Updated Management on Advanced NSCLC Driver Mutant Tumors

Edgardo S. Santos, MD, FACP, FASCO
Medical Director- Broward County, Florida
The Oncology Institute of Hope and Innovation (TOIHI)
Clinical Associate Professor
Charles E. Schmidt School of Medicine/Florida Atlantic University
Vice-President, Florida Society of Clinical Oncology (FLASCO)
President, FLASCO Foundation

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

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[qq]

Preferred

Osimertinib[rr] (category 1)

Other Recommended

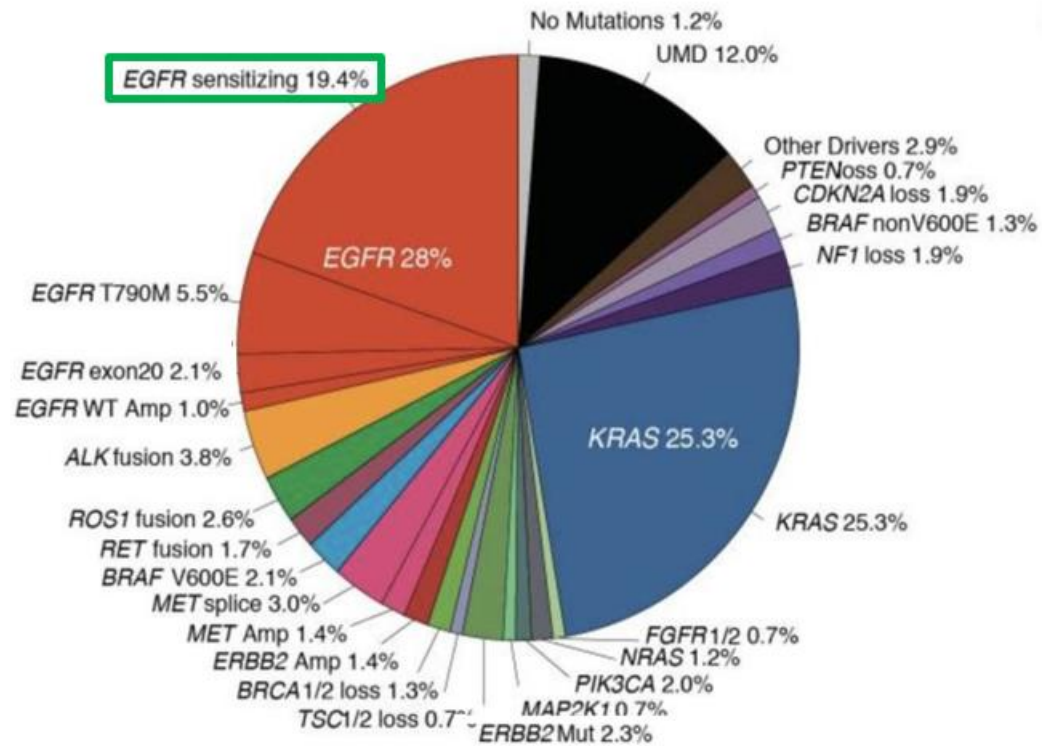
Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous) (category 1)
or Amivantamab-vmjw + lazertinib (category 1)[ss]

Useful in Certain Circumstances

Erlotinib + ramucirumab
or Erlotinib + bevacizumab[tt,uu]
or Dacomitinib[rr] (category 1)
or Afatinib[rr] (category 1)
or Erlotinib[rr] (category 1)
or Gefitinib[rr] (category 1)

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

Complete planned systemic therapy,[vv] including maintenance therapy, or interrupt, followed by osimertinib (preferred) or amivantamab-vmjw + lazertinib[ss]
or
erlotinib + ramucirumab or erlotinib + bevacizumab[tt,uu] or dacomitinib or afatinib or erlotinib or gefitinib



NCCN Version 1.2025, 12/20/24

FLAURA2: 1L Osimertinib + Chemotherapy vs Osimertinib

Safety run-in period (N=30)
Published in ESMO Open, 2021[1]

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‡

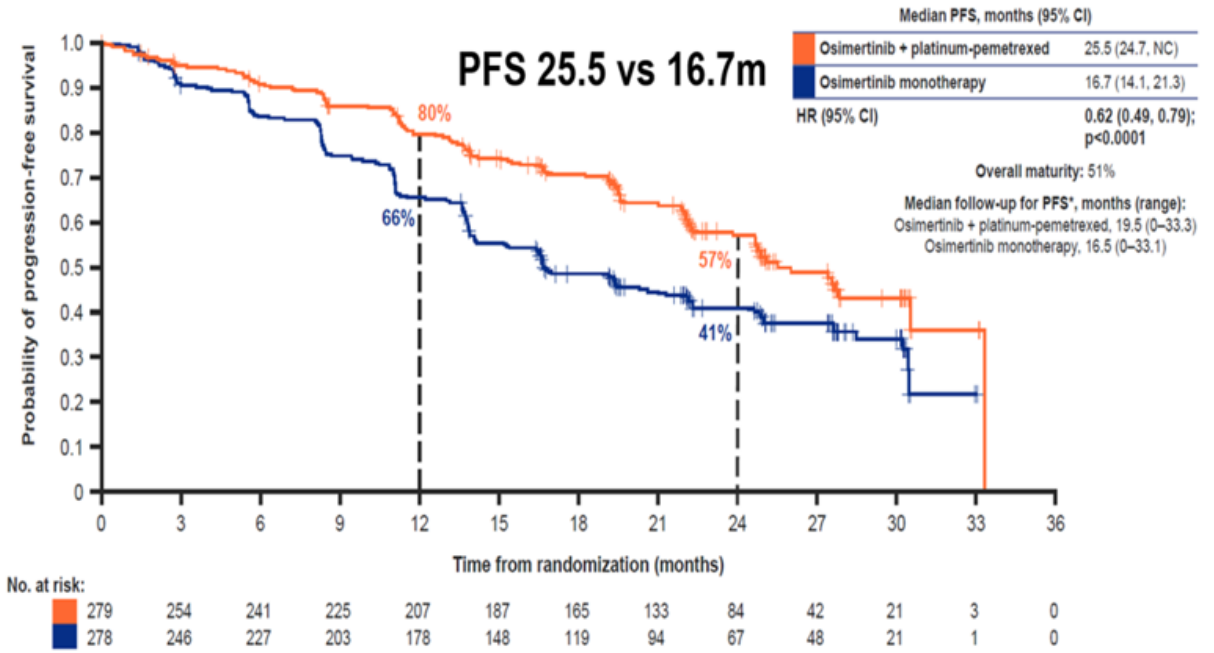
Presented by P. Janne, IASLC WCLC 2023, PL03.13

FDA approves osimertinib with chemotherapy for EGFR-mutated non-small cell lung cancer

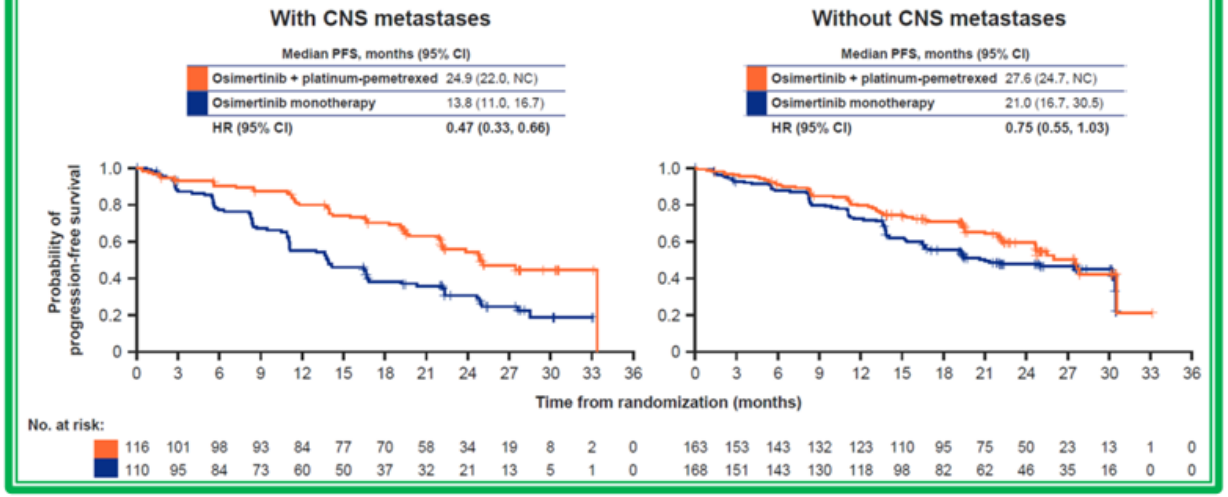
February 16, 2024

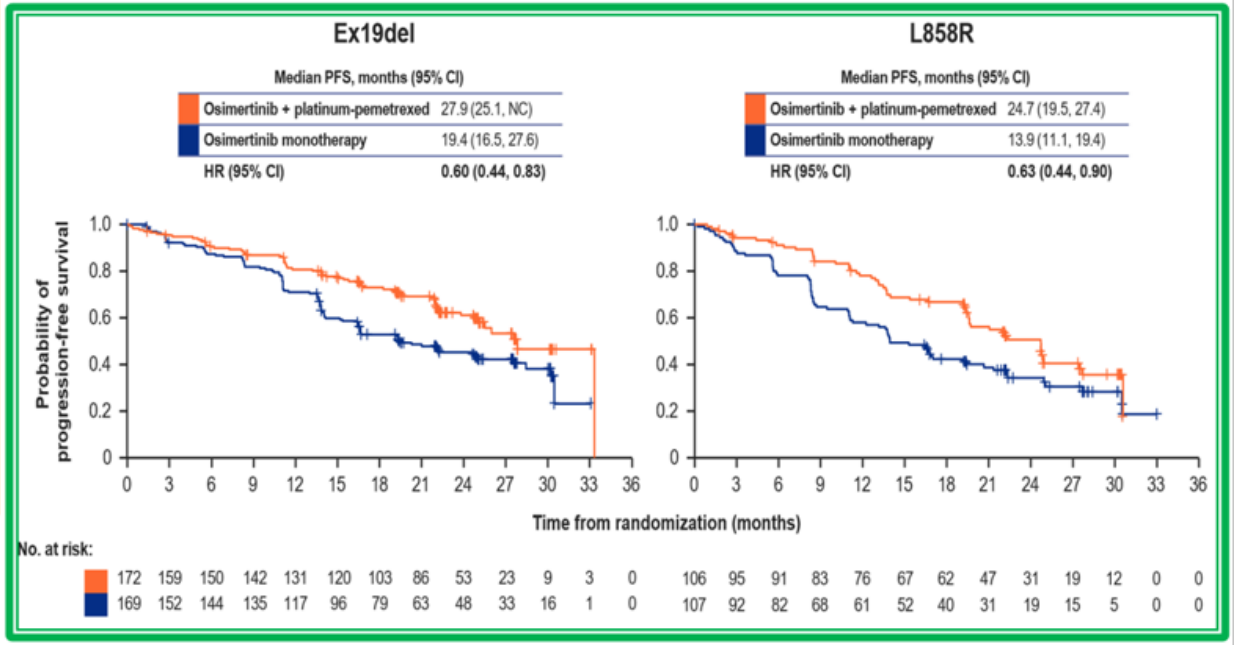
On February 16, 2024, the Food and Drug Administration approved osimertinib (, with platinum-based chemotherapy for patients with locally advanced or metastatic non-small cell lung cancer (Ia/mNSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

FLAURA2: PFS per investigator



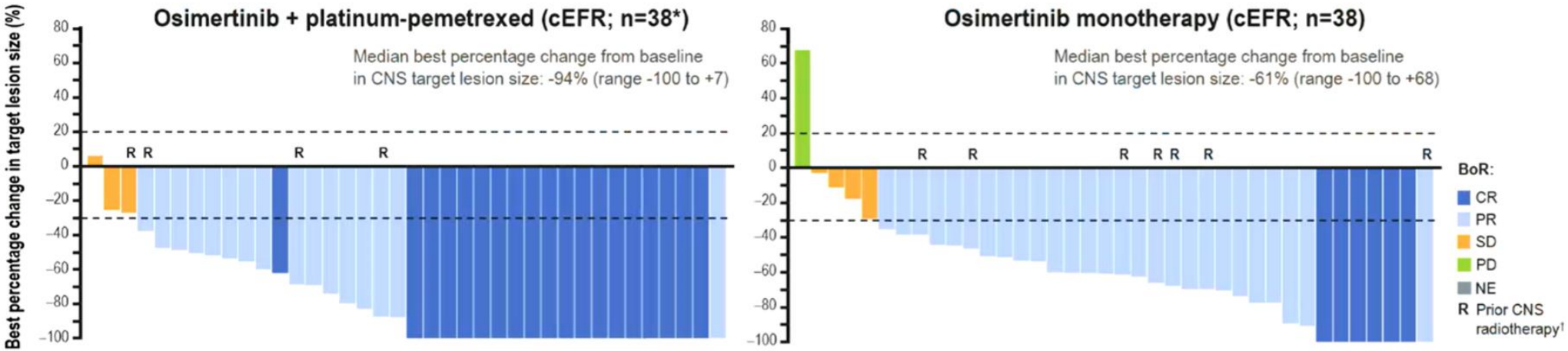
FLAURA2: PFS per investigator by CNS Metastases





FLAURA2: Updated CNS Data ESMO 2023

OSIMERTINIB WITH THE ADDITION OF CTx DEMONSTRATED A HIGH PROPORTION OF COMPLETE RESPONSES IN THE CNS BY CNS BICR



	cFAS (n=222) Measurable + non-measurable BM		cEFR (n=78) Measurable BM	
CNS response‡	**Osi + CTx (n=118)**	**Osi mono (n=104)**	**Osi + CTx (n=40)**	**Osi mono (n=38)**
CNS ORR, % (95% CI)	**73 (64 to 81)**	**69 (59 to 78)**	**88 (73 to 96)**	**87 (72 to 96)**
Complete response, n (%)	70 (59)	45 (43)	19 (48)	6 (16)
Partial response, n (%)	16 (14)	27 (26)	16 (40)	27 (71)
CNS DCR, % (95% CI)	91 (84 to 95)	93 (87 to 97)	95 (83 to 99)	97 (86 to 100)
Median DoR, months (95% CI)§	**NR (23.8, NC)**	**26.2 (19.4, NC)**	**NR (21.6, NC)**	**20.9 (12.6, NC)**

*Two pts had ≥1 measurable CNS lesion at baseline by CNS BICR but died before the follow-up CNS BICR scan; †In the cEFR, 4/40 pts (10%) in the osimertinib + platinum-pemetrexed arm and 7/38 pts (18%) in the osimertinib arm had received prior CNS radiotherapy; stable neurological status for ≥2 weeks after completion of definitive treatment and steroids was required before study entry, if received; ‡Responses did not require confirmation, per RECIST guidance on randomized studies; §Kaplan–Meier estimates.

