Front Line Targeted Therapy in NSCLC: Thyrosine Kinase Inhibitors

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January 20, 2024

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Outline (in 15 mins, to cover 6 pathways)

- Osimertinib adjuvant: **ADAURA**, OS data.
- Osimertinib in front line metastatic **[FLAURA2]**
- Lazertinib (3rd Gen EGFR TKI plus Ami) front line therapy **[MARIPOSA]**
- Sunvozertinib (new agent, watch out); new standard now for EGFRex20ins (chemo/ami) and Mobocertinib was voluntarily withdraw from US market **[EXCLAIM-2 negative]**
- Alectinib adjuvant: **ALINA** study
- Repotrectinib approved November 21, 2023 **[TRIDENDT]**
- Encorafenib/Binimetinib combo approved BRAFV600E **[PHAROS]**
- Selpercatinib front line vs Chemo/IO- **[LIBRETTO 431]**

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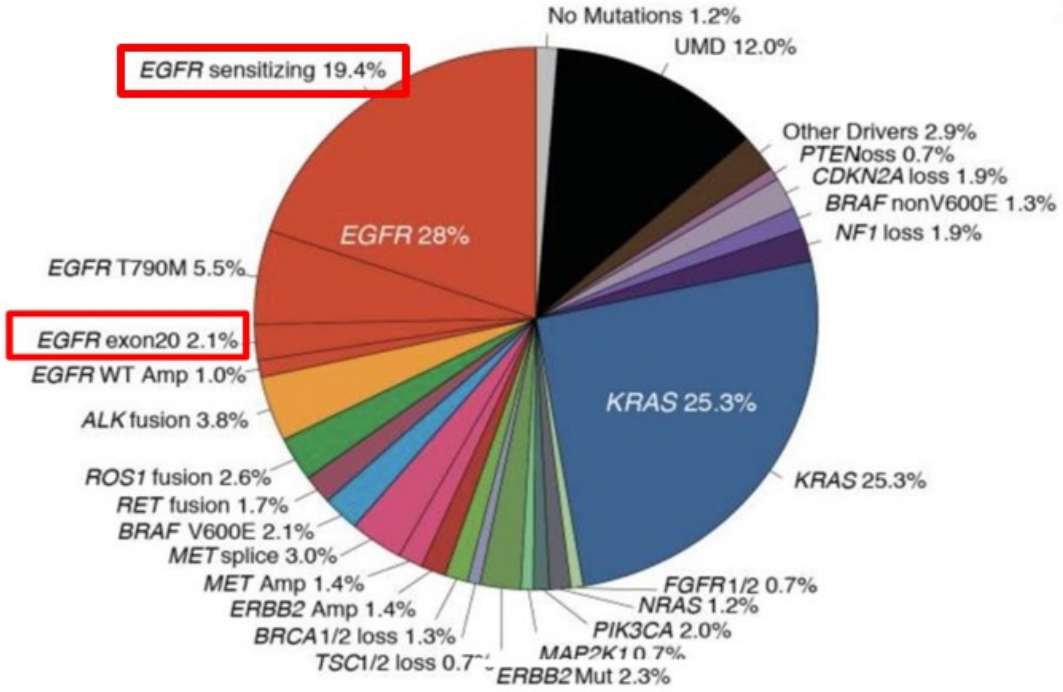
EGFRex19del, L858R (ex21) & EGFRex20ins



Osimertinib- EGFR TKI

Adjuvant setting
Where are we now?

The ADAURA study has demonstrated a statistically significant and clinically meaningful OS benefit with adjuvant osimertinib vs placebo in patients with resected EGFRm stage IB–IIIA NSCLC

>2 million
new cases of lung cancer worldwide annually[1]

NSCLC represents **~80%** of all diagnoses[1]

Approximately **30%** of patients have resectable disease[2–4]

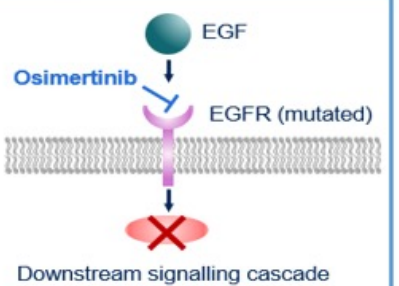
EGFR mutation prevalence ranges from **10–50%** in patients with NSCLC[5–9]

ADAURA

Surgery → Adjuvant Therapy

Osimertinib vs placebo

Adjuvant osimertinib



Osimertinib is the first EGFR-TKI to show significant OS benefit in a Phase III adjuvant study

Reinforces osimertinib as standard of care

EGFR mutation testing

Best treatments early

New era for targeted treatment in early-stage disease

1. Cancer.net 2023. Available at: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics; 2. Datta et al. Chest 2003;123:2096–2103; 3. Le Chevalier Ann Oncol 2010;21(Suppl 7):vii196–8; 4. Cagle et al. Arch Pathol Lab Med 2013;137:1191–1198; 5. Pi et al. Thorac Cancer 2018;9:814–819; 6. Hondelink et al. Eur J Cancer 2023;181:53–61; 7. Zhang et al. Oncotarget 2016;7:78985–78993; 8. Stone et al. Intern Med J 2014;44:1188–1192; 9. Kim et al. Pathology 2020;52:410–420.

