323	NCT05150691
GQ1001	NCT04450732
Disitamab Vedotin	NCT06003231

HER2 Bispecific AB, T/NK engagers, other (solid tumors)	
DF1001	NCT04143711
Zanidatamab	NCT06695845
XMT-2056	NCT05514717

Andrea Saltos, MD. IASLC Targeted Therapy in Lung Cancer 2025. Huntington Beach, CA. February 19-22, 2025

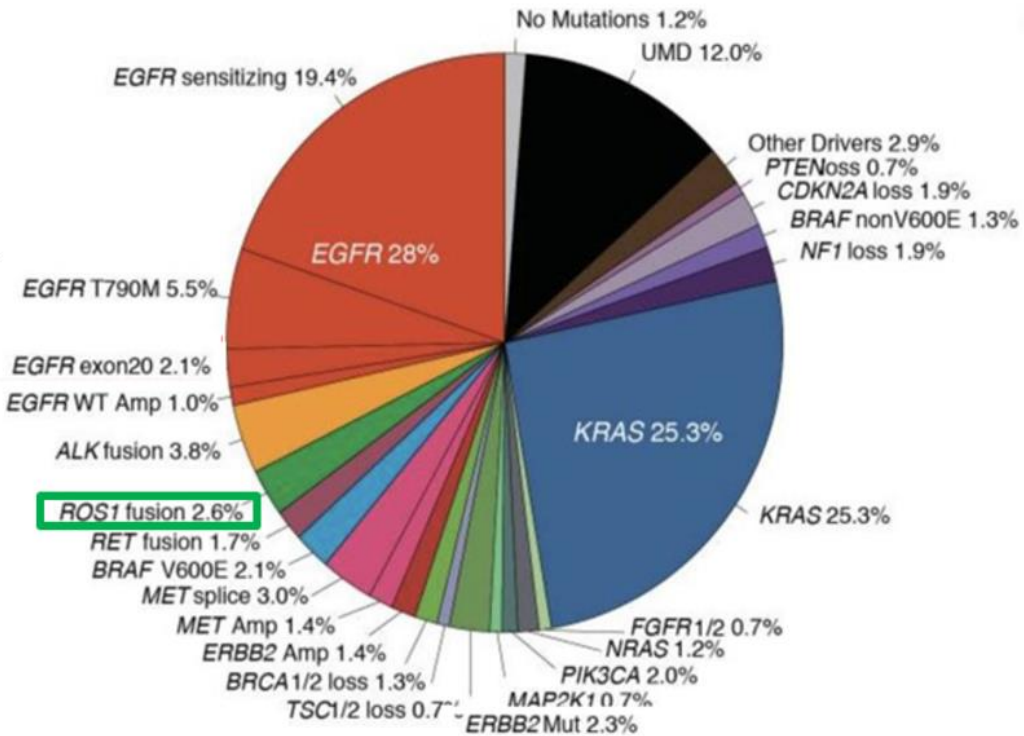
ROS1 Pathway

NCCN Version 3.2025, 1/14/25

FIRST-LINE THERAPY[rr]

***ROS1* rearrangement**

- ***ROS1* rearrangement discovered prior to first-line systemic therapy** → **Preferred**
  Crizotinib[ss]
  or
  Entrectinib[ss,ooo]
  or
  Repotrectinib[ss,ooo]
- ***ROS1* rearrangement discovered during first-line systemic therapy** → **Interrupt current therapy[xx] and start**
  Crizotinib (preferred) or
  Entrectinib[ooo] (preferred) or
  Repotrectinib[ooo] (preferred)



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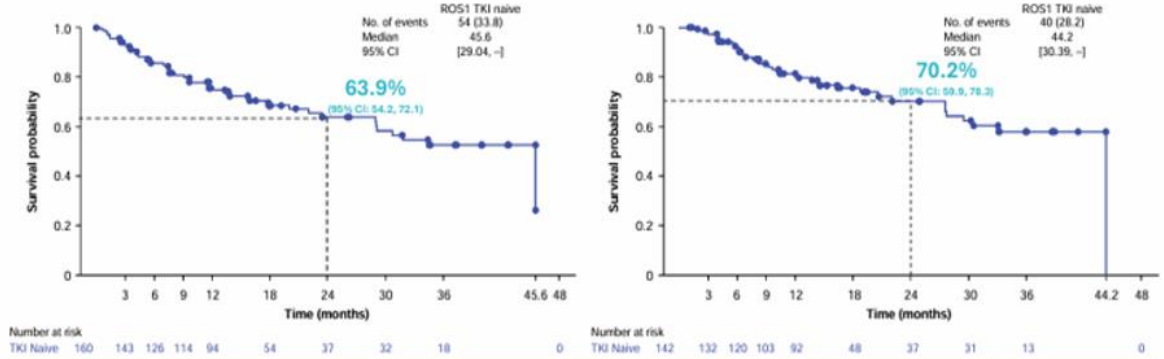
Taletrectinib in ROS1+ NSCLC (Phase 2; TRUST-1 Study):