BICR, blinded independent central review; BM, brain metastases; BoR, best overall response; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; CI, confidence interval; CNS, central nervous system; CR, complete response; CTx, chemotherapy; DCR, disease control rate; DoR, duration of response; mono, monotherapy; NC, not calculable; NE, not evaluable; NR, not reached; ORR, objective response rate; osi, osimertinib; PD, progressive disease; PR, partial response; pts, patients; SD, stable disease

Data cut-off: 03 April 2023

MADRID 2023 ESMO congress

Measurable CNS lesions: CR rate 16% vs 48%

Presented Planchard et al. ESMO 2023 Abstract LBA68

Updated Management on Advanced NSCLC Driver Mutant Tumors. Edgardo S. Santos, MD, FACP, FASCO. EdgardoSantosMD

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY — The Oncology Institute of Hope & Innovation

MARIPOSA: Phase 3 Study Design

Key Eligibility Criteria

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

Stratification Factors

- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases[a] (yes or no)

Serial brain MRIs were required for all patients[a]

2:2:1 Randomization (N=1074)

- **Amivantamab + Lazertinib** (n=429; open-label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

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

Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:

- **Amivantamab + lazertinib** vs osimertinib

Secondary endpoints of amivantamab + lazertinib vs osimertinib:

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

Lazertinib monotherapy arm was included to assess the contribution of components

MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

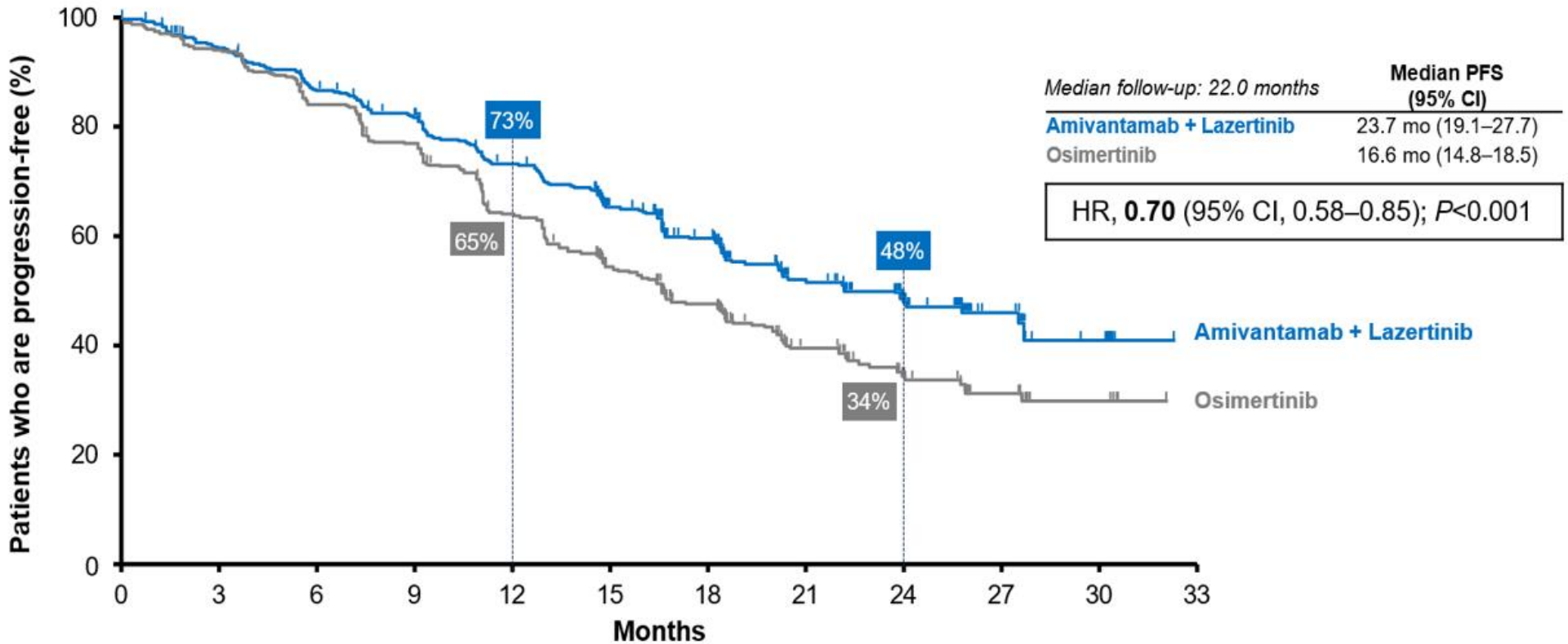
[a]Baseline brain MRI was required for all patients and performed ≤28 days prior to randomization; patients who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis 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.
[b]Key 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.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Byoung Chul Cho et al. 2023 ESMO Congress, Madrid, Spain.

Primary Endpoint: Progression-free Survival by BICR[a]

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



Median follow-up: 22.0 months	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

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

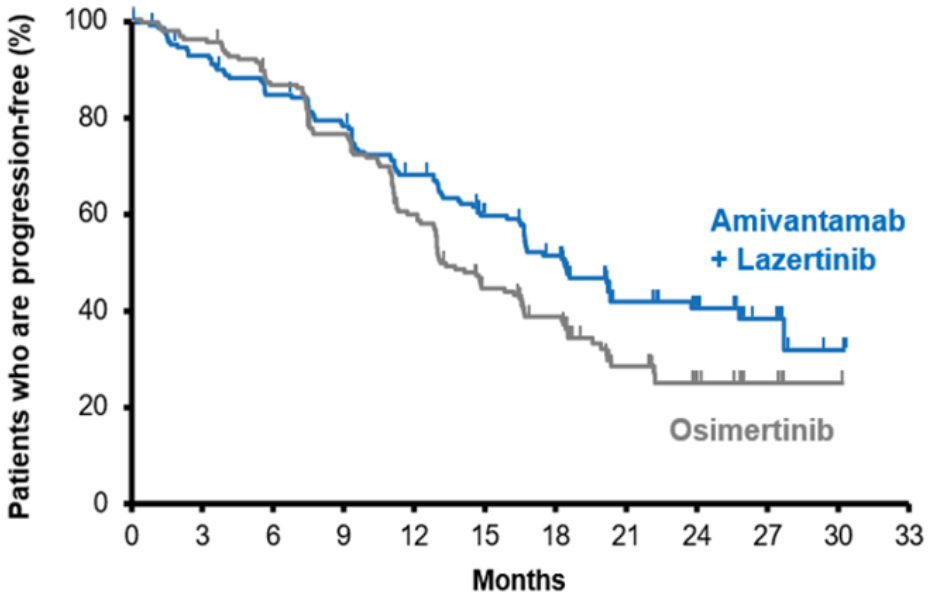
[a]At time of the prespecified final PFS analysis, there were a total of 444 PFS events in the amivantamab + lazertinib and osimertinib arms combined.

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

Consistent PFS (BICR) Benefit With or Without Brain Metastases

With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

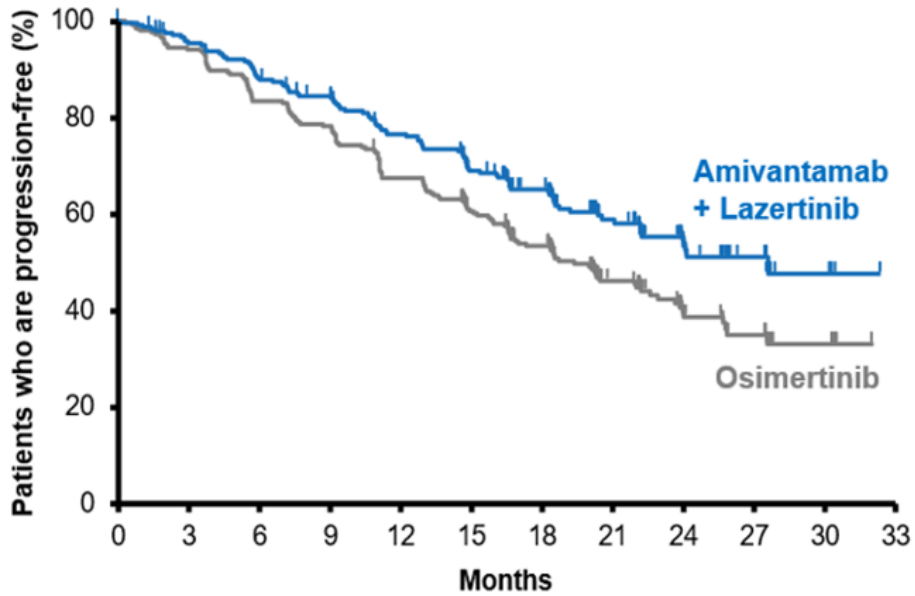
HR, **0.69** (95% CI, 0.53–0.92)



No. at risk												
Amivantamab + Lazertinib	178	162	146	134	115	92	71	34	24	12	3	0
Osimertinib	172	164	146	126	95	64	47	21	11	6	1	0

Without History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	27.5 mo (22.1–NE)
Osimertinib	19.9 mo (16.6–22.9)

HR, **0.69** (95% CI, 0.53–0.89)



No. at risk												
Amivantamab + Lazertinib	251	229	211	198	176	152	123	72	36	21	5	0
Osimertinib	257	240	212	199	171	141	113	69	37	22	9	0

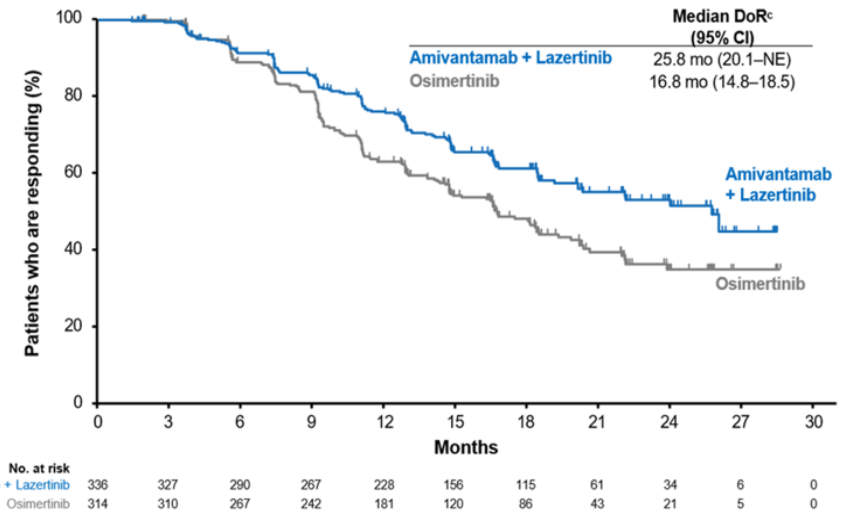
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; PFS, progression-free survival.

Byoung Chul Cho et al. 2023 ESMO Congress, Madrid, Spain.

ORR and DoR by BICR

*Amivantamab + lazertinib improved median DoR by **9** months, suggesting longer time to resistance and progression*

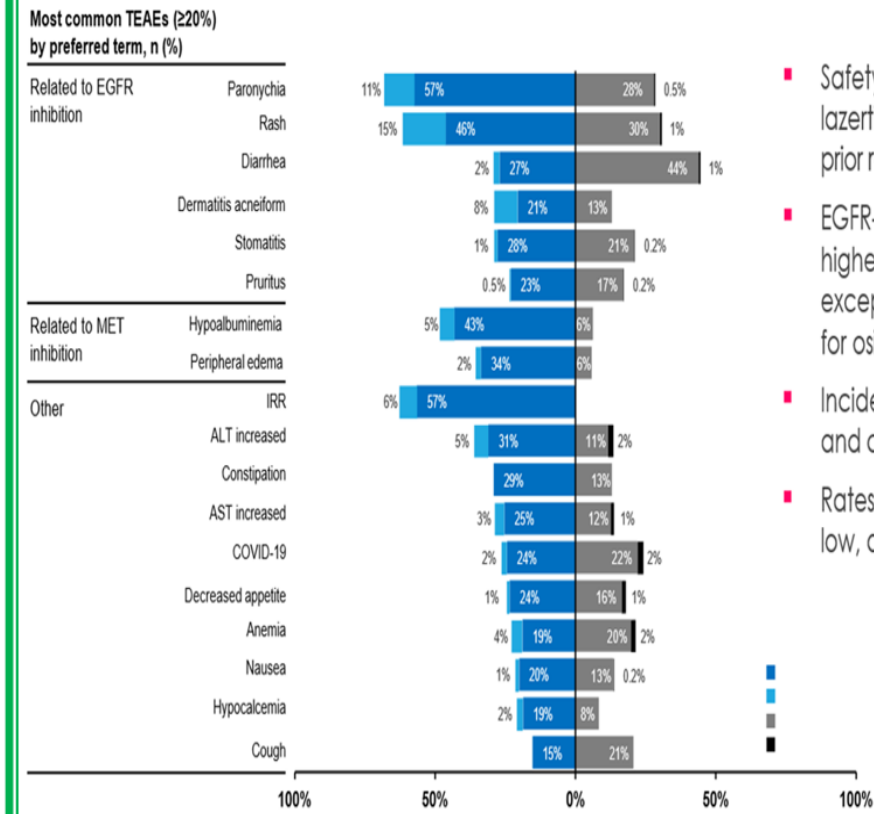
BICR-assessed response, n (%)[a]	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)
ORR		
All responders	86% (95% CI, 83–89)	85% (95% CI, 81–88)
Confirmed responders	80% (95% CI, 76–84)	76% (95% CI, 71–80)
Best response[b]		
CR	29 (7)	15 (4)
PR	334 (79)	335 (81)
SD	30 (7)	42 (10)
PD	7 (2)	11 (3)
NE/UNK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



[a]No. of patients with measurable disease at baseline by BICR was 421 for amivantamab + lazertinib and 414 for osimertinib. [b]Includes all responders. [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; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Safety Profile



- Safety profile of amivantamab + lazertinib was consistent with prior reports, mostly grades 1-2
- EGFR- and MET-related AEs were higher for amivantamab + lazertinib except diarrhea, 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

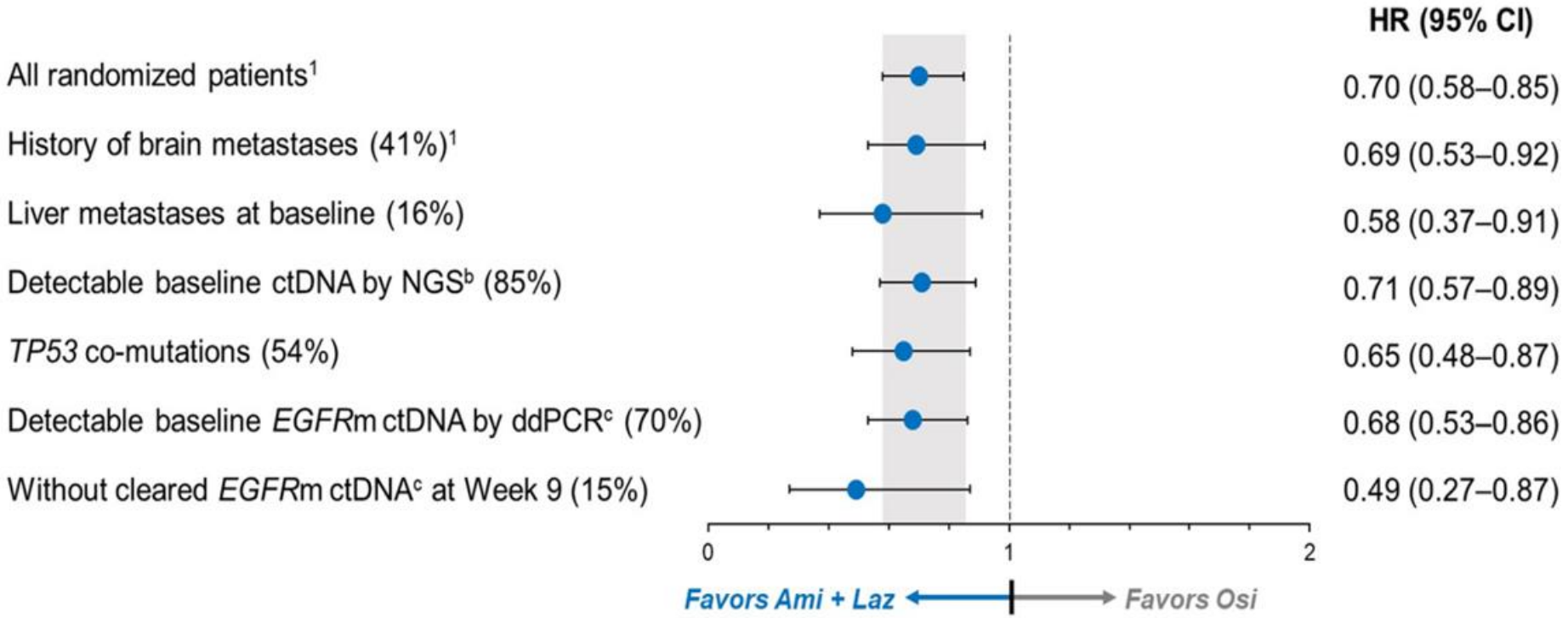
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease (includes pneumonitis); IRR, infusion-related reaction; TEAE, treatment-emergent AE.