ADAURA Phase III study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Maximum interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
Stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
Race (Asian vs non-Asian)

Randomization 1:1 (N=682)

Osimertinib 80 mg, once daily

Placebo, once daily

Planned treatment duration: 3 years

Treatment continued until:
- Disease recurrence
- Treatment completion
- Discontinuation criterion met

Follow-up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

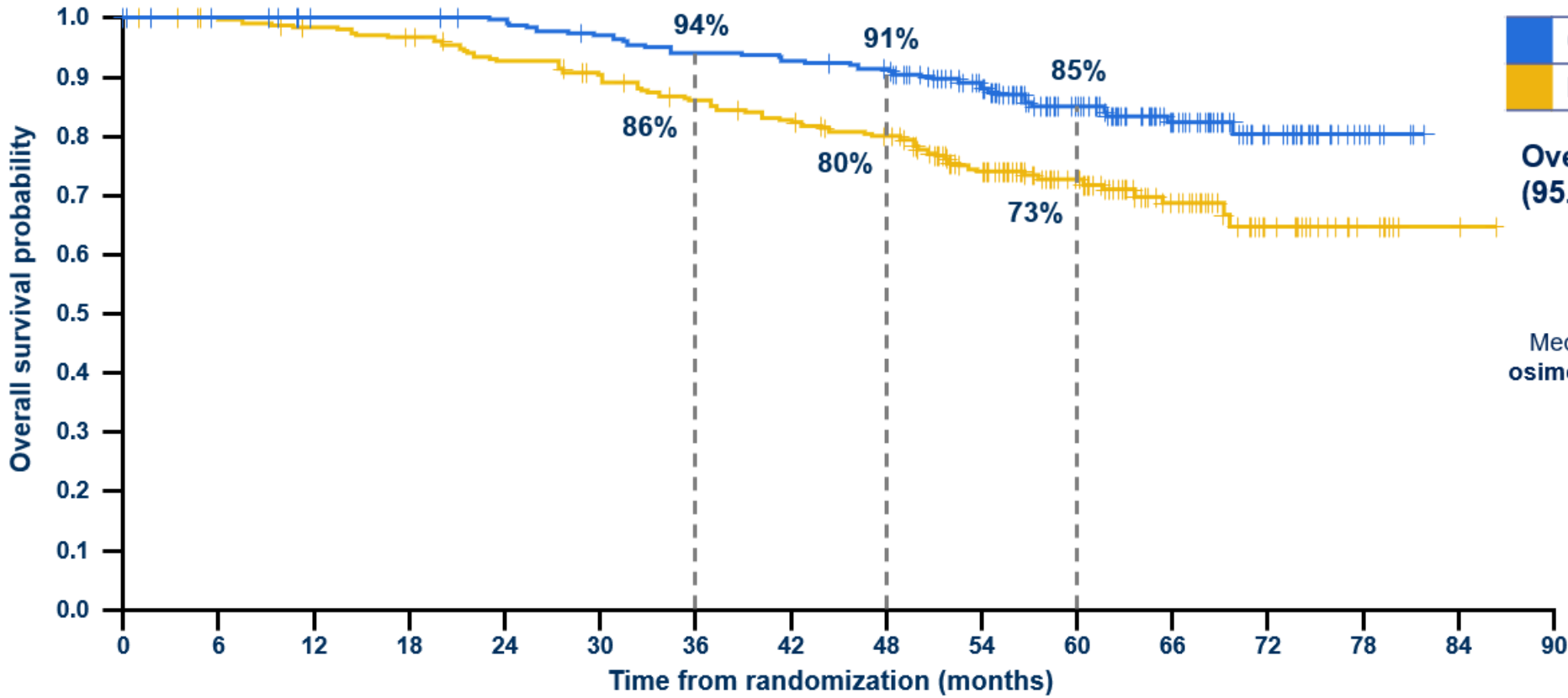
Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

*At the time of recruitment, staging was determined by the AJCC / UICC Staging Manual 7th edition. Patients with stage IB disease were not eligible in Japan. †Pre-operative, post-operative, or planned radiotherapy was not allowed. ‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment.

AJCC, American Joint Committee on Cancer; CT, computerized tomography; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; UICC, Union for International Cancer Control; WHO, World Health Organization

Overall survival: patients with stage II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the primary population of stage II–IIIA disease



No. at risk																
Osimertinib	233	229	224	224	221	214	208	205	200	170	115	69	33	9	0	-
Placebo	237	232	226	221	210	202	190	182	171	138	94	53	25	8	2	0

5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)

Overall OS HR (95.03% CI) **0.49 (0.33, 0.73); p=0.0004**

Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Resected *EGFR*-Mutated NSCLC

Masahiro Tsuboi, M.D., Roy S. Herbst, M.D., Ph.D., Thomas John, M.B., B.S., Ph.D., Terufumi Kato, M.D., Margarita Majem, M.D., Ph.D., Christian Grohé, M.D., Jie Wang, M.D., Ph.D., Jonathan W. Goldman, M.D., Shun Lu, M.D., Wu-Chou Su, M.D., Filippo de Marinis, M.D., Frances A. Shepherd, M.D., Ki Hyeong Lee, M.D., Ph.D., Nhieu Thi Le, M.D., Arunee Dechaphunkul, M.D., Dariusz Kowalski, M.D., Ph.D., Lynne Poole, M.Sc., Ana Bolanos, M.D., Yuri Rukazenkov, M.D., Ph.D., and Yi-Long Wu, M.D., for the ADAURA Investigators*