Efficacy in TKI-Naive Patients

Median PFS: **45.6 months**
95% CI: 29.0, NR

Median DOR[a]: **44.2 months**
95% CI: 30.4, NR



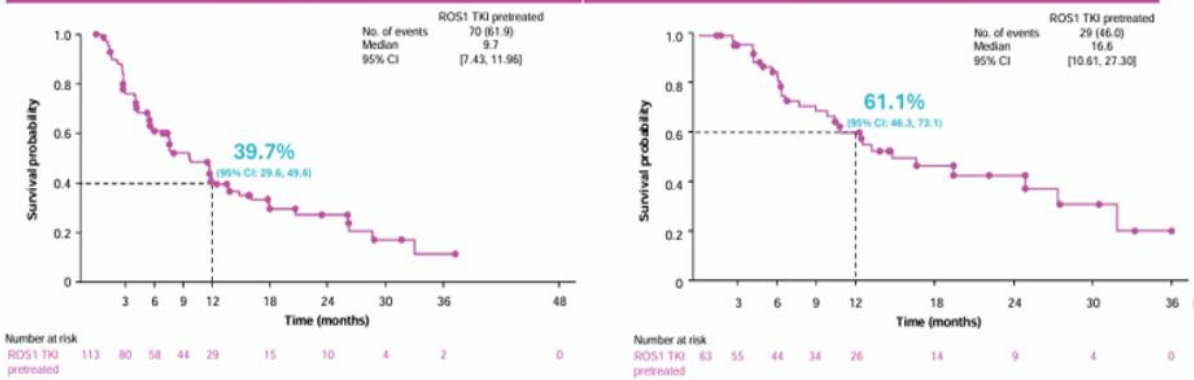
Median follow-up: **21.2 months**
(Range: 3.6–46.6)

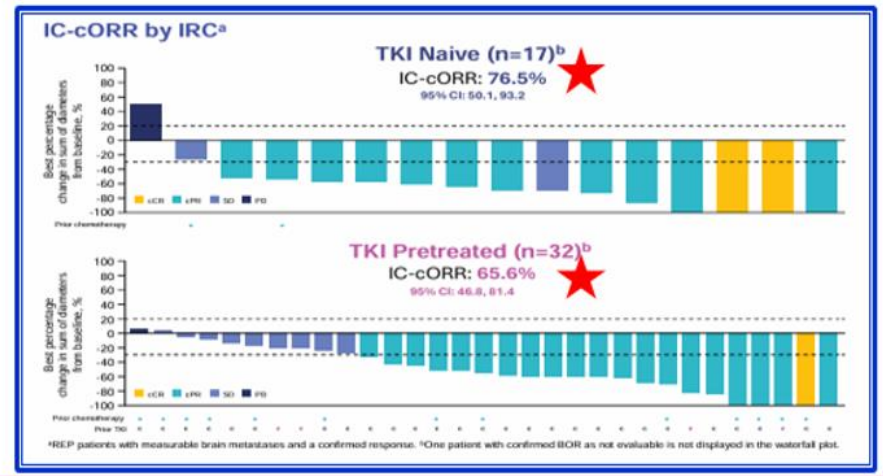
[a]REP patients with a confirmed objective response.