Byoung Chul Cho et al. 2023 ESMO Congress, Madrid, Spain.

PFS for Patients With High-risk Features

In the MARIPOSA study, 89% of patients had ≥1 high-risk feature detected at baseline[a]

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



ASCO 2024 Updates

[a]Patients with analyzable ctDNA by NGS at baseline were included in this pooled analysis. High-risk features included baseline detectable ctDNA by NGS or baseline metastases of the liver or brain. For patients with detectable ctDNA, it was assumed that *TP53* co-mutations would be identified if present. [b]Pathogenic mutations were detected with the Guardant Health G360® panel. [c]Ex19del and L858R by Biodesix ddPCR.

Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; NGS, next-generation sequencing.

1. Cho BC, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

Enriqueta Felip et al. 2024 ASCO Annual Meeting

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 week

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.

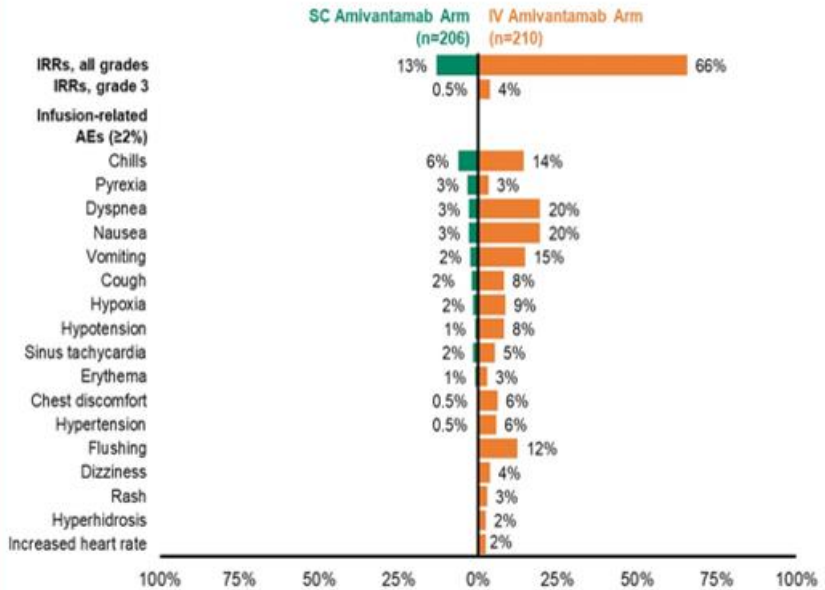
[a]SC amivantamab was co-formulated with rHuPH20 at a concentration of 160 mg/mL. [b]C1 for IV: Days 1 to 2 (Day 2 applies to IV split dose only [350 mg on Day 1 and the remainder on Day 2]), 8, 15, and 22; C1 for SC: Days 1, 8 , 15, and 22; after C1 for all: Days 1 and 15 (28-day cycles). [c]For calculating 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

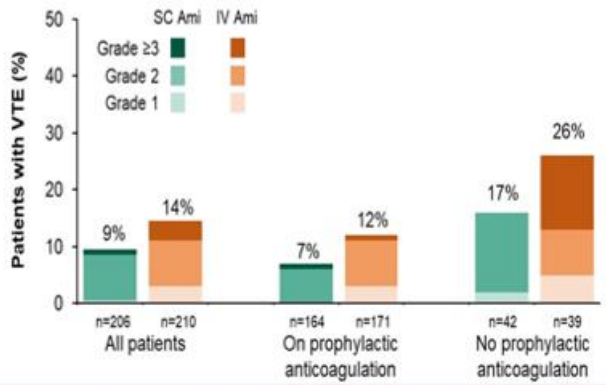
Approved on August 19, 2024

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



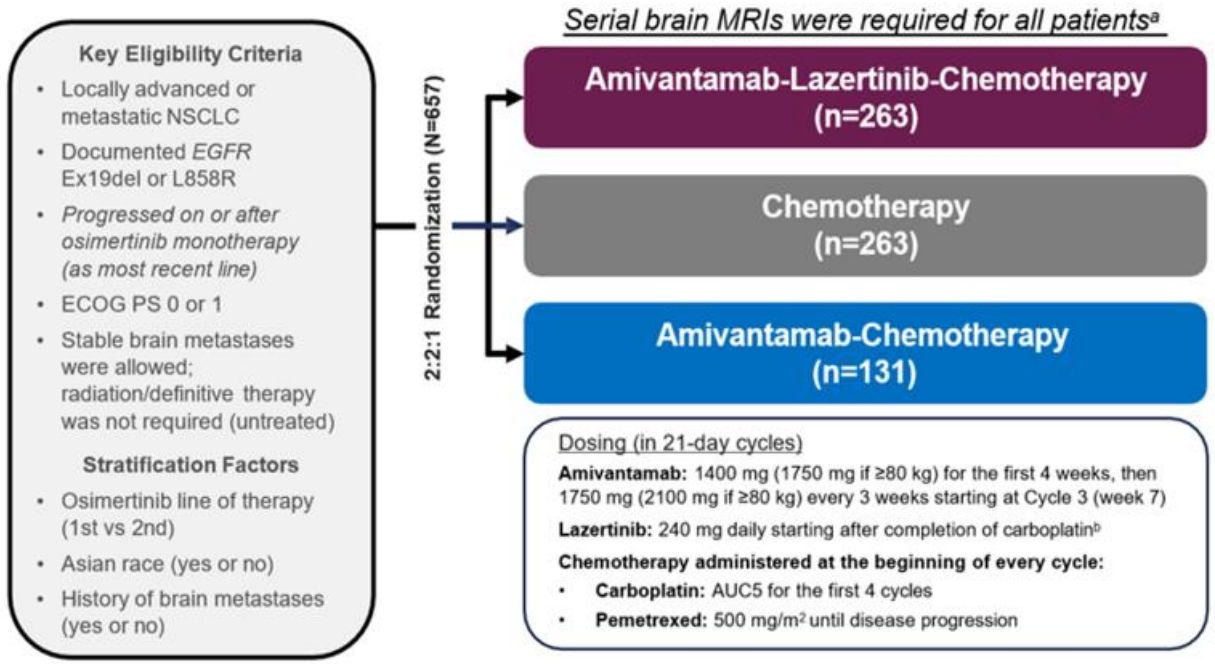
- Between study arms, incidence of VTE was less frequent in the SC amivantamab arm compared to the IV arm, regardless of prophylactic anticoagulation status

Updated Management on Advanced NSCLC Driver Mutant Tumors. Edgardo S. Santos, MD, FACP, FASCO. EdgardoSantosMD

The Oncology Institute of Hope & Innovation

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.

EGFR Pathway

ERBB2 | HER-2 mutation

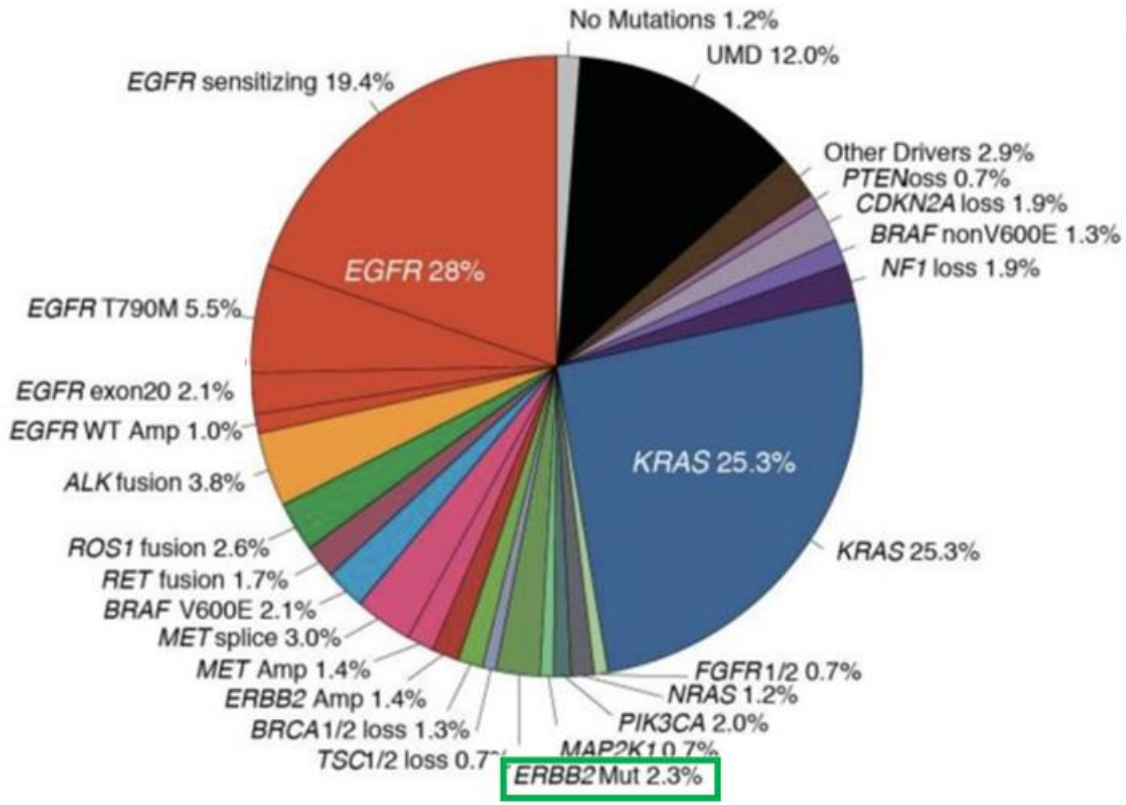
ERBB2 (HER2) MUTATION[nn]

FIRST-LINE THERAPY[eee]

ERBB2 (HER2) mutation[mmm] → **Systemic therapy**
Adenocarcinoma (NSCL-K 1 of 5)
or
Squamous Cell Carcinoma (NSCL-K 2 of 5)
→ **Tumor response evaluation**

- **Progression** → **Preferred** ★
  Fam-trastuzumab deruxtecan-nxki
  or
  Other Recommended
  Ado-trastuzumab emtansine
- **Response or stable disease** → **4–6 cycles (total)[fff]** → **Tumor response evaluation**

NCCN Version 1.2025, 12/20/24



DESTINY-Lung02 (5.4 mg/kg and 6.4 mg/kg)

Final analysis

Efficacy summary	T-DXd 5.4 mg/kg n = 102	T-DXd 6.4 mg/kg n = 50
cORR,[a,b] n (% [95% CI])	51 (50.0 [39.9-60.1])	28 (56.0 [41.3-70.0])
CR	3 (2.9)	4 (8.0)
PR	48 (47.1)	24 (48.0)
SD	44 (43.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Non-evaluable	3 (2.9)	2 (4.0)
DCR,[c] n (% [95% CI])	95 (93.1 [86.4-97.2])	46 (92.0 [80.8-97.8])
DoR,[b] median (95%CI), months	12.6 (6.4 to NE)	12.2 (7.0 to NE)

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg n = 101[a]	T-DXd 6.4 mg/kg n = 50[a]
Total	15 (14.9)	16 (32.0)
Grade 1	4 (4.0)	3 (6.0)
Grade 2	9 (8.9)	11 (22.0)
Grade 3	1 (1.0)	1 (2.0)
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

Data cutoff: August 25, 2023.
ILD, interstitial lung disease; PD-(L)1, programmed death (ligand) 1; T-DXd, trastuzumab deruxtecan.
[a]Randomly assigned patients who received ≥1 T-DXd dose.