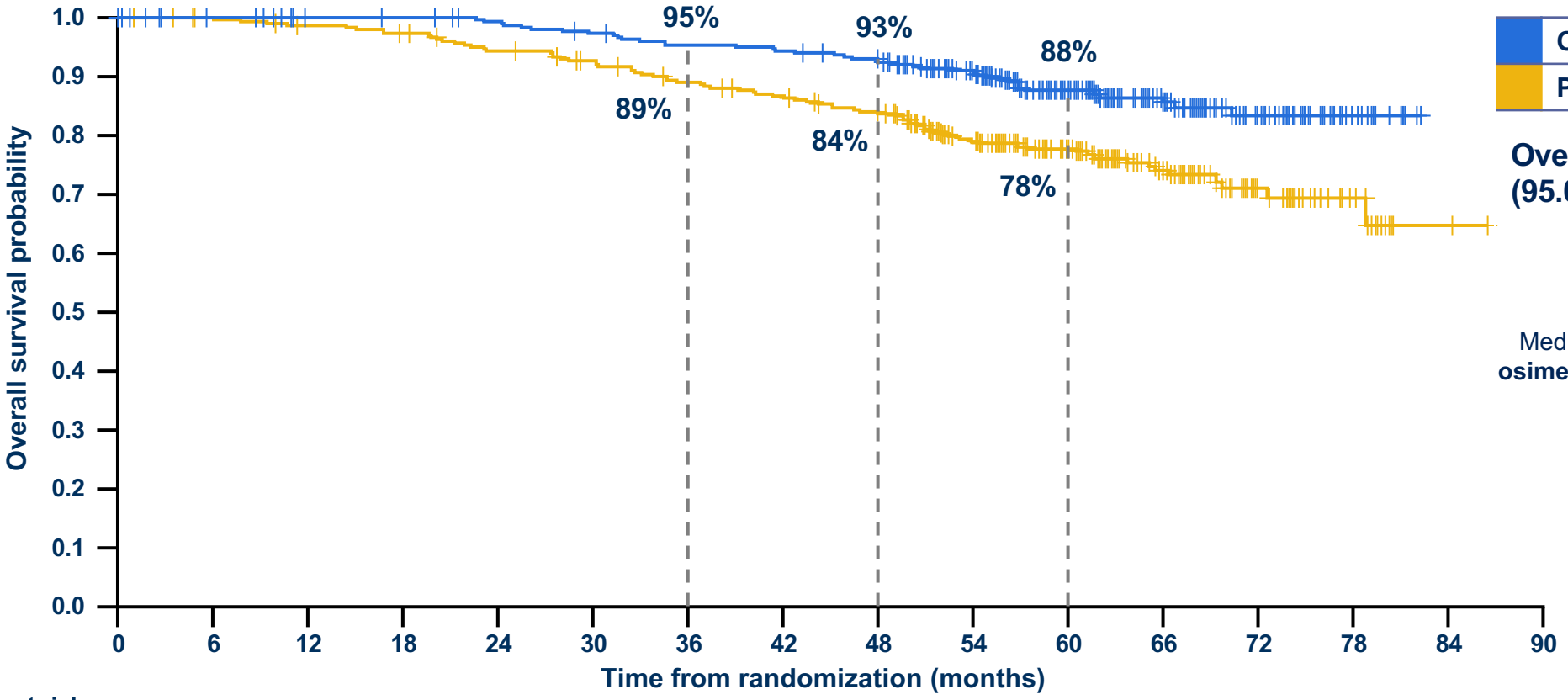
Data cut-off: January 27, 2023.

Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 59.9 months, placebo 56.2 months.

CI, confidence interval; HR, hazard ratio; OS, overall survival

Overall survival: patients with stage IB / II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the overall population of stage IB–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) **0.49 (0.34, 0.70); p<0.0001**

Maturity: 18%
osimertinib 12%, placebo 24%

Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

No. at risk

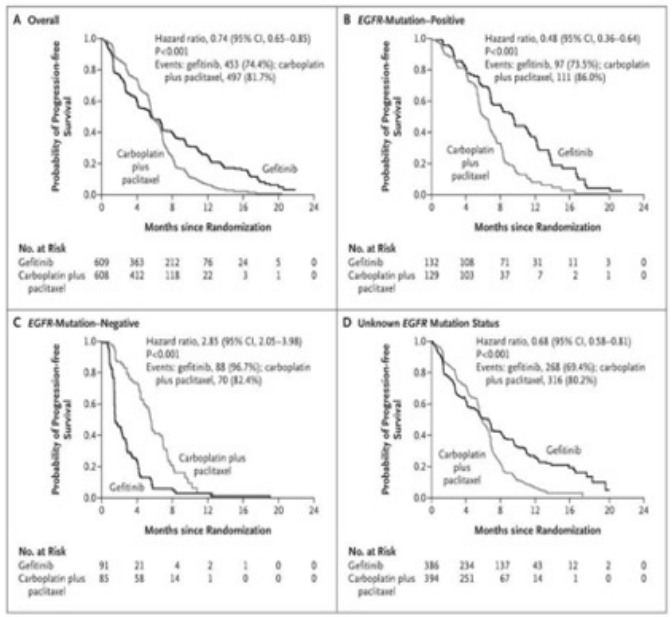
Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	-
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

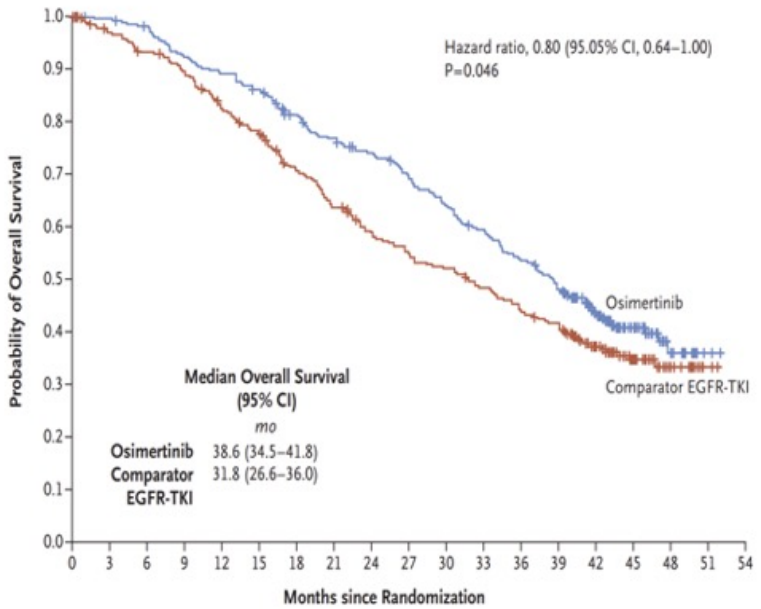
Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.

CI, confidence interval; HR, hazard ratio; OS, overall survival

Osimertinib- EGFR TKI

Metastatic setting
Where are we going?