Efficacy in TKI-Pretreated Patients

Median PFS: **9.7 months**
95% CI: 7.4, 12.0

Median DOR[a]: **16.6 months**
95% CI: 10.6, 27.3





Conclusions

Integrated analysis from the TRUST-I and TRUST-II studies establishes taletrectinib as a potential best-in-class ROS1 TKI for people living with advanced ROS1+ NSCLC

- High and durable overall response rates were observed in both cohorts
- In TKI-naive patients, median DOR and median PFS were 44.2 months and 45.6 months, respectively
- In TKI-pretreated patients, median DOR and median PFS were 16.6 months and 9.7 months, respectively
- IC responses were robust in both cohorts, and G2032R response rates were high in TKI-pretreated patients
- Response rates were consistent among the subgroups analyzed

Taletrectinib demonstrated a favorable tolerability and safety profile in people living with advanced ROS1+ NSCLC

- TEAEs were mostly grade 1-2
- Rates of neurologic TEAEs were low (dizziness: 21.1%; dysgeusia: 14.5%), and most were grade 1
- Low incidence of discontinuations (6.5%) due to TEAEs

Overall, taletrectinib demonstrated a favorable benefit risk profile at the recommended phase 2 dose of 600 mg QD

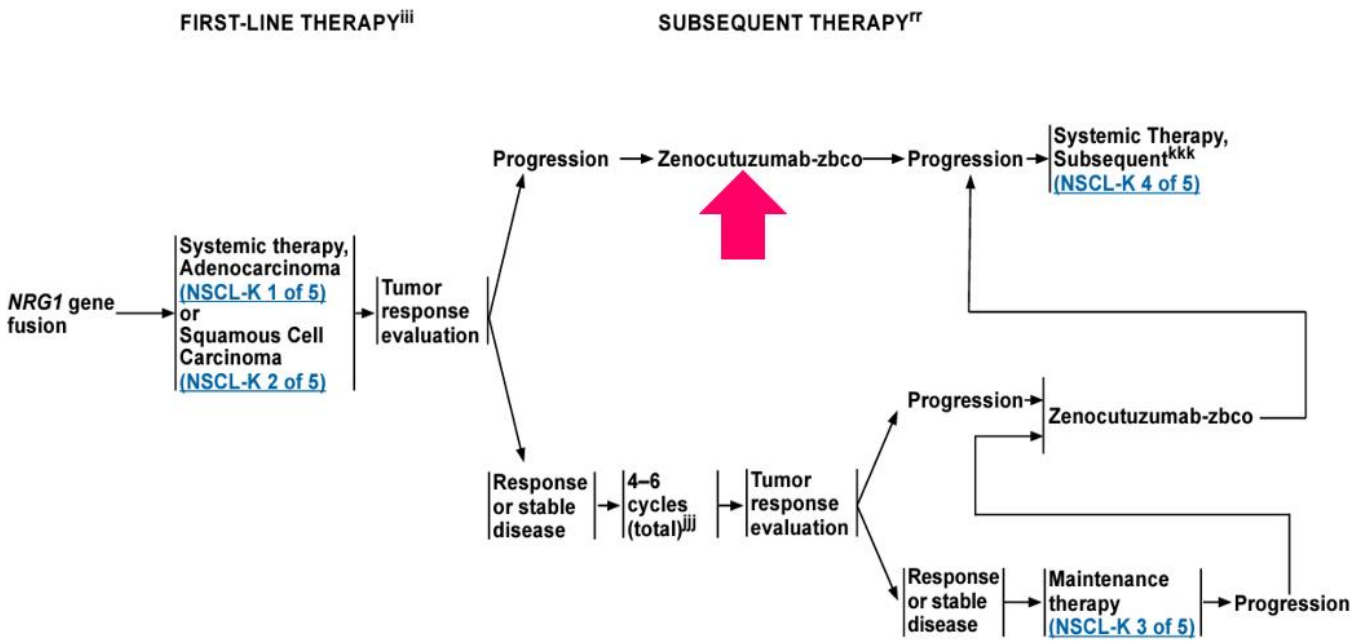
Maurice Perol et al. ESMO 2024, Barcelona, Spain.