Median time to onset of first adjudicated ILD, days (range)	67.5 (40-207)	41.0 (36-208)

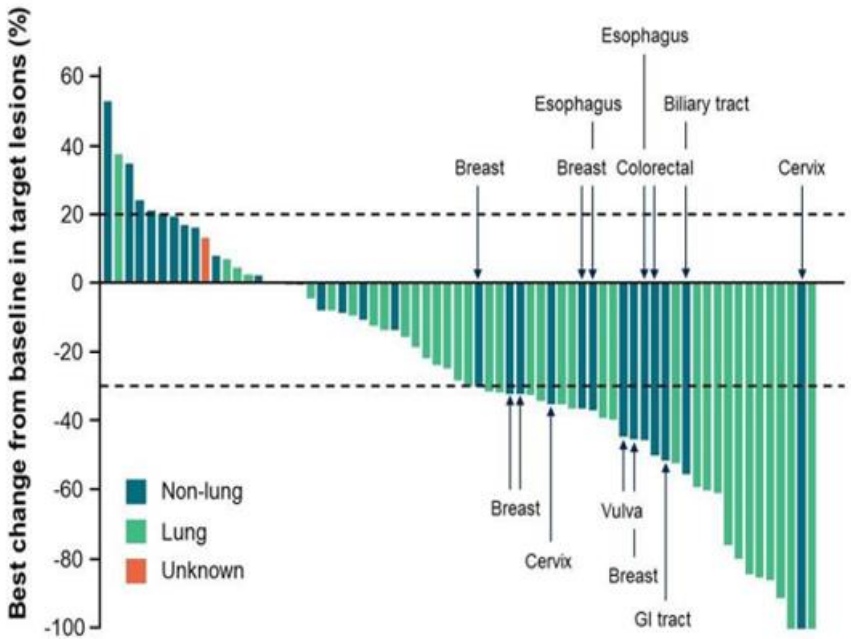
Zongertinib (Beamion LUNG1)

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%

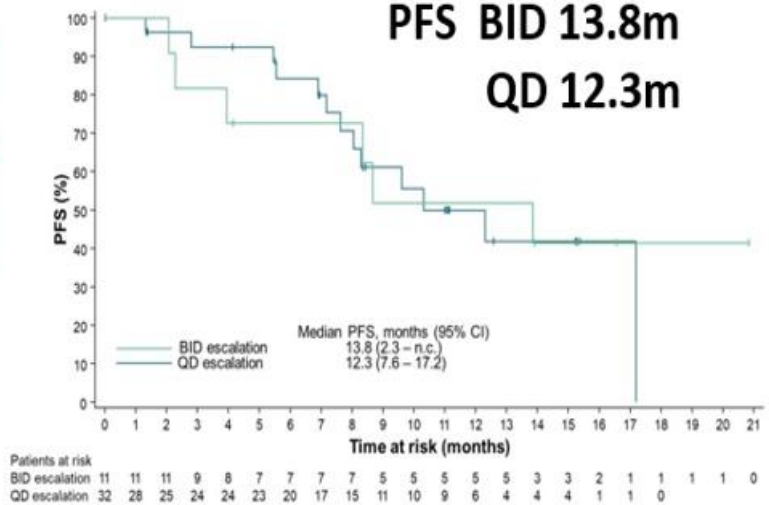


Ph 1a: Safety

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)

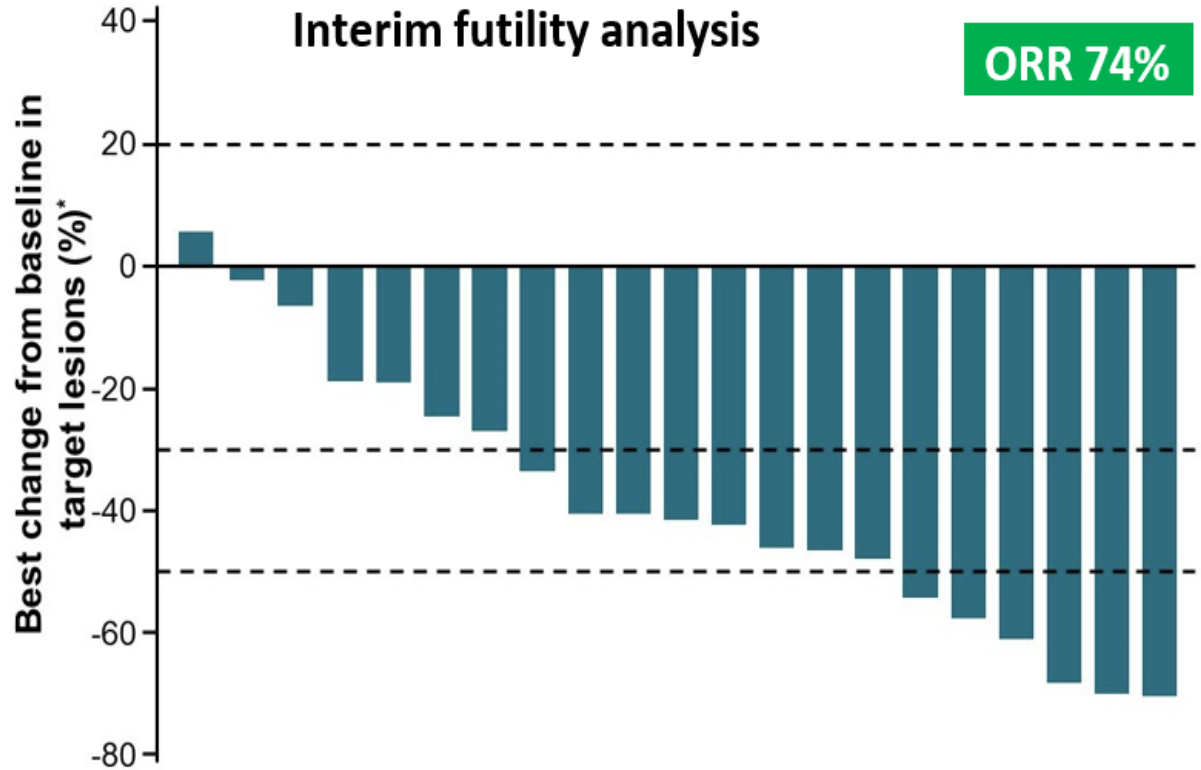
HER2 covalent, selective TKI ($EGFR_{wt}$-sparing)

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

ALK Pathway

***ALK* REARRANGEMENT[nn]**

ALK rearrangement → ***ALK*** rearrangement discovered prior to first-line systemic therapy →

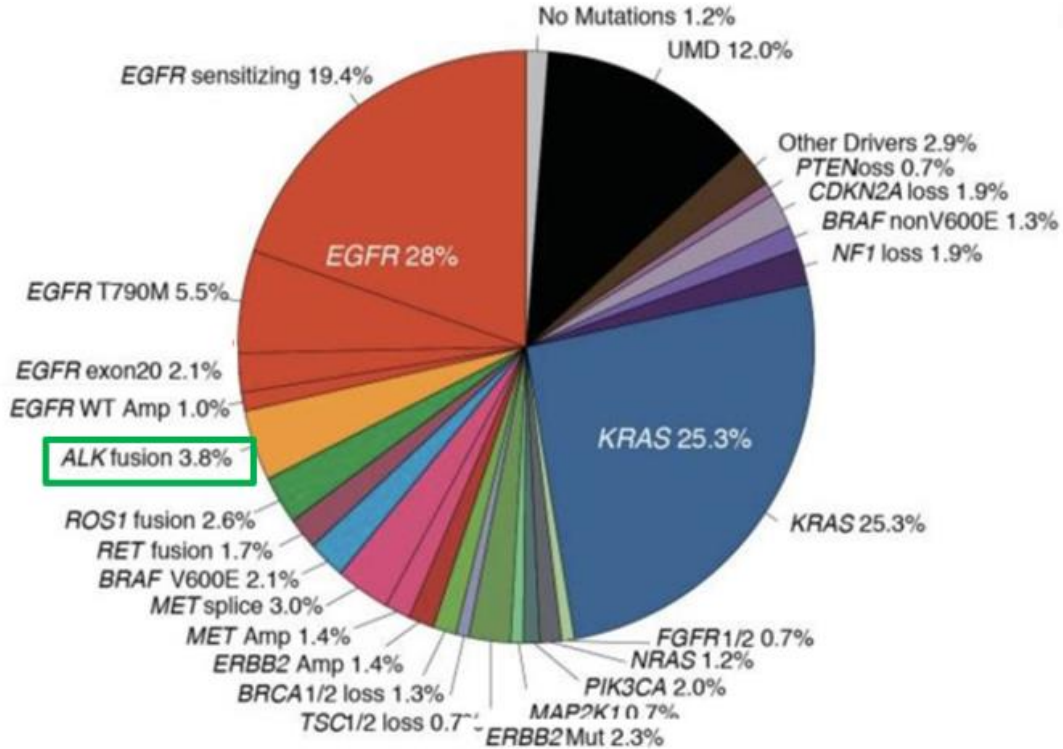
FIRST-LINE THERAPY[qq]

Preferred
- Alectinib[rr] (category 1)
- or
- Brigatinib[rr] (category 1)
- or
- Lorlatinib[rr] (category 1)

Other Recommended
- Ceritinib[rr] (category 1)

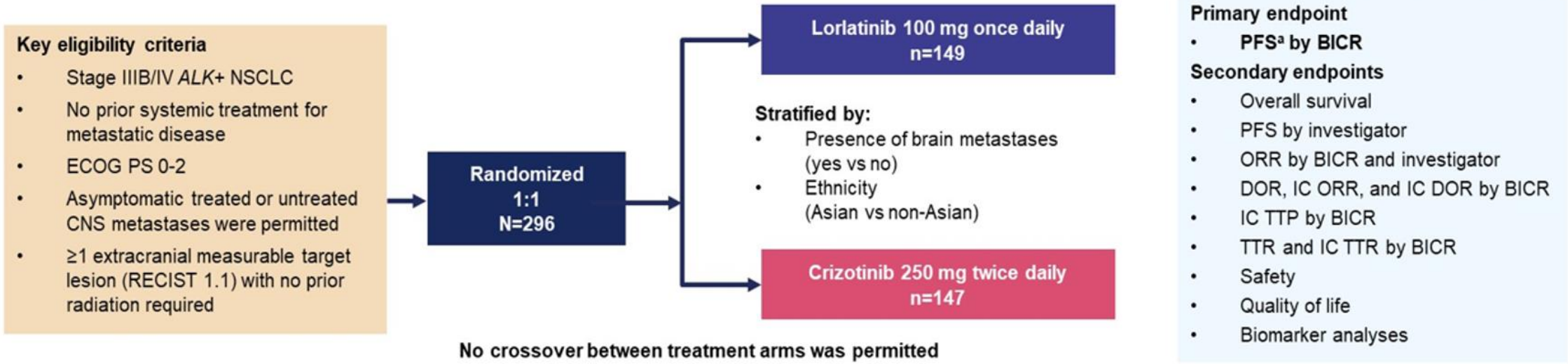
Useful in Certain Circumstances
- Crizotinib[rr] (category 1)

NCCN Version 1.2025, 12/20/24



CROWN: A Randomized Global Phase 3 Study

- Lorlatinib is a brain-penetrant, third-generation ALK TKI that has broader coverage of *ALK* resistance mutations than second-generation ALK TKIs[1,2]

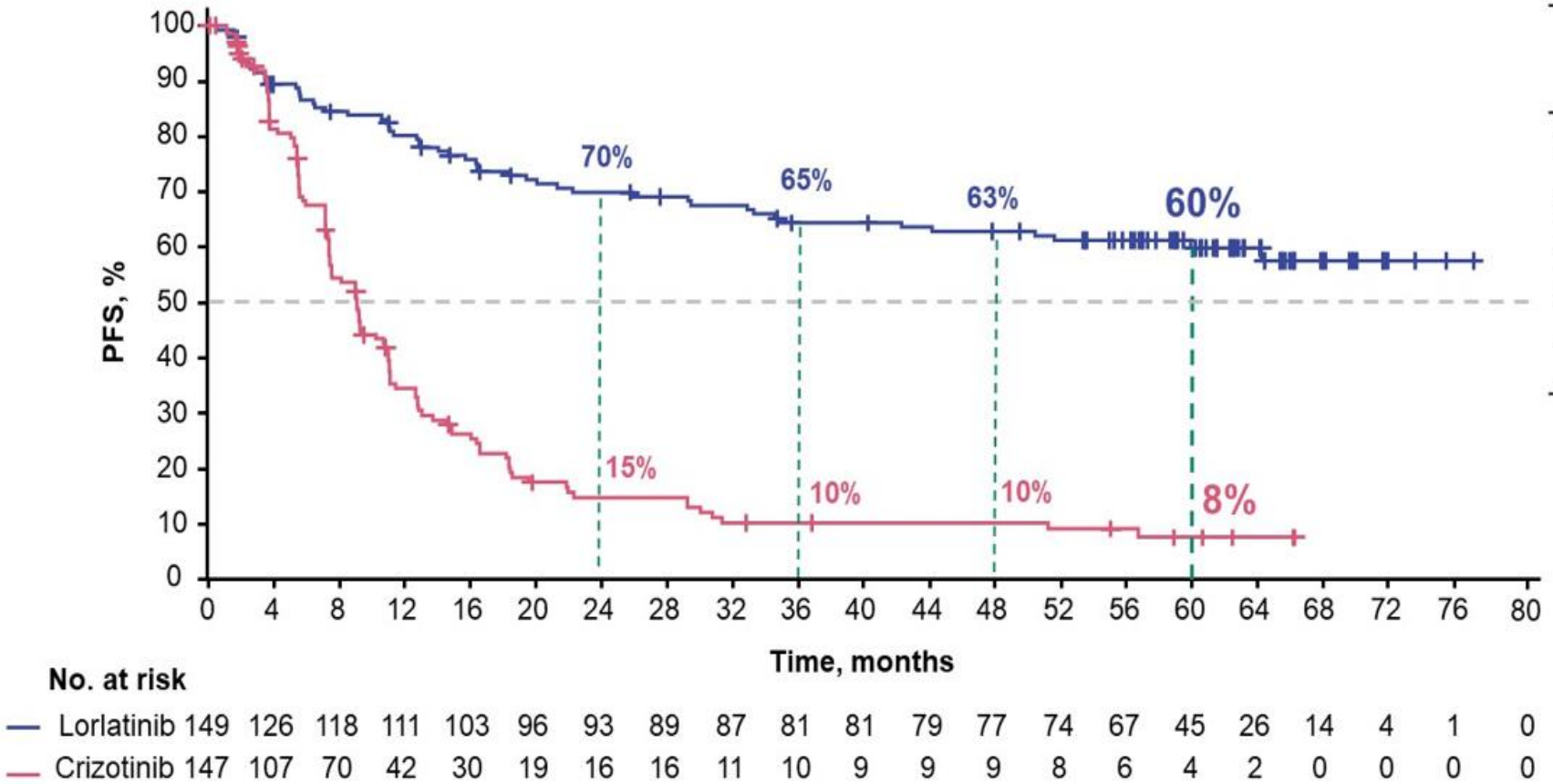


- At the planned interim analysis, at 18.3 months of median follow-up in the lorlatinib arm, median PFS by BICR was not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib, with an HR of 0.28 (95% CI, 0.19-0.41) and P<0.001[3]
- In a subsequent post hoc analysis, at 3 years of follow-up, median PFS by BICR was still not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (HR, 0.27; 95% CI, 0.18-0.39)[4]

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IC, intracranial; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TTP, time to tumor progression; TTR, time to tumor response.
[a]Defined as the time from randomization to RECIST-defined progression or death due to any cause.
1. Johnson TW, et al. *J Med Chem*. 2014;57:4720-4744. 2. Shaw AT, et al. *Lancet Oncol*. 2017;18:1590-1599. 3. Shaw AT, et al. *N Engl J Med*. 2020;383:2018-2029. 4. Solomon BJ, et al. *Lancet Respir Med*. 2023;11:354-366.

Benjamin J. Solomon. 2024 ASCO Annual Meeting.