1L Treatment of EGFRm NSCLC November 2023

+ Chemo

FLAURA2: Osimertinib + Chemotherapy > Osimertinib

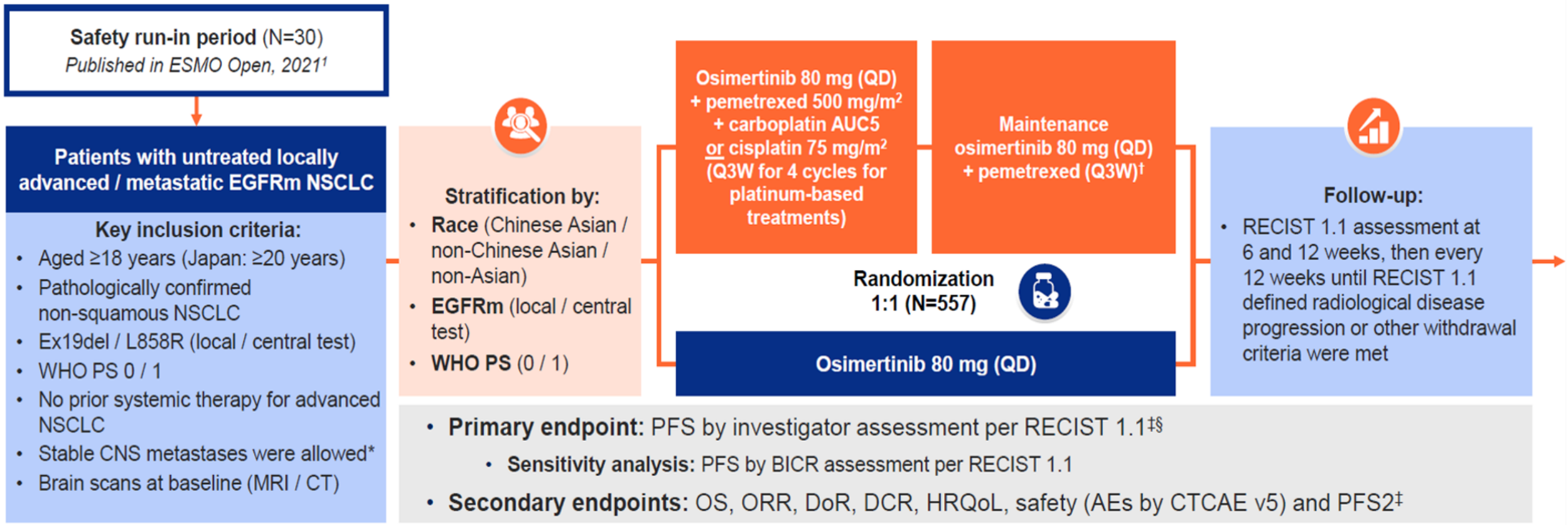
+ EGFR/MET mAb

MARIPOSA: Amivantamab + Lazertinib > Osimertinib, Lazertinib

IPASS 2009 | **FLAURA 2018** | **2023**

IPASS Mok TS et all NEJM 2009; FLAURA Soria JC et al NEJM 2018; FLAURA2 Janne P et al NEJM 2023; MARIPOSA Cho et al ESMO 2023

FLAURA2: 1L Osimertinib + Chemotherapy vs Osimertinib



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

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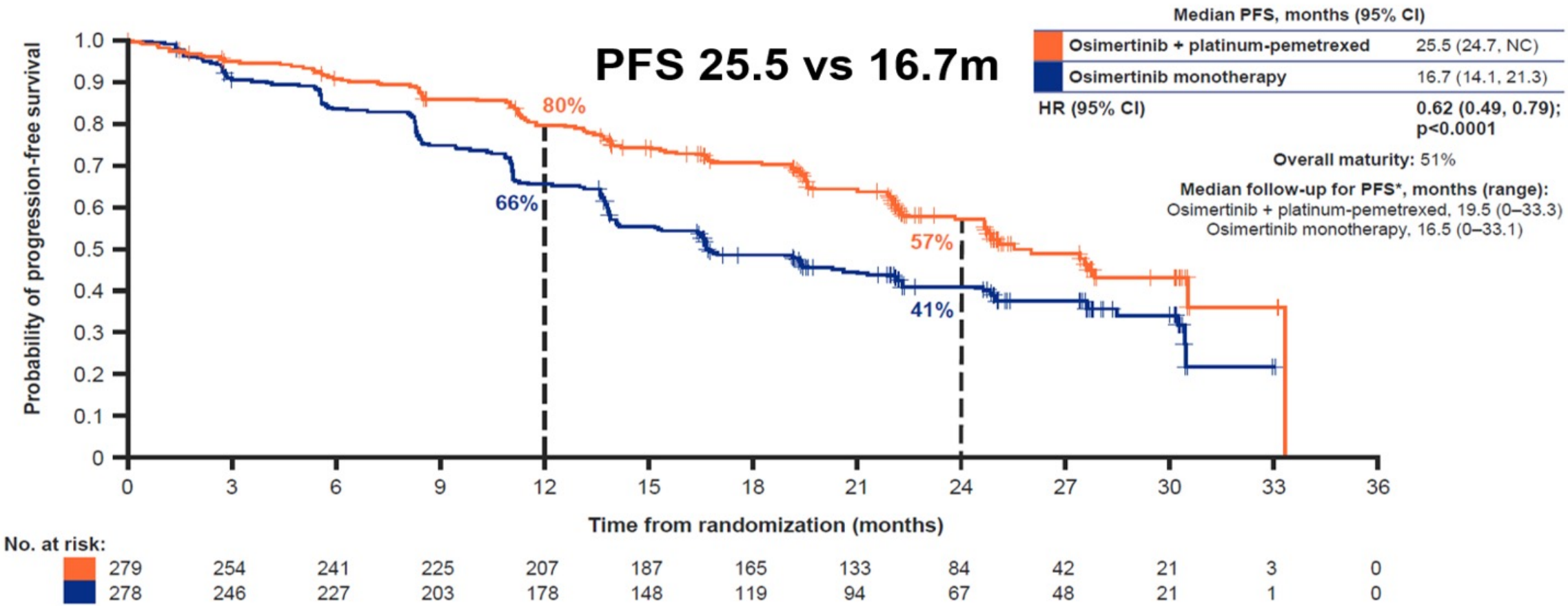
FLAURA2: PFS per investigator