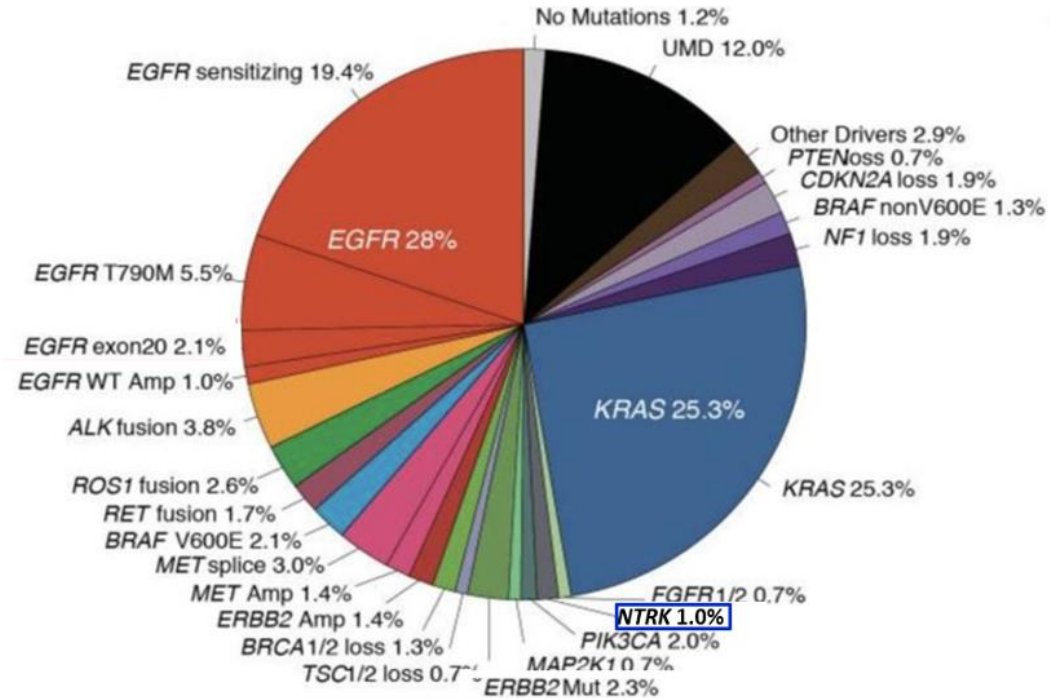
NRG1 Pathway

FDA grants accelerated approval to zenocutuzumab-zbco for non-small cell lung cancer and pancreatic adenocarcinoma

On December 4, 2024, the Food and Drug Administration granted accelerated approval to zenocutuzumab-zbco ( ) for adults with the following:

- advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy, or
- advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion with disease progression on or after prior systemic therapy.





NCCN Version 3.2025, 1/14/254

First-Line Targeted Therapies in NSCLC: What's New? Edgardo S. Santos, MD, FACP, FASCO. EddieSantosMD

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NRG1 Fusions Result in Increased Cell Signaling and Growth[1,2]

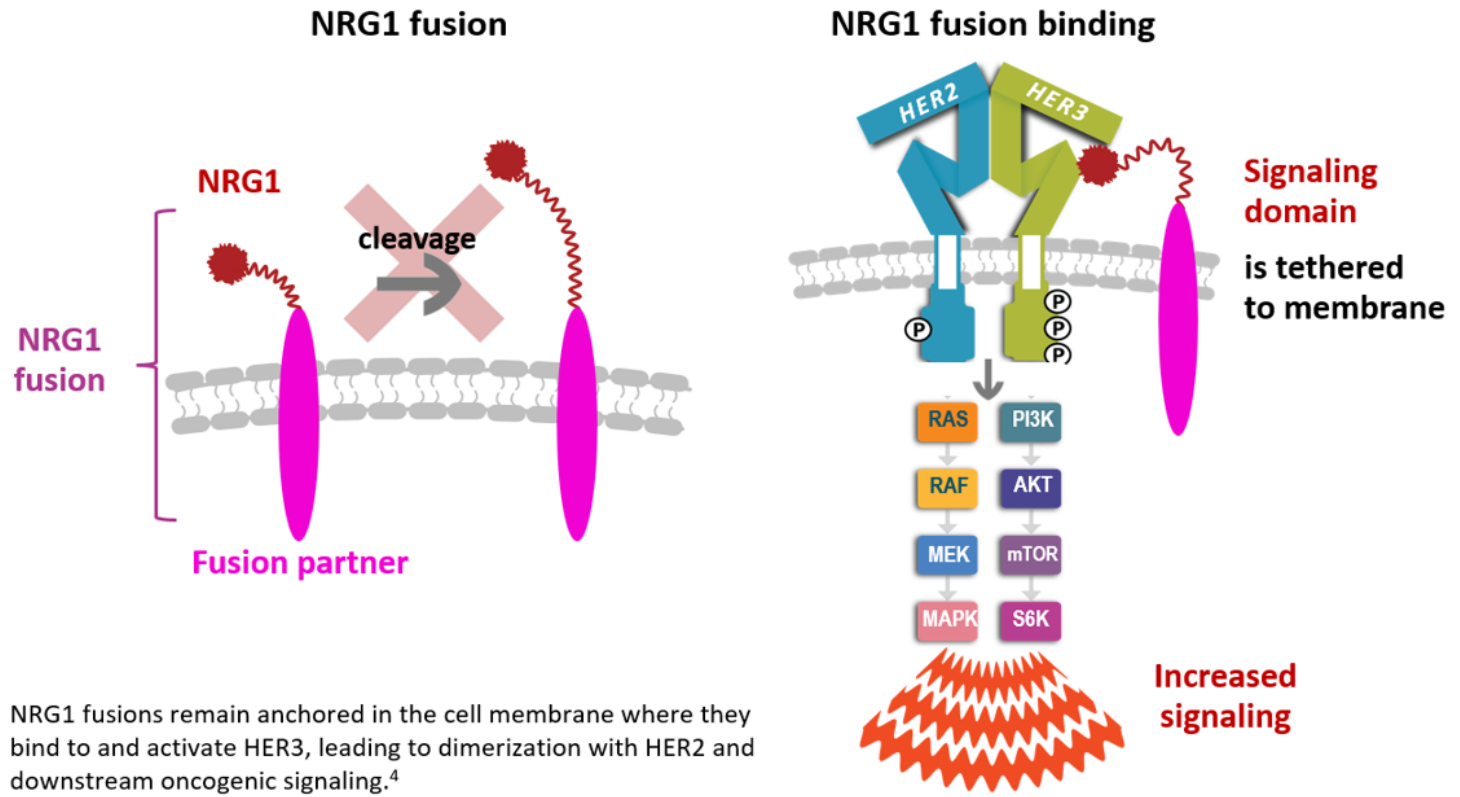
NRG1 fusions induce receptor dimerization and result in aberrant cell signaling[3,4]