At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

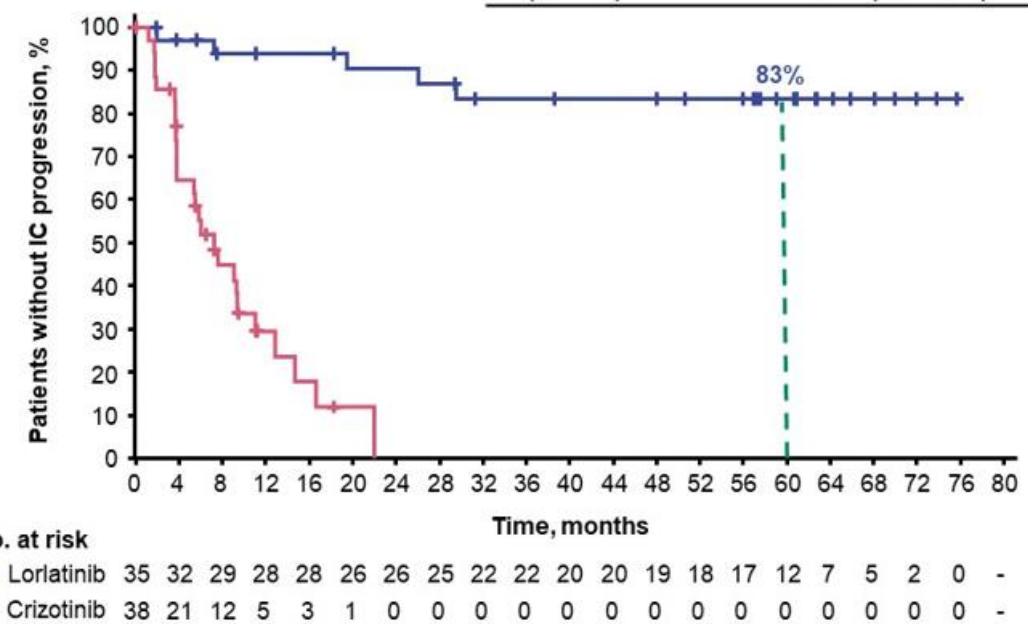
At the time of this analysis, the required number of OS events for a protocol-specified second interim analysis **has not been reached**. OS follow up is ongoing

HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

Time to IC Progression Was Longer With Lorlatinib in Presence or Absence of Baseline Brain Metastases

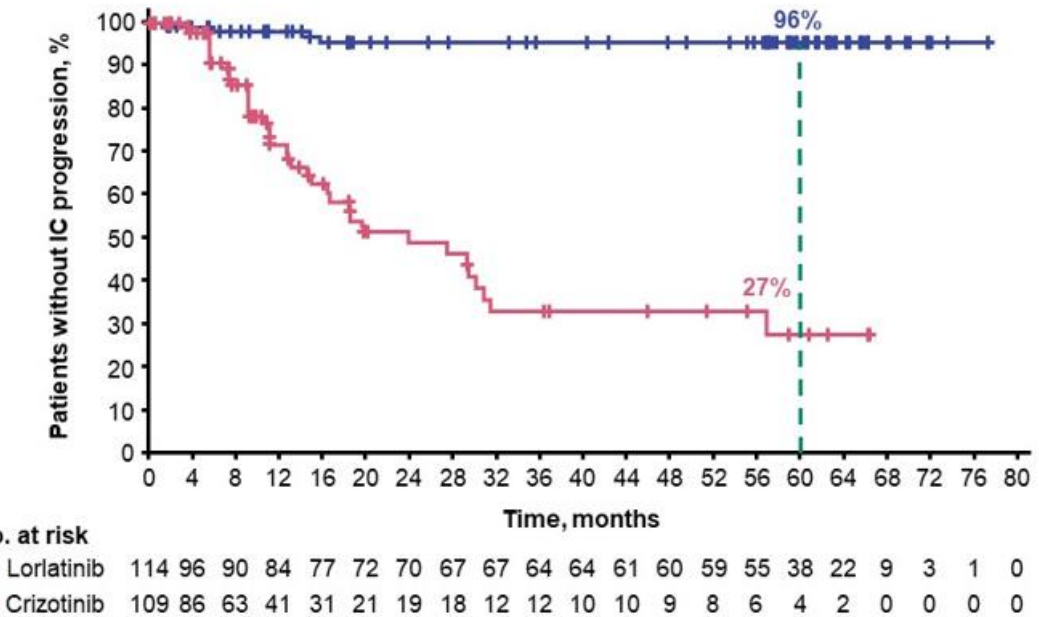
With Baseline Brain Metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, median (95% CI), months	NR (NR-NR)	7.2 (3.7-11.0)
HR (95% CI)	**0.03 (0.01-0.13)**	



Without Baseline Brain Metastases

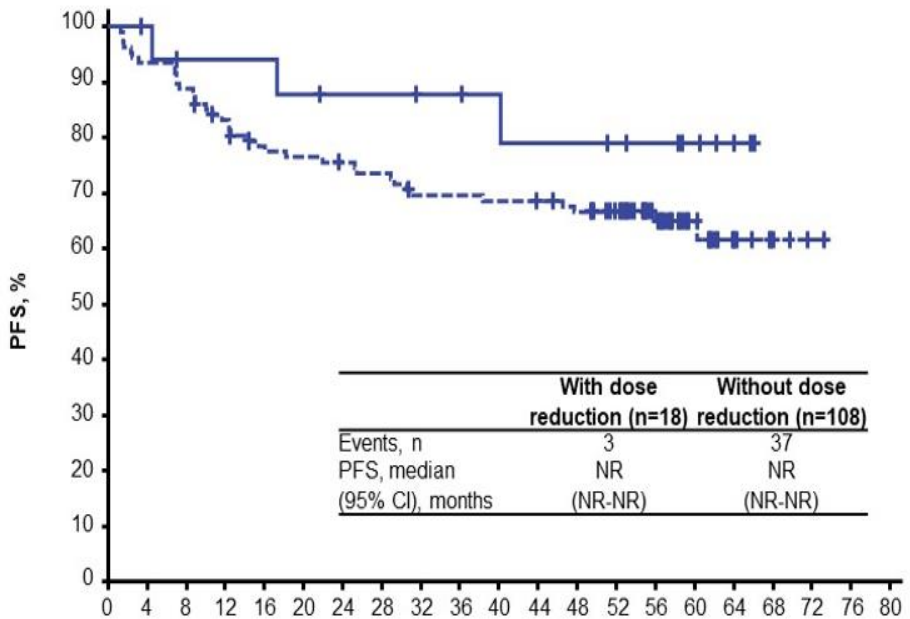
	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	4	39
Time to IC progression, median (95% CI), months	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	**0.05 (0.02-0.13)**	



HR, hazard ratio; IC, intracranial; NR, not reached.

Dose Reduction Did Not Impact Efficacy of Lorlatinib in Patients Who Had Dose Reduction in the First 16 Weeks

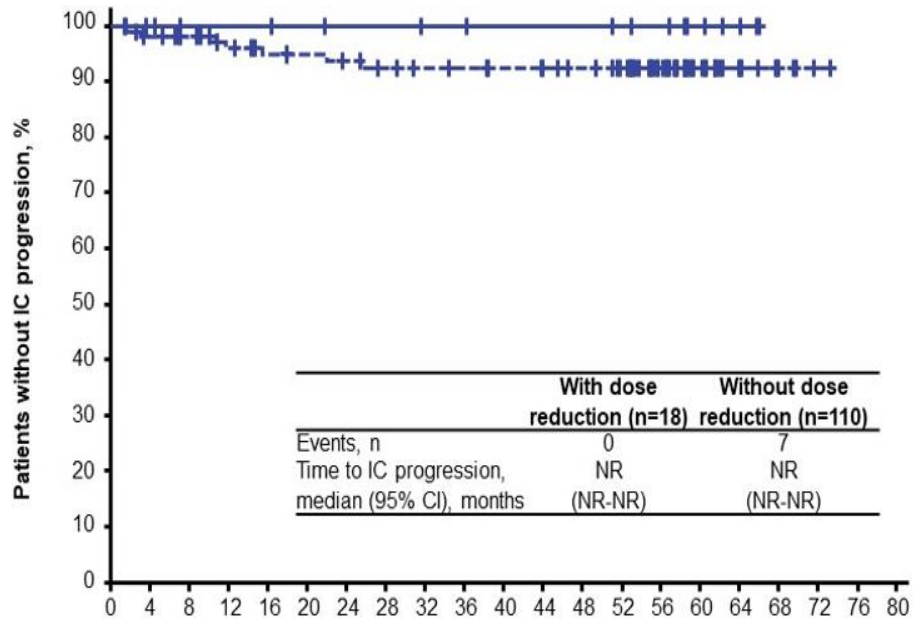
PFS



	With dose reduction (n=18)	Without dose reduction (n=108)
Events, n	3	37
PFS, median (95% CI), months	NR (NR-NR)	NR (NR-NR)

No. at risk																					
With dose reduction	18	17	15	15	15	14	12	12	11	11	10	9	9	8	7	5	3	0	0	0	-
Without dose reduction	108	101	96	88	81	79	77	75	70	70	69	68	65	59	38	21	11	4	1	0	-

Time to IC Progression



	With dose reduction (n=18)	Without dose reduction (n=110)
Events, n	0	7
Time to IC progression, median (95% CI), months	NR (NR-NR)	NR (NR-NR)

No. at risk																					
With dose reduction	18	17	15	15	15	14	12	12	11	11	10	10	10	9	8	5	3	0	0	0	-
Without dose reduction	110	102	97	90	83	82	80	77	75	73	71	69	67	63	42	24	11	5	1	0	-

IC, intracranial; NR, not reached; PFS, progression-free survival.

ALKove-1

A Global First-in-Human Phase 1/2 Clinical Trial of NVL-655 in Advanced ALK-Positive NSCLC and Other Solid Tumors (NCT05384626)

PATIENT POPULATION

- Advanced solid tumors harboring an ALK fusion or activating mutation (by local testing)
- Patients with NSCLC: ≥ 1 prior 2G or 3G ALK TKI
- ≤ 2 prior chemotherapies/immunotherapies
- Excluded: concurrent oncogenic drivers (e.g., EGFR/ROS1/MET/RET/BRAF alterations) [a]
- Evaluable but non-measurable disease allowed [a]

PHASE 1 OBJECTIVES

- Primary: Selection of RP2D and, if applicable, MTD
- Overall safety and tolerability
- PK characterization
- Preliminary antitumor activity
- Intracranial activity

PHASE 1 DOSE-ESCALATION COMPLETED, FOLLOW-UP CONTINUES

Enrollment June 2022 to February 2024 (Data cut-off: 15 June 2024)

NVL-655 Phase 1	All Doses	15 mg QD	25 mg QD	50 mg QD	100 mg QD	RP2D 150 mg QD	200 mg QD
All-Treated Population	N = 133	3	12	12	32	52	22
NSCLC Response-Evaluable Population	N = 103	3	7	10	27	39	17

2G, 2nd generation ALK TKI (i.e., ceritinib, alectinib, or brigatinib); **3G**, 3rd generation ALK TKI (i.e., lorlatinib); **MTD**, maximum tolerated dose; **NSCLC**, non-small cell lung cancer; **PK**, pharmacokinetics; **QD**, once daily; **RP2D**, recommended phase 2 dose; **TKI**, tyrosine kinase inhibitor

[a] Response evaluable population prospectively defined as all NSCLC patients with measurable disease, without concurrent oncogenic driver, and who undergo ≥1 post-baseline response assessment (or discontinue treatment due to clinical progression/death prior to the first response assessment). Patients unevaluable for response: no measurable disease at baseline (n = 18); tumor with alternate oncogenic driver (MET amplification [n = 4], BRAF G469A [n = 2], BRAF fusion [n = 1], NTRK fusion [n = 1]); no post-baseline scan and discontinued treatment for reasons other than progressive disease (n = 2); other solid tumor (n = 2).

A. Drilon. 2024 ESMO, Barcelona, Spain

Patient Population: Heavily Pretreated ALK-Positive Solid Tumors

Patient Characteristic	All Treated (N = 133)	RP2D (N=52)
Age, median (range)	57 (24, 83)	59 (24, 83)
Female	84 (63%)	35 (67%)
ECOG PS		
0	60 (45%)	24 (46%)
1	73 (55%)	28 (54%)
Non-smoker	95 (71%)	36 (69%)
Tumor Type		
NSCLC	131 (98%)	52 (100%)
Pancreatic adenocarcinoma	1 (1%)	0
Atypical carcinoid, lung	1 (1%)	0
History of CNS metastases [a]	**75 (56%)**	**31 (60%)**
ALK Fusion	133 (100%)	52 (100%)
Secondary ALK mutation [b]	68 (51%)	28 (54%)
Single ALK mutation	34 (26%)	15 (29%)
Compound (i.e., ≥2) ALK mutations [c]	**34 (26%)**	**13 (25%)**
ALK G1202R (single or compound)	35 (26%)	15 (29%)

Treatment History	All Treated (N = 133)	RP2D (N=52)
Prior lines of anticancer treatment		
1	13 (10%)	4 (8%)
2	32 (24%)	13 (25%)
≥3	88 (66%)	35 (67%)
Median (range)	**3 (1, 9)**	**4 (1, 8)**
Prior treatments		
1 ALK TKI	18 (14%)	6 (12%)
2 ALK TKIs	54 (41%)	20 (39%)
≥3 ALK TKIs	61 (46%)	26 (50%)
Chemotherapy	74 (56%)	30 (58%)
ALK TKIs received [d]		
1G (crizotinib)	57 (43%)	24 (46%)
2G	127 (96%)	49 (94%)
alectinib	120 (90%)	46 (89%)
brigatinib	29 (22%)	12 (23%)
ceritinib	17 (13%)	8 (15%)
3G (lorlatinib)	**111 (84%)**	**44 (85%)**
Any 2G or lorlatinib	133 (100%)	52 (100%)
≥2 ALK TKIs, including 2G and lorlatinib	105 (79%)	41 (79%)
≥3 ALK TKIs, including 2G and lorlatinib	**58 (44%)**	**24 (46%)**

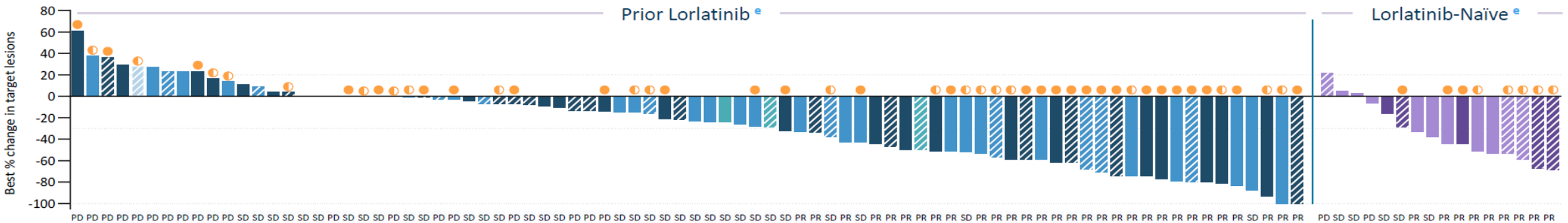
Data-cut off: 15 June 2024. All data shown as n (%) unless otherwise specified.

1G, 1st generation ALK TKI; **2G**, 2nd generation ALK TKI; **3G**, 3rd generation ALK TKI; **CNS**, central nervous; **TKI**, tyrosine kinase inhibitor.

[a] Includes patients with untreated CNS lesions and patients with prior disease progression on the brain-penetrant TKI lorlatinib. [b] ALK mutations as per local or central testing of blood (ctDNA) or tissue.

Preliminary Activity: Radiographic Tumor Responses Across Previously Treated Patients with ALK+ NSCLC

RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [b]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	**38%** (39/103)	**52%** (30/58)	**69%** (22/32) [d]	**35%** (30/85)	**47%** (23/49)	**54%** (15/28)	**53%** (9/17)	**88%** (7/8)
RP2D	**38%** (15/39)	**55%** (12/22)	**71%** (10/14)	**35%** (11/31)	**50%** (8/16)	**64%** (7/11)	**57%** (4/7)	**80%** (4/5)



Data cut-off: 15 June 2024. Response-evaluable patients with NSCLC. All responses were confirmed.

NSCLC, non-small cell lung cancer; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **RP2D**, Recommended Phase 2 dose (150 mg QD); **SD**, stable disease; **TKI**, tyrosine kinase inhibitor.

[a] Includes all patients with ≥1 identified ALK resistance mutation as per local or central testing of blood (ctDNA) or tissue. Responses observed in patients with ALK I1171N/S, V1180L, L1196Q, L1198F, D1203N, or E1210K mutations, including where multiple mutations co-occur, in addition to those with G1202R.