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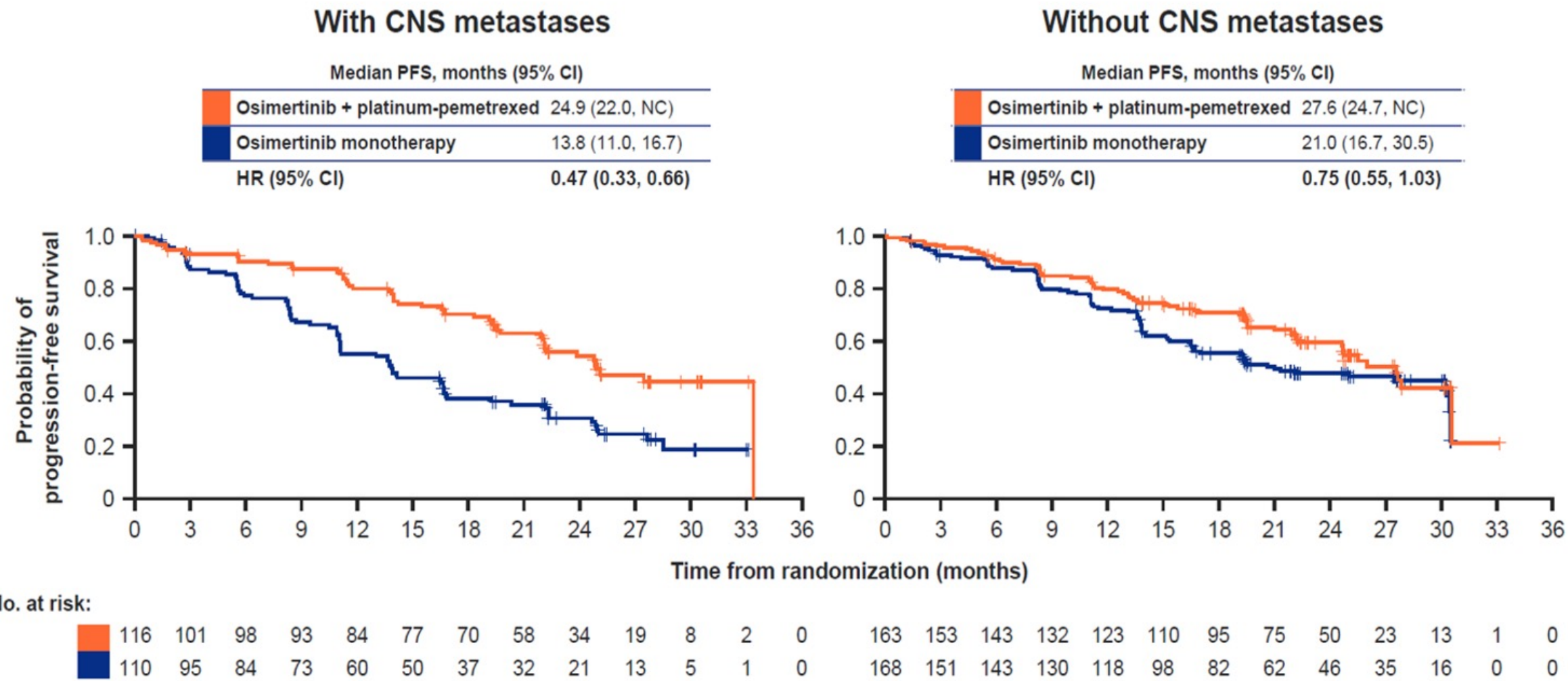
FLAURA2: PFS per investigator by CNS Metastases



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

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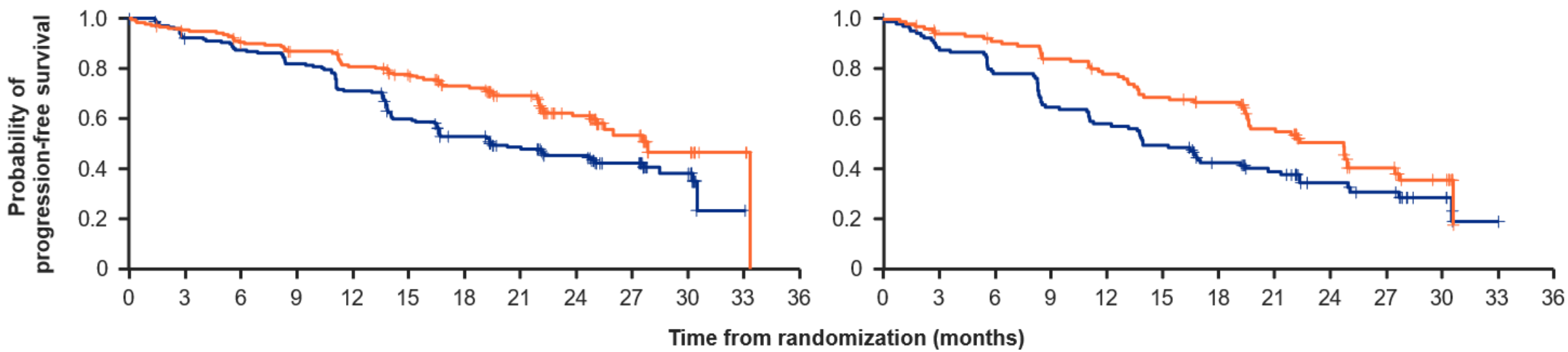
PFS per investigator by EGFR mutation type at baseline*

Ex19del

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

L858R

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



No. at risk:

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

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

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

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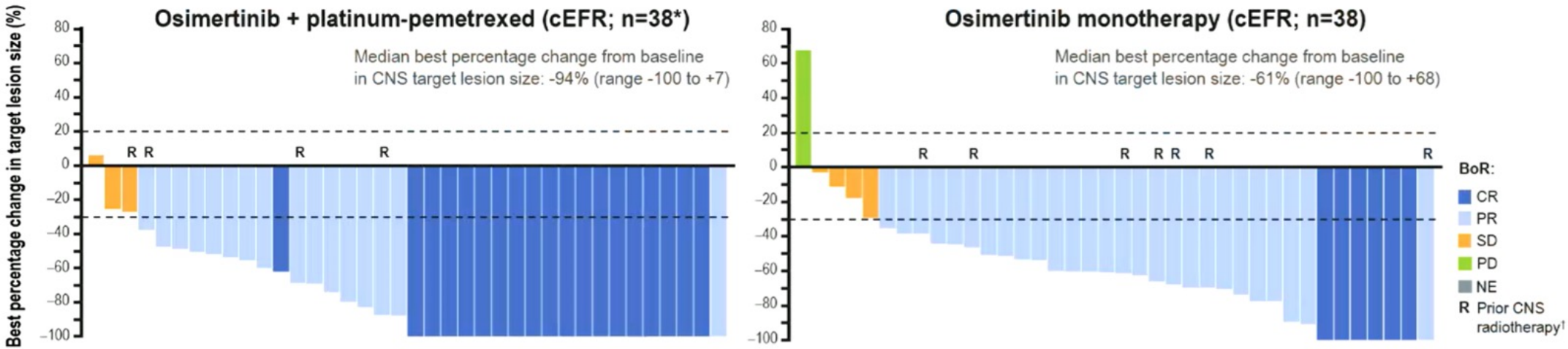
FLAURA2: Updated CNS Data ESMO 2023

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

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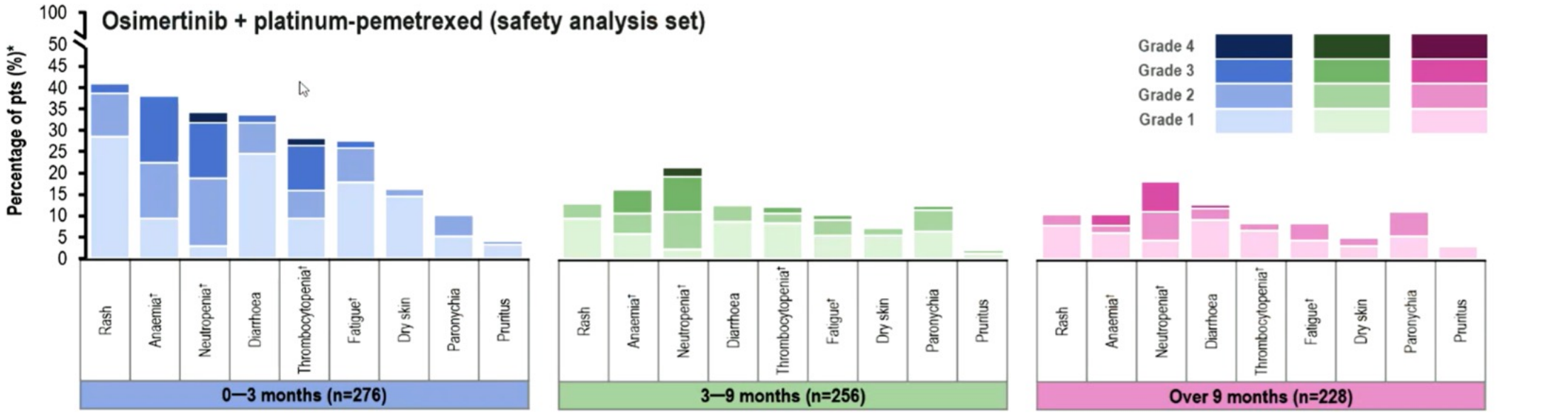
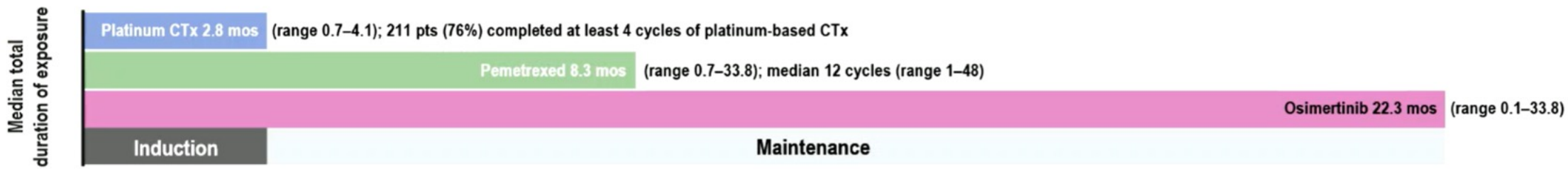
What about toxicity?

AE ONSET FREQUENCY AND SEVERITY WERE HIGHEST DURING THE INDUCTION PERIOD, AND GRADUALLY REDUCED OVER TIME

- In the osi + CTx arm, the onset of ≥Grade 3 AEs reduced by ~50% between 0–3 mos (n=135; 49%) and 3–9 mos (n=62; 24%)





Presented Planchard et al. ESMO 2023 Abstract LBA68

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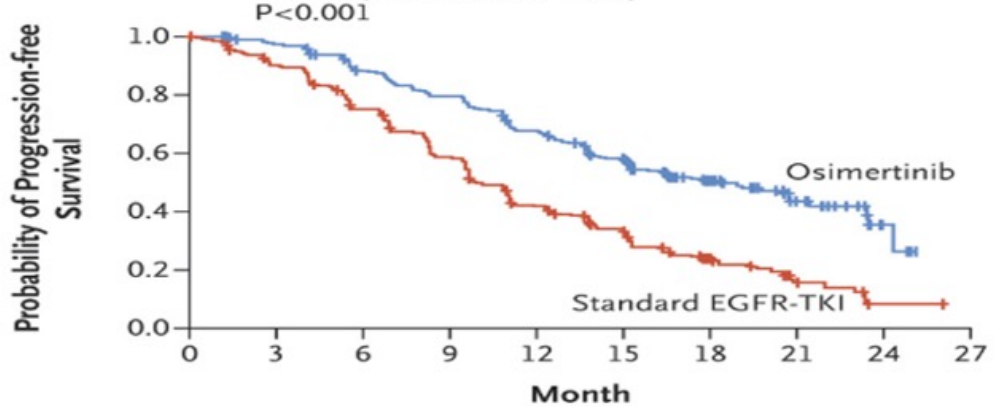
Just to Remember…..