NRG1 fusions

- Are heterogenous and have many different gene partners and breakpoints[5]
- **Cannot be cleaved by cell surface proteases** resulting in increased expression of the fusions at the cell surface[3]
- Retain the signaling domain of WT NRG1[4,6]

Certain NRG1 fusions are membrane bound resulting in increased cell signaling[4]

NRG1 Fusion Signaling



NRG1 fusions remain anchored in the cell membrane where they bind to and activate HER3, leading to dimerization with HER2 and downstream oncogenic signaling.[4]

1. Schram AM et al. *Cancer Discov*. 2022;12(5):1233-1247. doi:10.1158/2159-8290.CD-21-1119 **2.** Geuijen CAW et al. *Cancer Cell*. 2018;33(5):922-936. doi:10.1016/j.ccell.2018.04.003 **3.** Laskin J et al. *Ann Oncol*. 2020;31(12):1693-1703. doi:10.1016/j.annonc.2020.08.2335 **4.** Zhang C et al. *Biochim Biophys Acta Rev Cancer*. 2022;1877(3):188707. doi:10.1016/j.bbcan.2022.188707 **5.** Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307 **6.** Howarth KD et al. *Breast Cancer Res*. 2021;23(1):3. doi:10.1186/s13058-020-01377-5

NRG1+ Tumors Can Be Aggressive and Respond Poorly to Existing Standard of Care[1,2]

In a retrospective global registry study of 110 patients, *NRG1*+ NSCLC was associated with limited response to available therapies[3]

Activity of Systemic Therapy in *NRG1*+ NSCLC[3,*]

	ORR, %	Median PFS, mo (95% CI)
Platinum-doublet chemotherapy (n=15)	**13**	**5.8** (2.2-9.8)
Taxane-based chemotherapy (n=7)	**14**	**4.0** (0.8-5.3)
Combination chemotherapy and immunotherapy (n=9)	**0**	**3.3** (1.4-6.3)
Single-agent immunotherapy (n=5)	**20**	**3.6** (0.9-undefined)
Targeted therapy with kinase inhibitor (n=20)	**25**	**2.8** (1.9-4.3)

ORR, overall response rate.

*Patients either diagnosed with or who developed metastatic disease during the course of their disease.