[b] Includes patients with G1202R single and compound (≥2) mutations.

[c] Cis-allelic configuration has not been confirmed for all patients with compound (≥2) ALK resistance mutations.

[d] **ORR = 67% (20/30) for G1202R patients with prior lorlatinib, and ORR= 100% (2/2) for lorlatinib-naïve G1202R patients.**

[e] Five response-evaluable patients (4 with no known ALK mutations and 1 with single ALK mutation) not shown due to incomplete or missing post-baseline tumor assessments in the setting of PD or symptomatic deterioration.

BARCELONA 2024 ESMO congress

KEY: PATIENT DETAILS

Lorlatinib Pre-treated:
- ≥ 3 prior ALK TKIs
- 2 prior, 2G + lorlatinib
- 2 prior, 1G + lorlatinib
- 1 prior (lorlatinib only)

Lorlatinib-naïve:
- ≥ 2 prior ALK TKIs
- 1 prior, alectinib

Patient treated at RP2D

- **ALK single resistance mutation**
- **ALK compound (≥2) resistance mutation**

NVL-655 is an ALK-selective, brain-penetrant, and TRK-sparing TKI:

- **In the fully-enrolled ALKOVE-1 phase 1 dose-escalation portion, NVL-655 was well tolerated and 150 mg QD was selected as the RP2D.**
  - The emerging safety profile was consistent with ALK-selective, TRK-sparing design.
- **Durable responses were observed in a heavily pre-treated population and across patient subgroups:**

Activity of NVL-655 at RP2D (RECIST 1.1)	ORR	mDOR
All ALK+ NSCLC response evaluable (1 – 5 prior ALK TKIs ± prior chemotherapy)	38%	Not reached (100% DOR ≥ 6 months)
Prior lorlatinib (≥2 prior ALK TKIs ± prior chemotherapy)	35%	Not reached (100% DOR ≥ 6 months)
With compound ALK resistance mutations	64%	Not reached (100% DOR ≥ 6 months)
Lorlatinib-naive (≥1 prior 2G ± 1G ALK TKI ± prior chemotherapy)	57%	Not reached (100% DOR ≥ 6 months)
With ALK resistance mutation(s)	80%	Not reached (100% DOR ≥ 6 months)

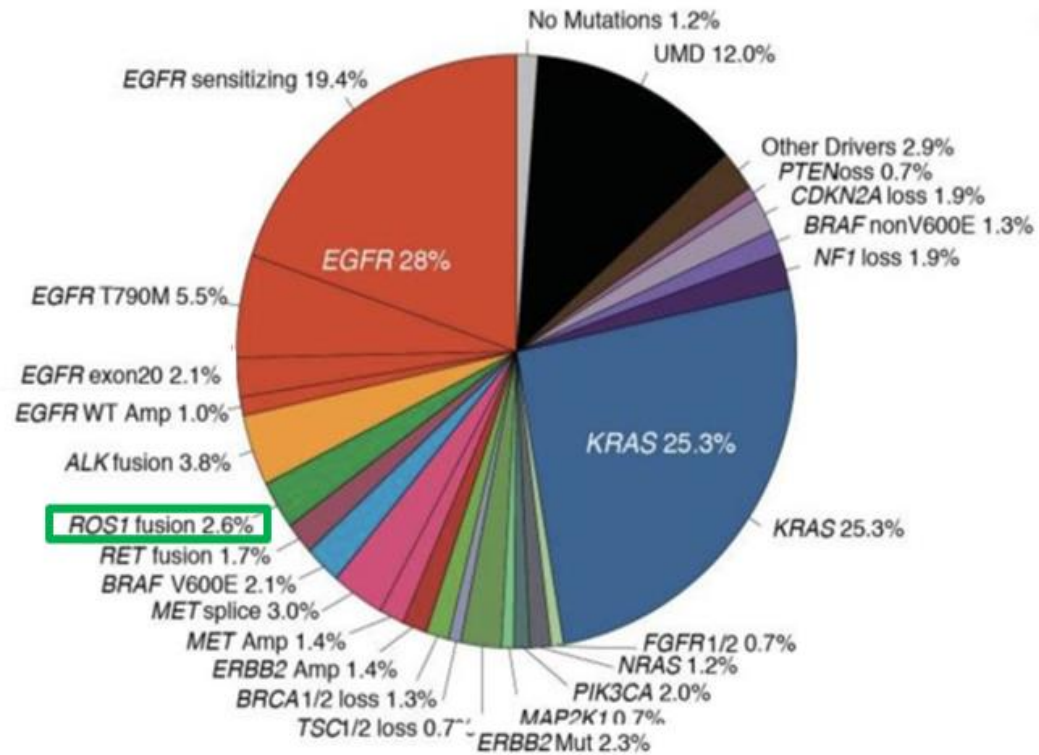
- **Durable intracranial responses were observed, including complete intracranial responses in patients who previously received the brain-penetrant TKI lorlatinib.**
- **Encouraging clinical activity in this heavily pre-treated population supports further investigation in less heavily pre-treated patients with ALK-positive NSCLC.**

ROS1 Pathway

FIRST-LINE THERAPY

ROS-1 rearrangement → *ROS1* rearrangement discovered prior to first-line systemic therapy → **Preferred**
Crizotinib[ss]
or
Entrectinib[ss,ooo]
or
Repotrectinib[ss,ooo] ★

NCCN Version 1.2025, 12/20/24



Updated Management on Advanced NSCLC Driver Mutant Tumors. Edgardo S. Santos, MD, FACP, FASCO. EdgardoSantosMD

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

TRIDENT-1 trial established the efficacy and safety of Repotrectinib in locally advanced or metastatic ROS1+ NSCLC:

TRIDENT-1: A multicenter, single-arm, open-label, multicohort clinical trial of patients with locally advanced or metastatic *ROS1*+ non-small cell lung cancer (NSCLC)[1]

KEY INCLUSION CRITERIA

- *ROS1*+ locally advanced or mNSCLC
- ECOG PS ≤1
- Measurable disease per RECIST v1.1
- ≥8 months from first dose
- Asymptomatic CNS metastases allowed

KEY EXCLUSION CRITERIA

History of:

- Interstitial lung disease
- Drug-related pneumonitis
- Symptomatic brain metastases
- Significant, uncontrolled, active cardiovascular disease
- Prolonged QTc interval

Phase 1 dose Escalation[a]

Repotrectinib RP2D 160mg QD x 14 days then 160mg BID

Phase 2 dose expansion cohorts[b]

***ROS1*+ advanced NSCLC**
Pooled population, inclusive of RP2D

EXP-1: *ROS1* TKI-naïve
(n=71)

EXP-4: 1 prior *ROS1* TKI AND no prior chemotherapy or immunotherapy
(n=56)

PRIMARY EFFICACY ENDPOINT:

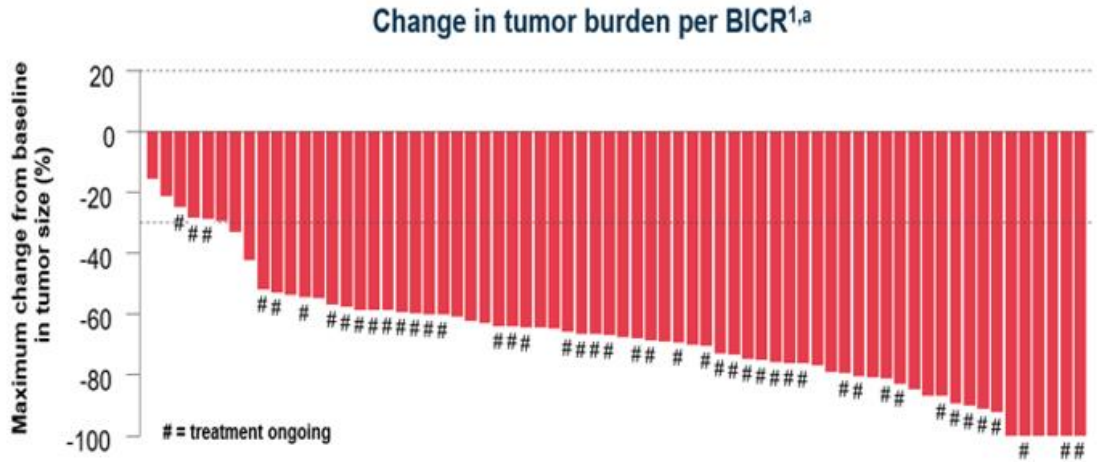
- ORR as assessed by BICR per RECIST v1.1

KEY SECONDARY ENDPOINTS:

- DOR, PFS [1,2]
- Intracranial response according to modified RECIST v1.1 as assessed by BICR

The ROS1+ NSCLC safety population included 264 patients in TRIDENT-1 who received the recommended dose of repotrectinib.

Overall response rate in TKI-naïve population:



TKI-naïve (n=71)	
ORR,[1,2,a] % (95% CI)	79% (68, 88)
n/n	56/71
CR (n,%)	4 (6)
PR (n,%)	52 (73)

Database lock: June 20, 2022; median follow-up: 18.1 months

mDOR and icORR with Repotrectinib in the TKI-naïve population:

Secondary Endpoint

34 Month

mDOR[1,2,a]

(95% CI: 25.6, NE; range: 1.4+, 42.4+ months)

Median follow-up for DOR data: 24.0 months.[2]

70% *of patients*

were still responding at 12 months of treatment[1,c]

Secondary Endpoint

icORR seen in 7/8 patients[1]

with measurable CNS metastasis at baseline[b]

Median follow-up for icORR data: 18.1 months.[3]

Pooled Efficacy and Safety From 2 Pivotal Phase 2 Trials of Taletrectinib in Patients With Advanced or Metastatic ROS1+ Non–Small Cell Lung Cancer

Maurice Pérol,[1] Wei Li,[3] Nathan A. Pennell,[2] Geoffrey Liu,[4] Yuichiro Ohe,[5] Filippo De Braud,[6] Misako Nagasaka,[7] Enriqueta Felip,[8] Anwen Xiong,[3] Yongchang Zhang,[9] Huijie Fan,[10] Xicheng Wang,[11] Bing Yan,[12] Shuanglian Li,[12] Michael Chen,[12] Lyudmila Bazhenova,[13] Caicun Zhou[3]

[1]Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France; [2]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [3]Department of Medical Oncology, Shanghai Pulmonary Hospital and Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China; [4]Princess Margaret Cancer Centre, Temerty School of Medicine, University of Toronto, Toronto, Canada; [5]National Cancer Center Hospital, Tokyo, Japan; [6]University of Milan, Milan, Italy; [7]University of California Irvine School of Medicine and Chao Family Comprehensive Cancer Center, Orange, CA, USA; [8]Vall d'Hebron University Hospital, Barcelona, Spain; [9]Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; [10]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [11]The First Affiliated Hospital/School of Clinical Medicine Guangdong Pharmaceutical University, Guangzhou, China; [12]Nuvation Bio, New York, NY, USA; [13]University of California San Diego Moores Cancer Center, San Diego, CA, USA

TRUST-1 Study:

Key Eligibility Criteria for Pivotal Cohorts

- Locally advanced or metastatic NSCLC
- Age ≥18 years[a]
- ECOG PS 0–1
- Evidence of ROS1 fusion
- Stable CNS involvement allowed
- At least 1 measurable lesion per RECIST v1.1

ROS1 TKI naive | **ROS1 TKI pretreated[b]**

Taletrectinib 600 mg QD[c]

Study Endpoints

Primary
- IRC-assessed cORR per RECIST v1.1

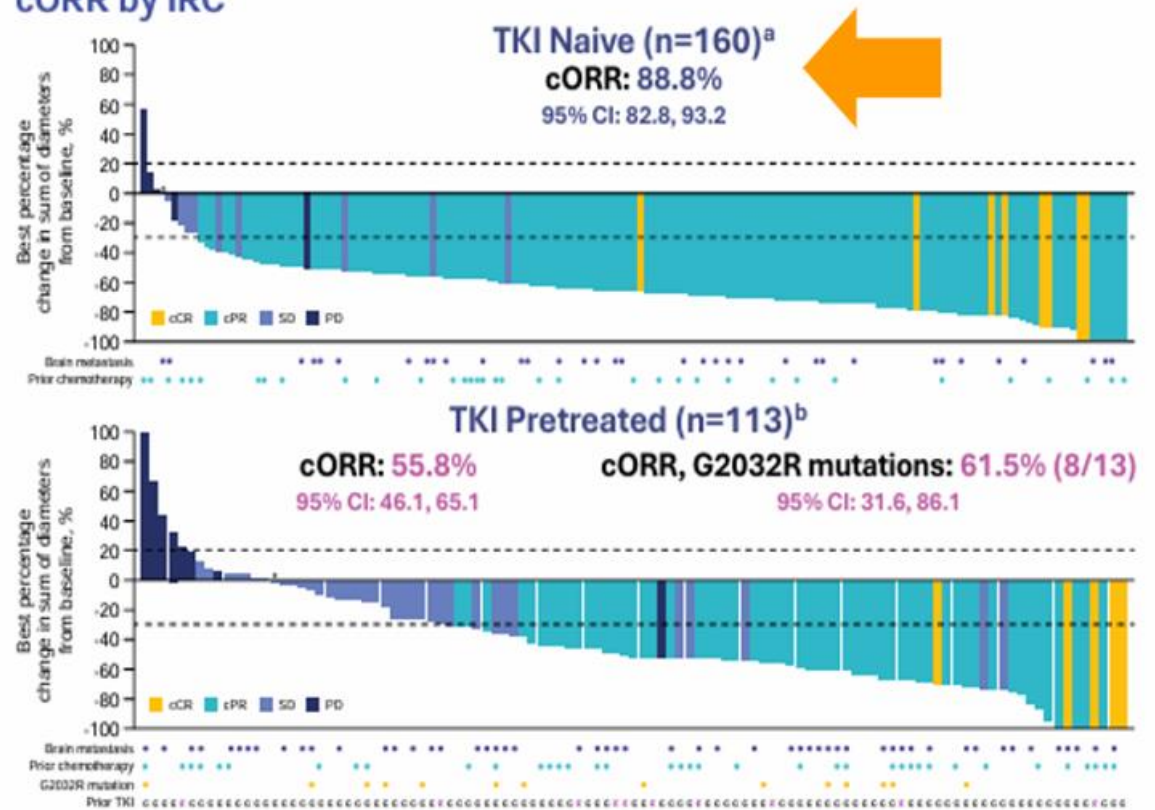
Key Secondary
- IC-cORR per mRECIST v1.1
- DOR
- PFS
- Safety

Study Populations
- Efficacy[c]: Response evaluable population (REP) included patients with ROS1+ NSCLC with ≥1 measurable lesion at baseline per RECIST V1.1 by IRC and who received ≥1 dose of taletrectinib; TKI naive (n=160) and TKI pretreated (n=113)
- Safety[c]: Patients with ROS1+ NSCLC who received ≥1 dose of taletrectinib 600 mg (n=337)

[a]Or ≥20 years, as required by local regulations. [b]One prior ROS1 TKI (crizotinib [C] or entrectinib [E]). [c]Three patients in TRUST-I started taletrectinib 400 mg and of these, 2 escalated to 600 mg.