FLAURA vs FLAURA2

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI) mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

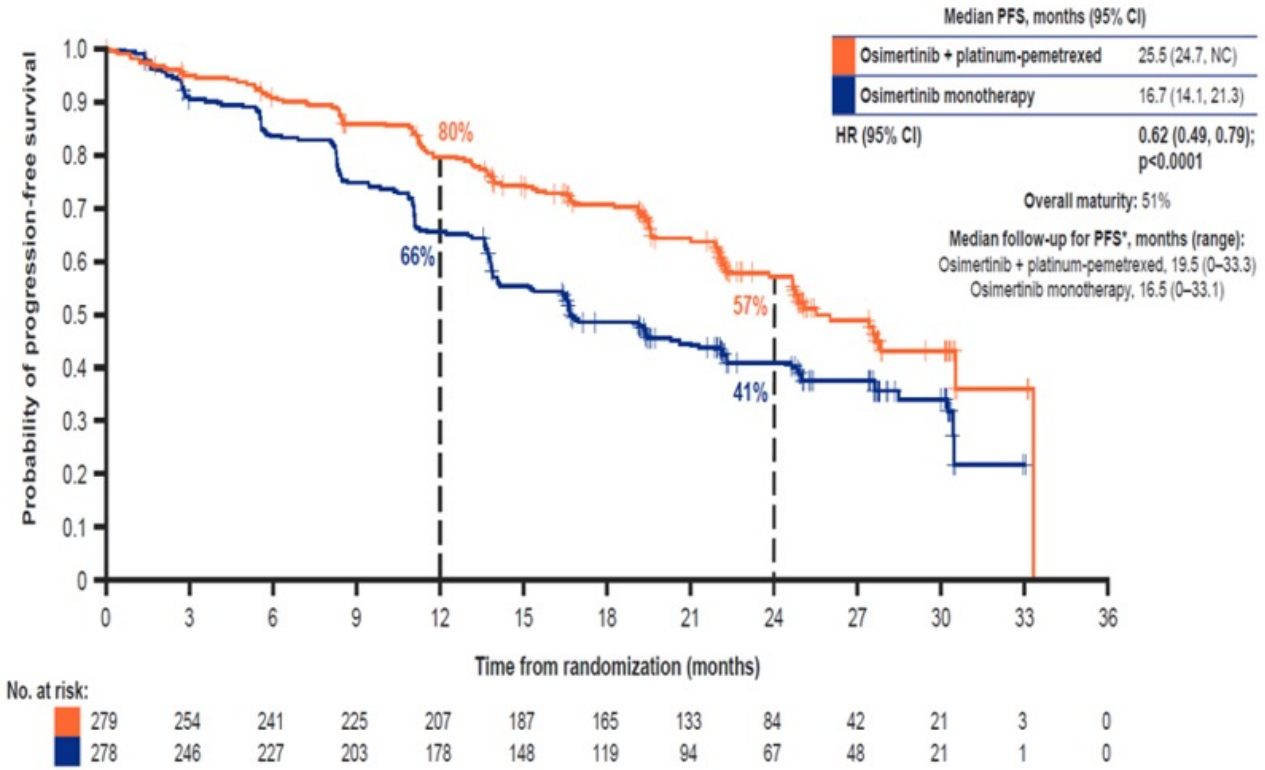
Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

FLAURA mPFS: 18.9 months

mOS 38.6 months



FLAURA2 mPFS: 25.5 months

mOS not mature

Edgardo Santos, MD. 2023 Updates in Cancer Therapies.

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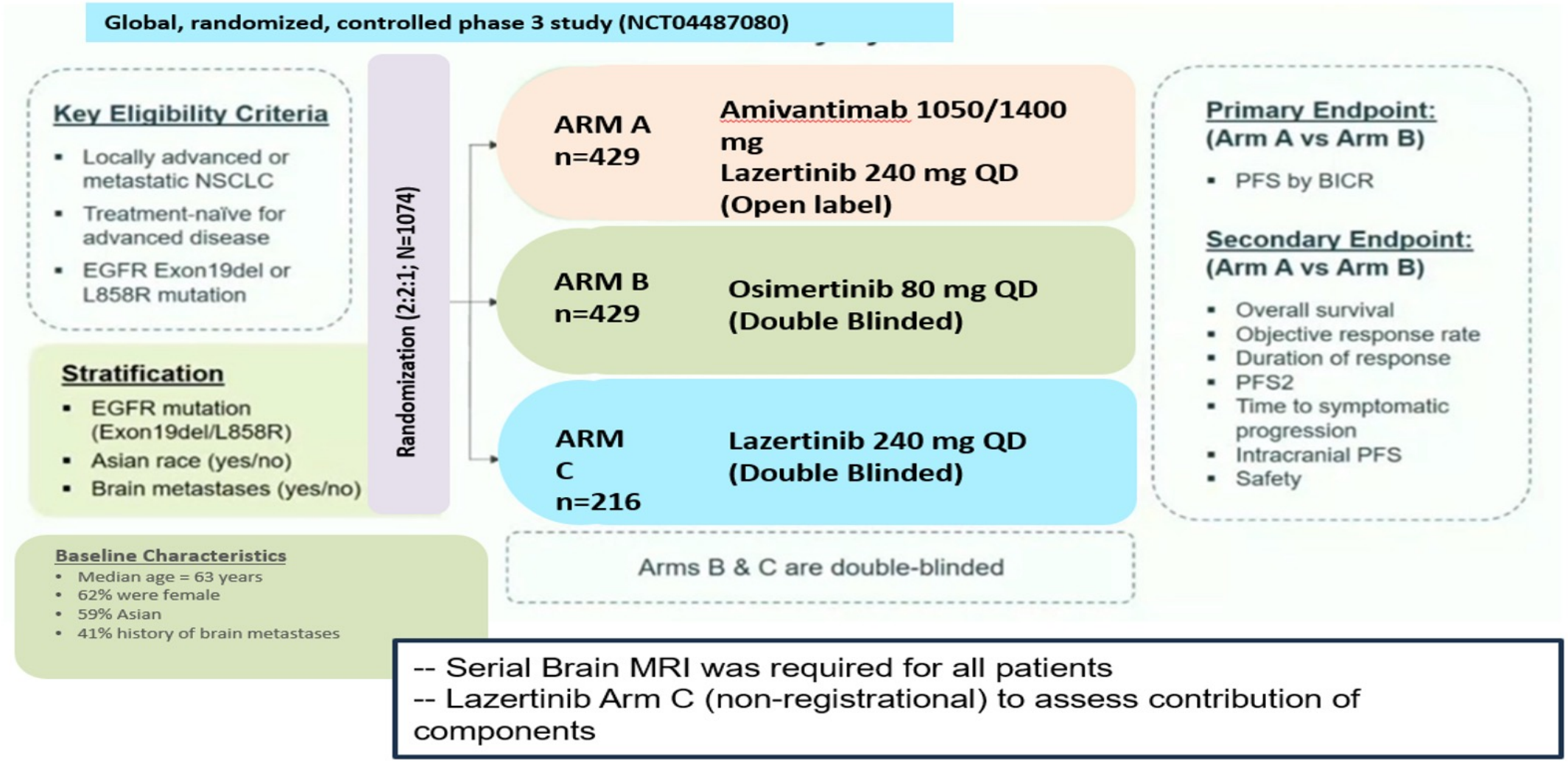
MARIPOSA: 1L Amivantamab + Lazertinib