1. Rosas D et al. *Cancers (Basel)*. 2021;13(20):5038. doi:10.3390/cancers13205038 **2**. National Institutes of Health, National Cancer Institute. Accessed April 24, 2023. https://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq **3**. Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802. doi:10.1200/JCO.20.03307

Schema

Global, Multicenter Zenocutuzumab NRG1+ Cancer Development Program

Ongoing phase 1/2 global, open-label clinical trial (eNRGy) + Early Access Program (EAP)

NSCLC, PDAC[a], and other solid tumors

Inclusion Criteria

- Locally advanced unresectable or metastatic solid tumor
- NRG1+ cancer
- Previously treated with or unable to receive standard therapy
- ≥ 18 years of age
- ECOG PS ≤ 2

Treatment Plan

- Zenocutuzumab 750 mg IV Q2W until PD
- Tumor assessment Q8W

Follow-up

Survival follow-up: up to 2 years

Endpoints and Population

Primary endpoint

Overall response rate (ORR)[b] using RECIST v1.1 per investigator assessment

Secondary endpoints

Duration of response (DOR)[c], ORR per central review, safety[d]

Primary analysis population

≥ 1 dose of zenocutuzumab, opportunity for ≥ 24 weeks follow-up at the data cutoff date, and met criteria for primary efficacy population

Enrollment and Analysis

Data cutoff date

July 31, 2023

Enrollment

105 patients with NRG1+ NSCLC

NSCLC primary analysis population

79 patients

87 patients with ≥ 24 weeks follow-up[e]; of them, 8 patients were excluded[f]

- 2 patients discontinued early for reasons not related to PD
- 2 patients with prior anti-HER3 inhibitor
- 2 patients with other genetic driver mutation
- 1 patient with concomitant anti-cancer medication use
- 1 patient with baseline scan > 5 weeks before first dose

AE, adverse event; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; Q2W, every 2 weeks; Q8W, every 8 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

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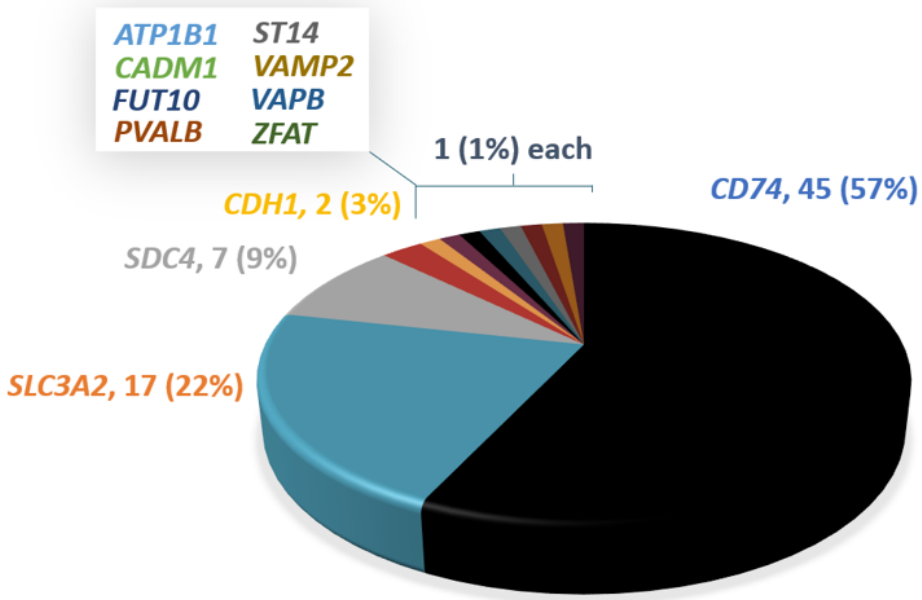
[a] Results from patients with NRG1+ PDAC are presented in **Poster 1618P**. [b] Defined as the proportion of patients with a best confirmed response of CR or PR per RECIST v1.1. [c] Defined as the time from date of first CR or PR to date of first PD or death due to trial indication. [d] AEs were coded using the MedDRA v25.0 and graded using CTCAE v4.03. [e] Patients received the first dose of treatment by 13 February, 2023, allowing for the opportunity of ≥ 24 weeks follow-up at data cut off date 31 July, 2023 [f] Per SAP