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

cORR by IRC

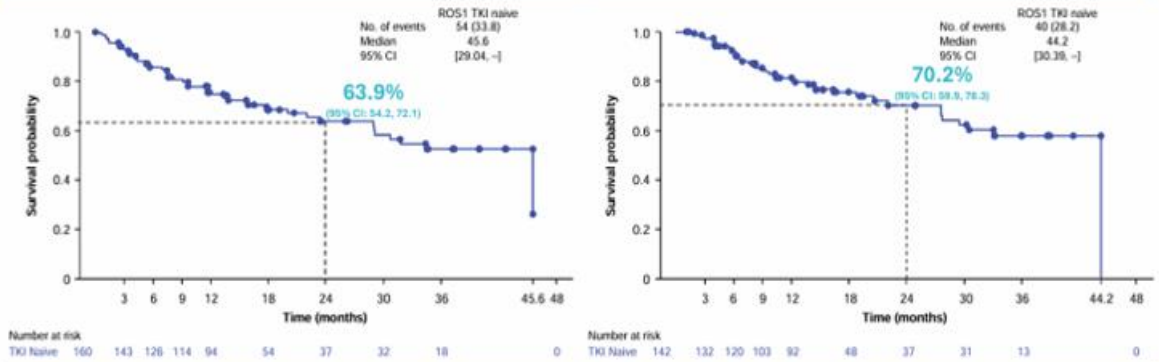


[a]Three patients with confirmed BOR as not evaluable are not displayed in the waterfall plot. [b]Six patients with confirmed BOR as not evaluable are not displayed in the waterfall plot. [c]One patient had a best percentage change of 0 and BOR as SD.

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

Efficacy in TKI-Naive Patients

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



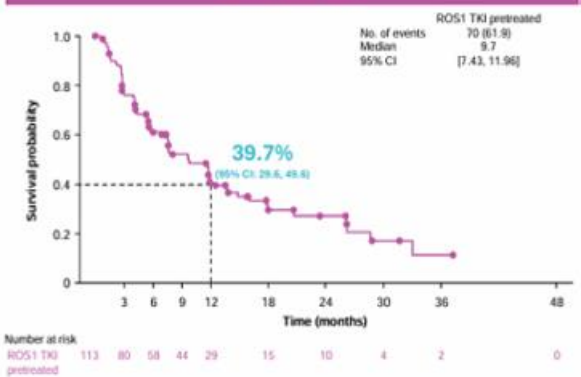
Median DOR[a]: 44.2 months
95% CI: 30.4, NR

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

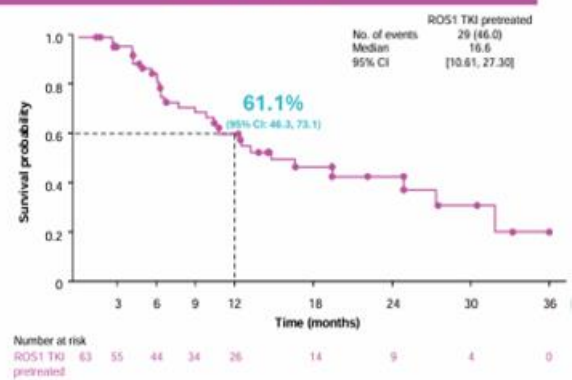
[a]REP patients with a confirmed objective response.

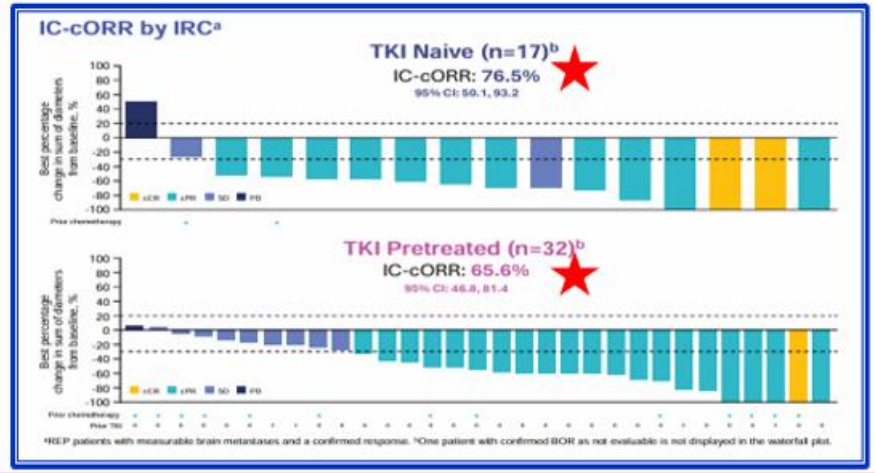
Efficacy in TKI-Pretreated Patients

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.

NTRK Pathway

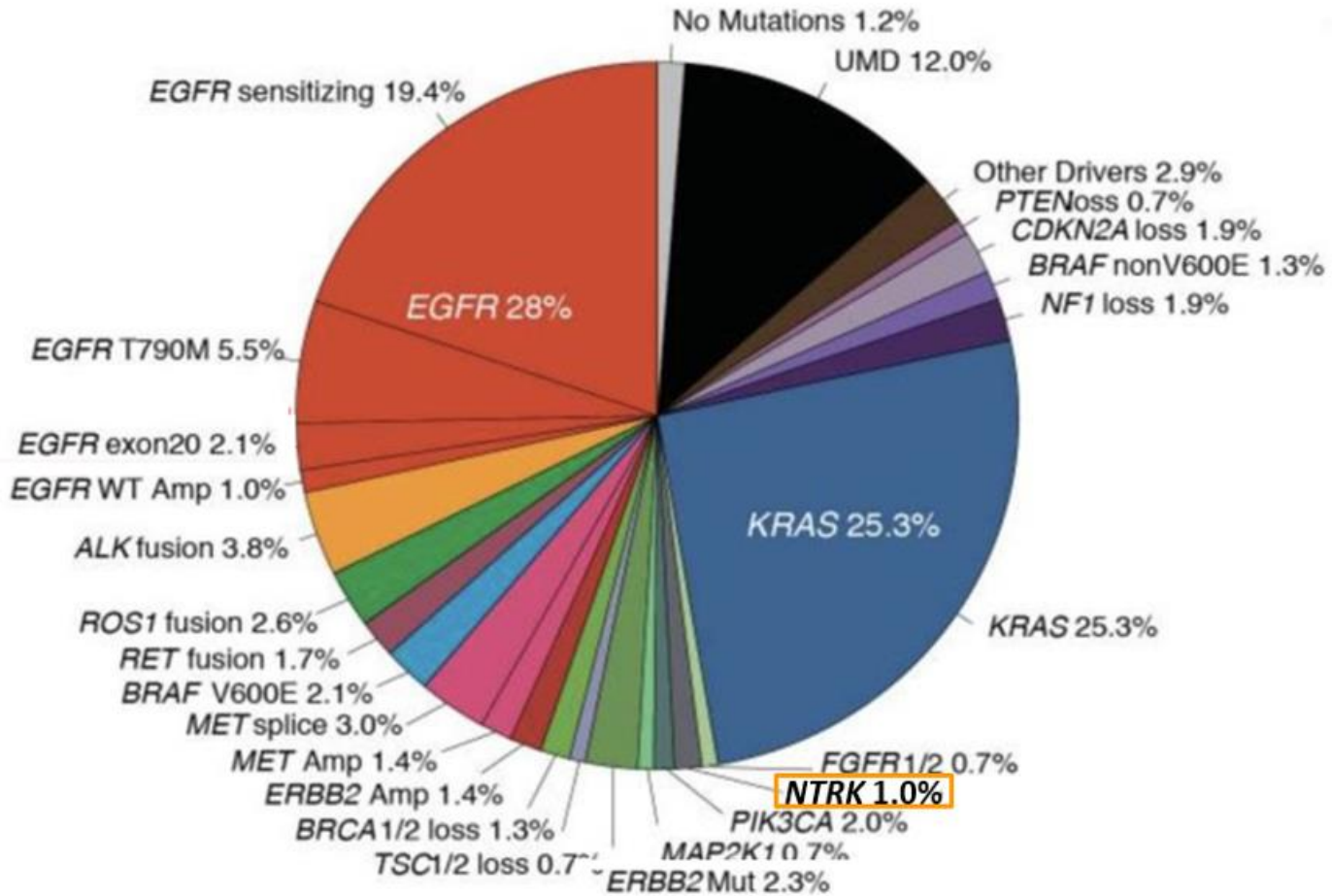
(Ctrl)

NTRK 1/2/3 → ***NTRK1/2/3*** **gene fusion discovered prior to first-line systemic therapy** →

Preferred
Entrectinib[ss]
or
Larotrectinib[ss]
or
Repotrectinib[ss]

Useful in Certain Circumstances
Systemic Therapy, Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)

NCCN Version 1.2025, 12/20/24



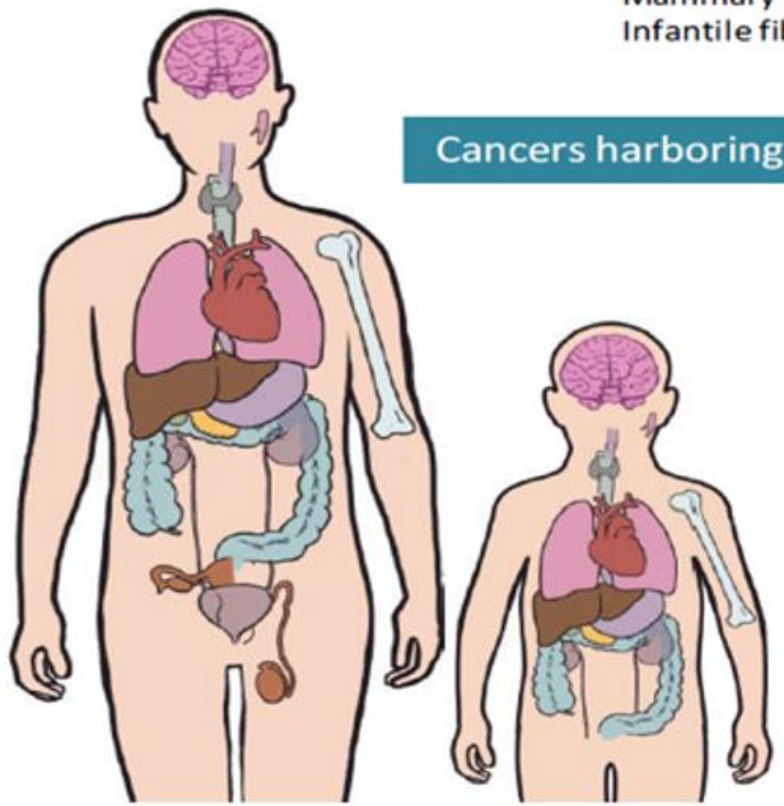
NTRK fusions are found in diverse cancers including lung cancers

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

Cancers enriched for TRK fusions

Secretory breast carcinoma
Mammary analogue secretory carcinoma
Infantile fibrosarcoma

Frequency
75% to >90%



Cancers harboring TRK fusions at lower frequencies

Congenital mesoblastic nephroma
Pontine glioma
Spitzoid melanoma
Thyroid Cancer
GIST ("pan-negative")

Frequency
5% to 25%

Lung cancer
Other sarcomas
Astrocytoma/Glioblastoma
Colorectal cancer
Cholangiocarcinoma
Pancreatic cancer
Head and neck squamous cancer
Breast cancer
Melanoma

Frequency
<1% to <5%

FDA grants accelerated approval to repotrectinib for adult and pediatric patients with NTRK gene fusion-positive solid tumors

June 13, 2024:

Efficacy and Safety

Efficacy was evaluated in TRIDENT-1 (NCT03093116), a multicenter, single-arm, open-label, multi-cohort trial in 88 adult patients with locally advanced or metastatic *NTRK* gene fusion-positive solid tumors who had either received a prior TRK tyrosine kinase inhibitor (TKI) (n=48) or were TKI-naïve (n=40). All patients were assessed for central nervous (CNS) lesions at baseline, and patients with symptomatic brain metastases were excluded. Tumor assessments were performed every 8 weeks.

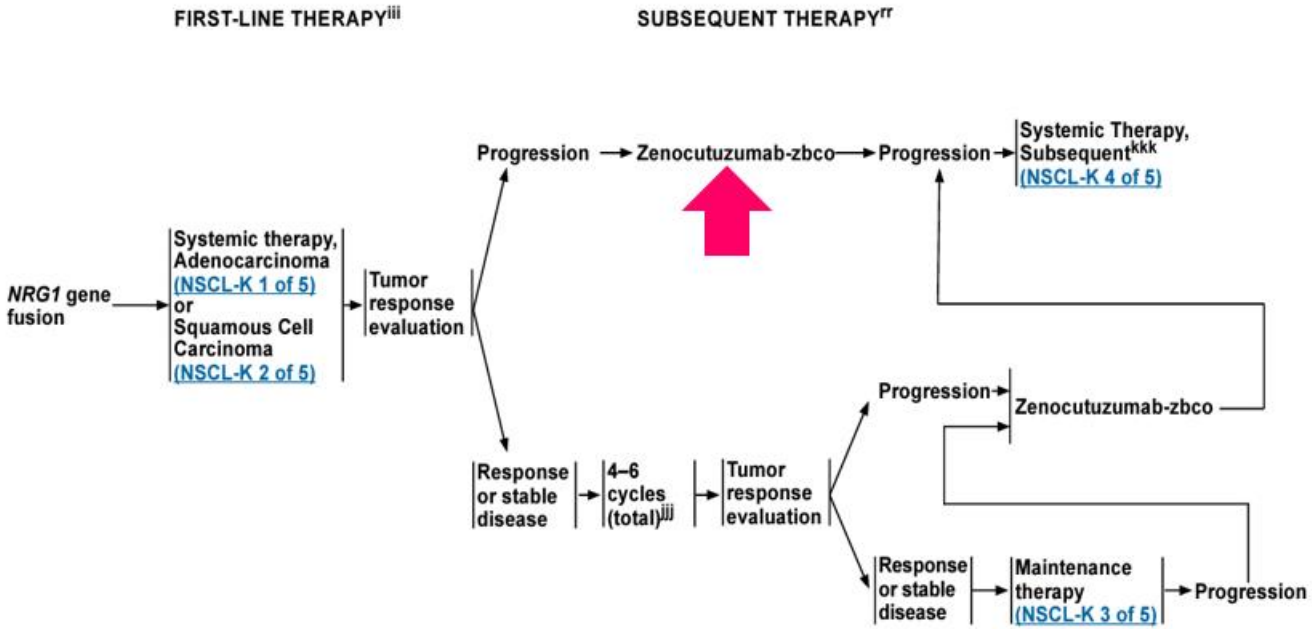
The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) according to RECIST v1.1 as assessed by blinded independent central review. Confirmed ORR in the TKI-naïve group was 58% (95% [confidence internal] CI: 41, 73) and 50% (95% CI: 35, 65) in the TKI-pretreated group. Median DOR was not estimable (NE) (95% CI: NE, NE) in the TKI-naïve group and 9.9 months (95% CI: 7.4, 13.0) in the TKI-pretreated group.