NRG1+ NSCLC Primary Efficacy Population

Demographics and Prior Therapy N = 79	
Age, years, median (range)	64 (32-88)
Male / female, n (%)	30 (38) / 49 (62)
ECOG PS 0 / 1 / 2 / Missing, n (%)	24 (30) / 50 (63) / 3 (4) / 2 (3)
Race, Asian / White / Other[a], n (%)	40 (51) / 30 (38) / 9 (11)
Prior lines of systemic therapy, median (range)	1 (0-6)
Platinum pre-treated, n (%)	57 (72)
Prior afatinib, n (%)	9 (11)
Treatment naïve, n (%)	12 (15)
Patient disposition, n (%)	
Treatment ongoing	20 (25)
Discontinued due to PD[b] / other reason[c]	58 (73) / 1 (1)
Number of metastatic sites, median (range)[d]	2 (0-8)
Histology, n (%)	
Adenocarcinoma	66 (84)
Invasive mucinous adenocarcinoma	11 (14)
Squamous cell carcinoma	1 (1)
Poorly differentiated carcinoma	1 (1)

NRG1 Fusion Partners N = 79



NRG1 identification technology, n (%)	
RNAseq	64 (81)
DNAseq	11 (14)
Nanostring	1 (1)
Missing	3 (4)

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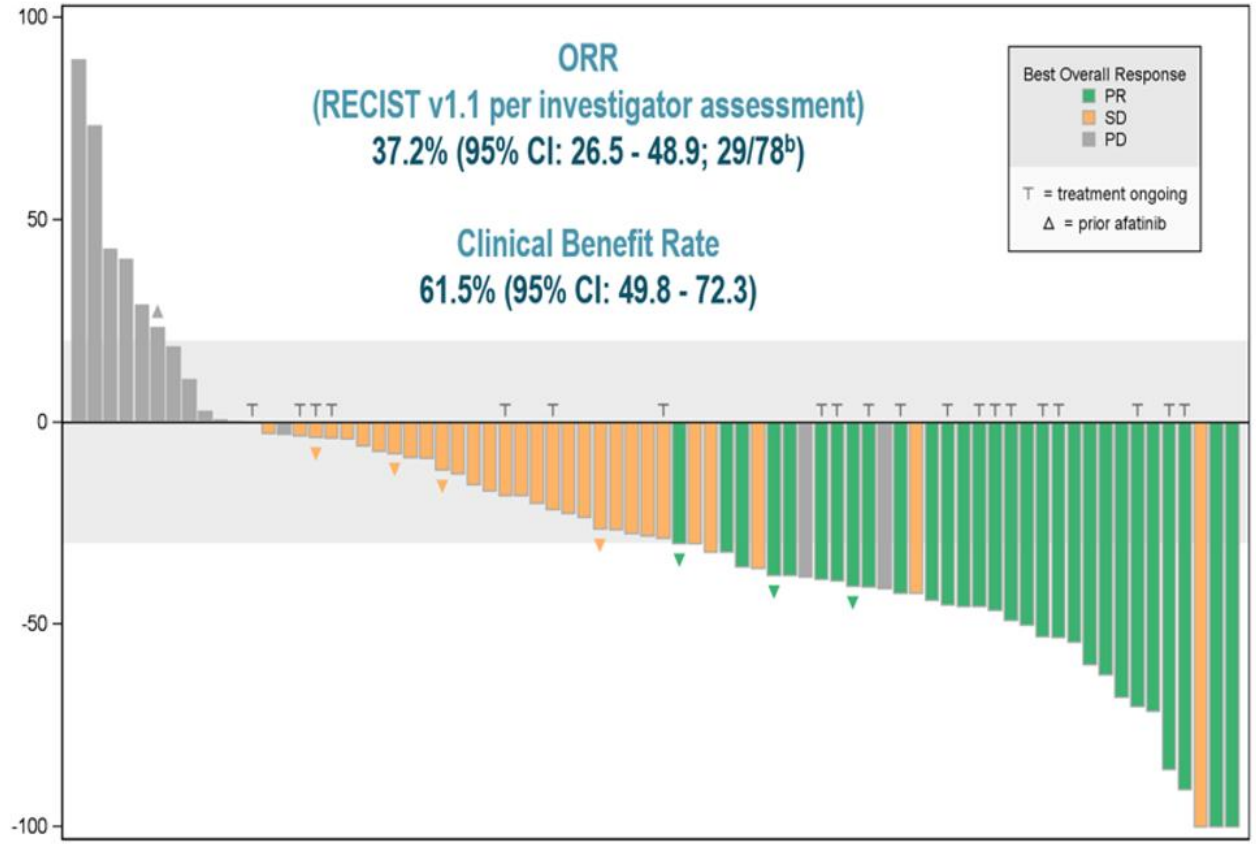
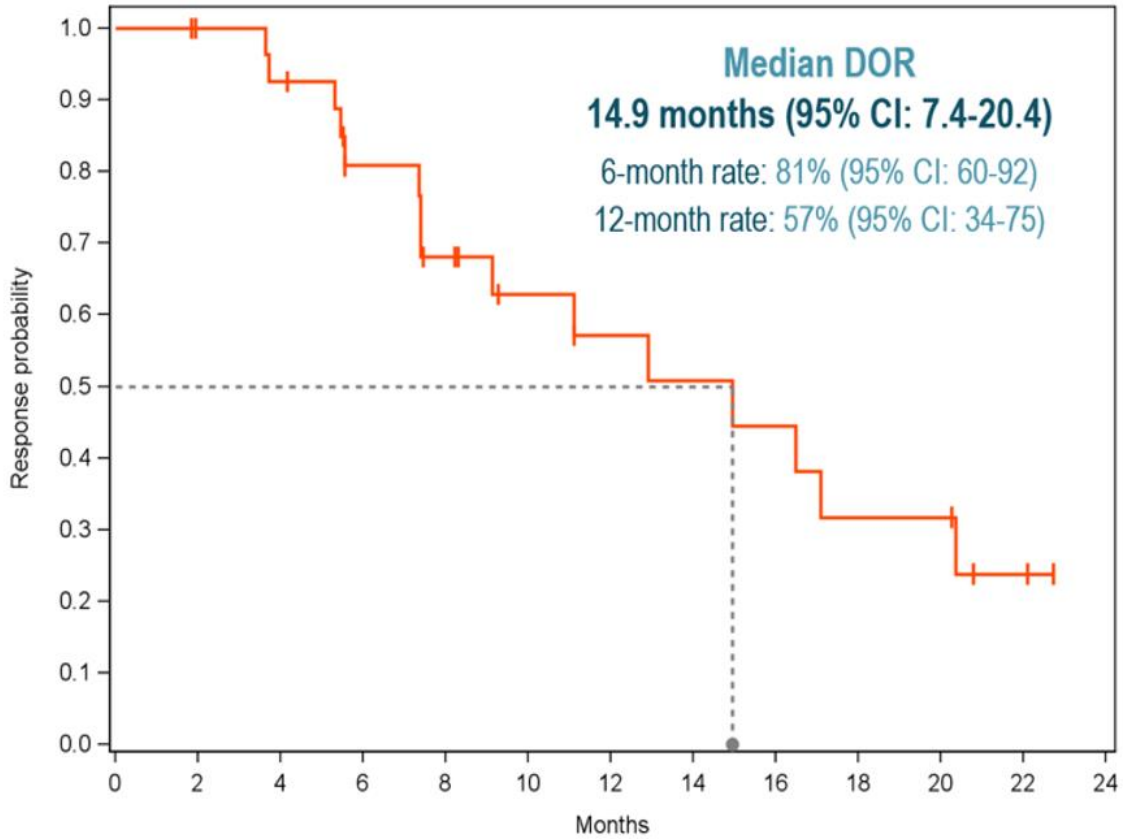
[a] Native Hawaiian or other Pacific islander (n = 1), unknown (n = 2), missing (n = 6); [b] Includes radiological and clinical progression, and 2 fatal cases; [c] Patient withdrew consent; [d] 1 patient had advanced non-metastatic disease

Zenocutuzumab Activity in NRG1+ NSCLC:





CI, confidence interval; SD, stable disease.

[a] Excludes 4 patients, 3 due to absence of post baseline assessment and 1 due to incomplete assessment of target lesion at first post baseline assessment.
[b] 1 patient with non-measurable disease was excluded from analysis.

Conclusions:

- Broad molecular testing at the time of diagnosis is essential to select the optimal treatment (NGS DNA & RNA); use both liquid and tissue NGS.
- First-line combination therapy improves PFS in EGFRm NSCLC; Ami/Laz improves mOS (press release January 7, 2025). The benefits of 1L combination regimens are greatest in patients with higher risk features.
- Selection of a first-line regimen impacts subsequent 2L+ treatment options in mEGFR tumors.
- Zongertinib received Priority Review from U.S. FDA for the treatment of HER2 (ERBB2)-mutant advanced NSCLC (02.19.2025).
- Zenocutuzumab targets NRG1 fusion proteins; the latest druggable pathway.