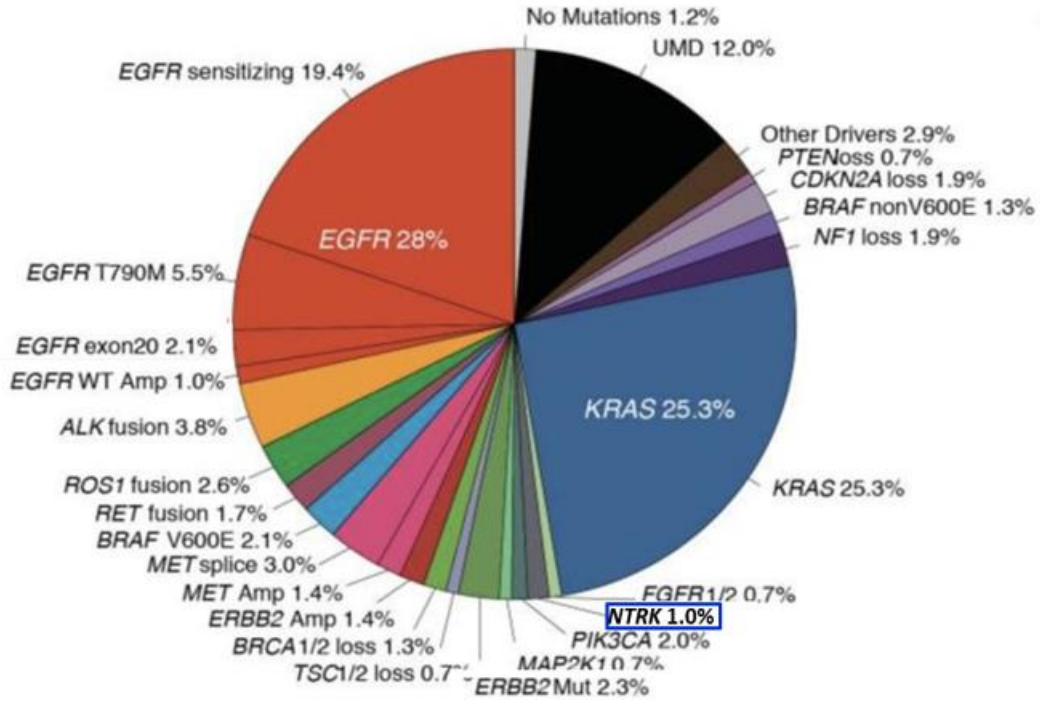
The most common (>20%) adverse reactions were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness, and nausea.

ORR TKI-naïve: 58%
ORR TKI-pretreated: 50%

DOR TKI-naïve: NE
DOR TKI-pretreated: 9.9 months

NRG1 Pathway





NCCN Version 1.2025, 12/20/24

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation

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

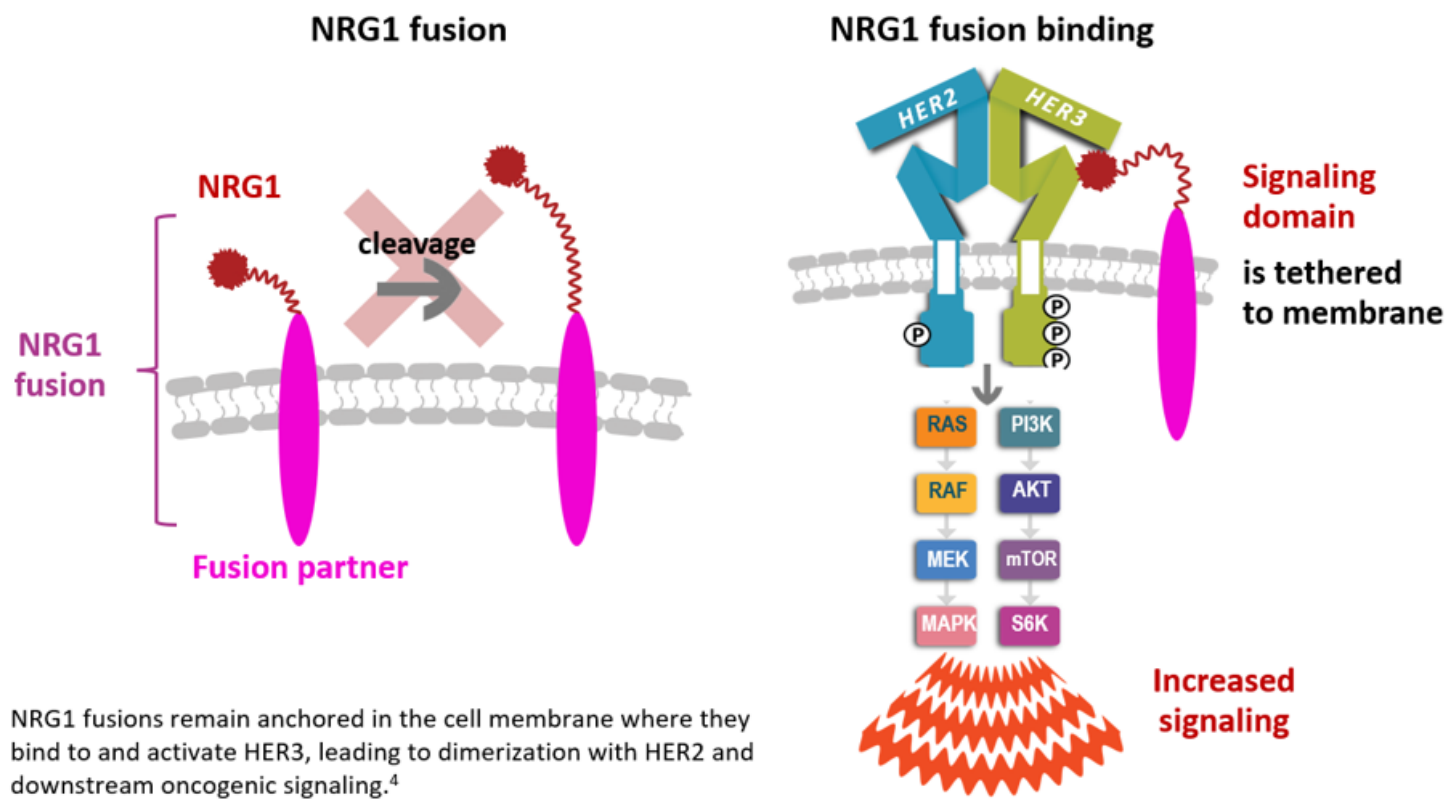
NRG1 fusions induce receptor dimerization and result in aberrant cell signaling[3,4]

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.

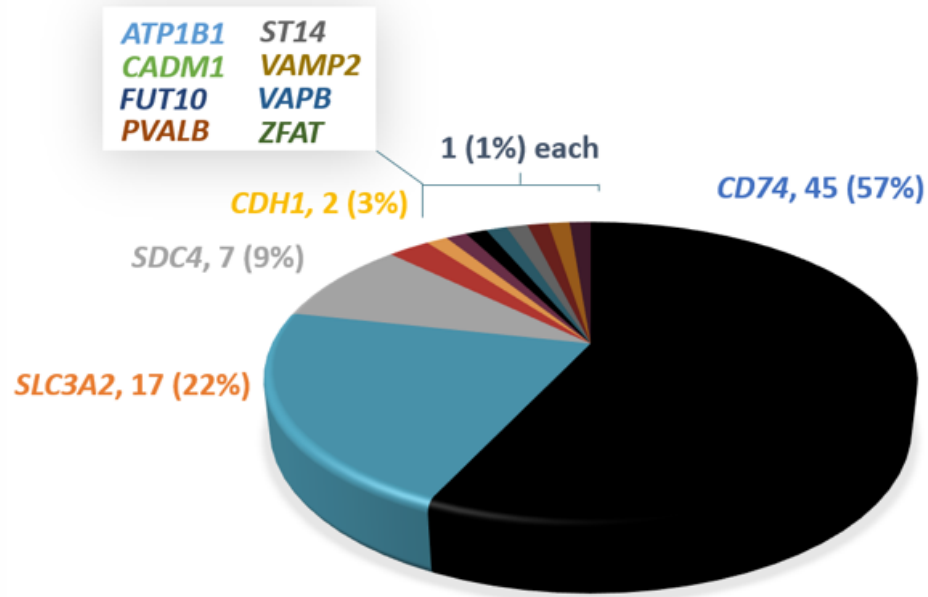
MADRID 2023 ESMO congress

[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

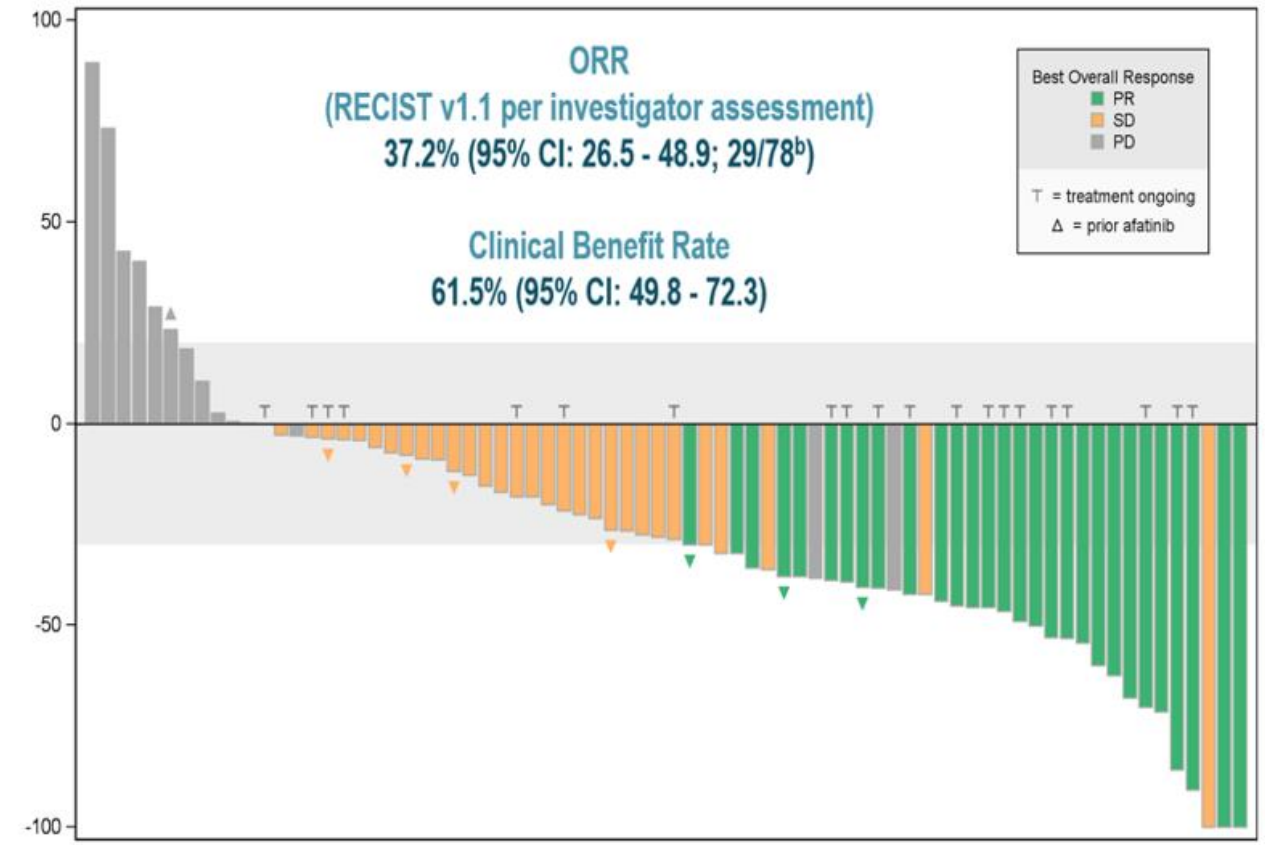


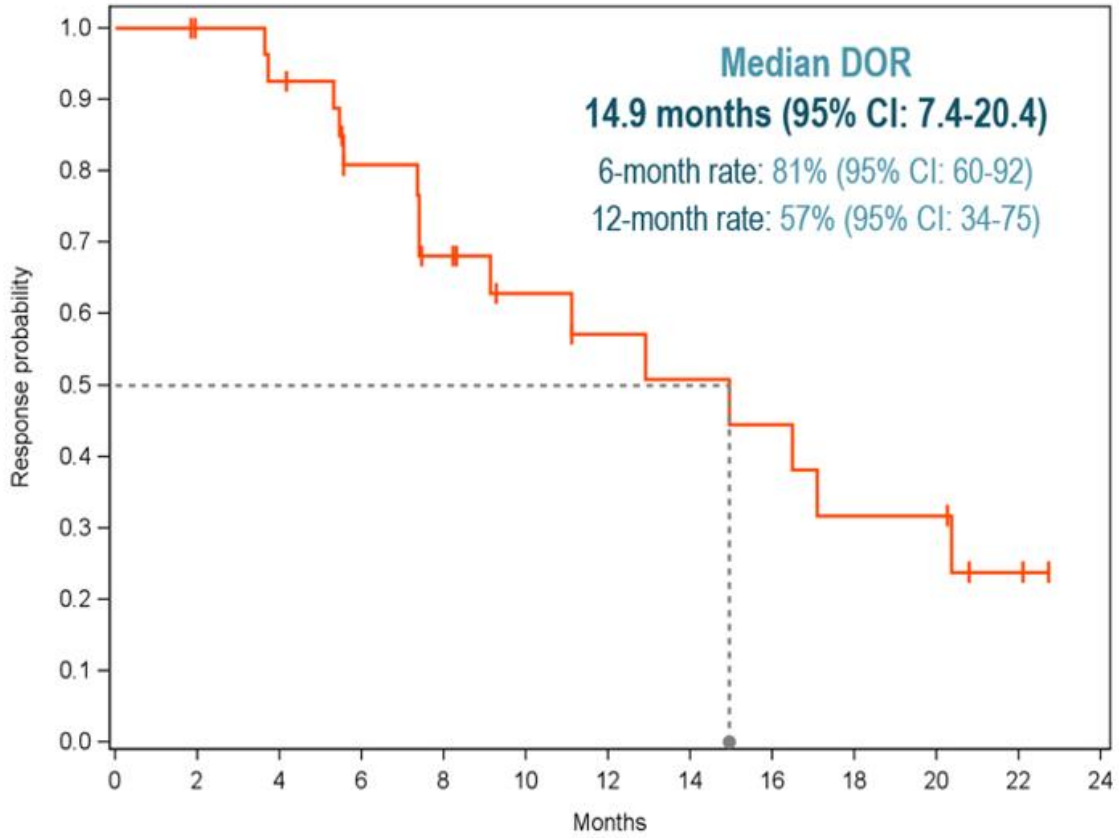
NRG1 identification technology, n (%)	
RNAseq	64 (81)
DNAseq	11 (14)
Nanostring	1 (1)
Missing	3 (4)

MADRID 2023 ESMO congress

[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:





Number of patients at risk

29	27	25	19	15	11	9	8	7	5	5	2	0

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)
- The number of targeted agents continues growing in several driven pathways: ALK, ROS1, NTRK, and HER2.
- NRG-1 is the latest driver abnormality with a druggable agent.
- MARIPOSA-2 regimen: first approval for Osimertinib resistance.
- Novel combinations for 1L EGFR sensitive mutations: FLAURA 2 and MARIPOSA trials.

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

The Oncology Institute of Hope & Innovation