-- Serial Brain MRI was required for all patients
-- Lazertinib Arm C (non-registrational) to assess contribution of components

Presented by B. Cho. ESMO 2023. LBA14

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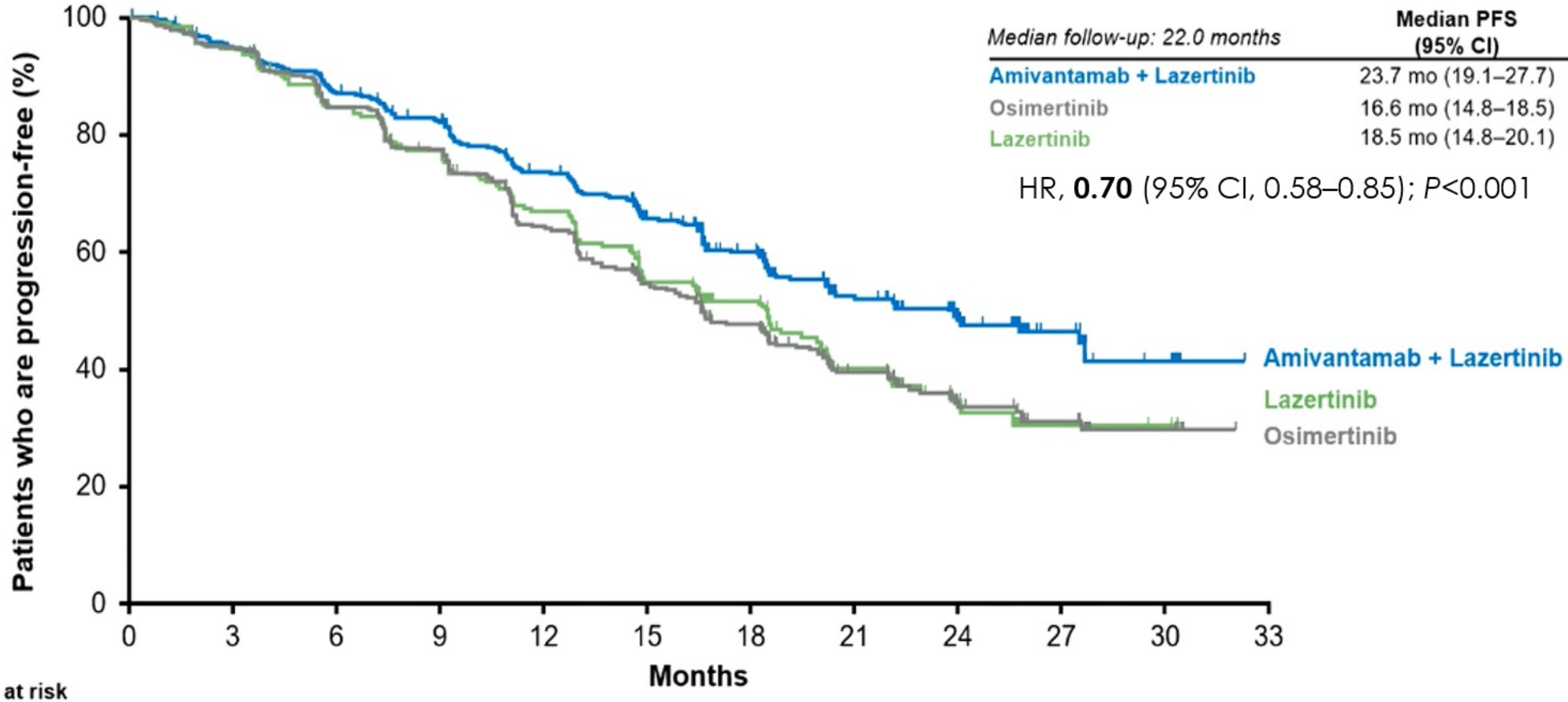
MARIPOSA: PFS by BICR

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)
Lazertinib	18.5 mo (14.8–20.1)

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
Lazertinib	216	200	174	157	134	103	83	41	19	6	2	0

Presented by B. Cho. ESMO 2023. LBA14

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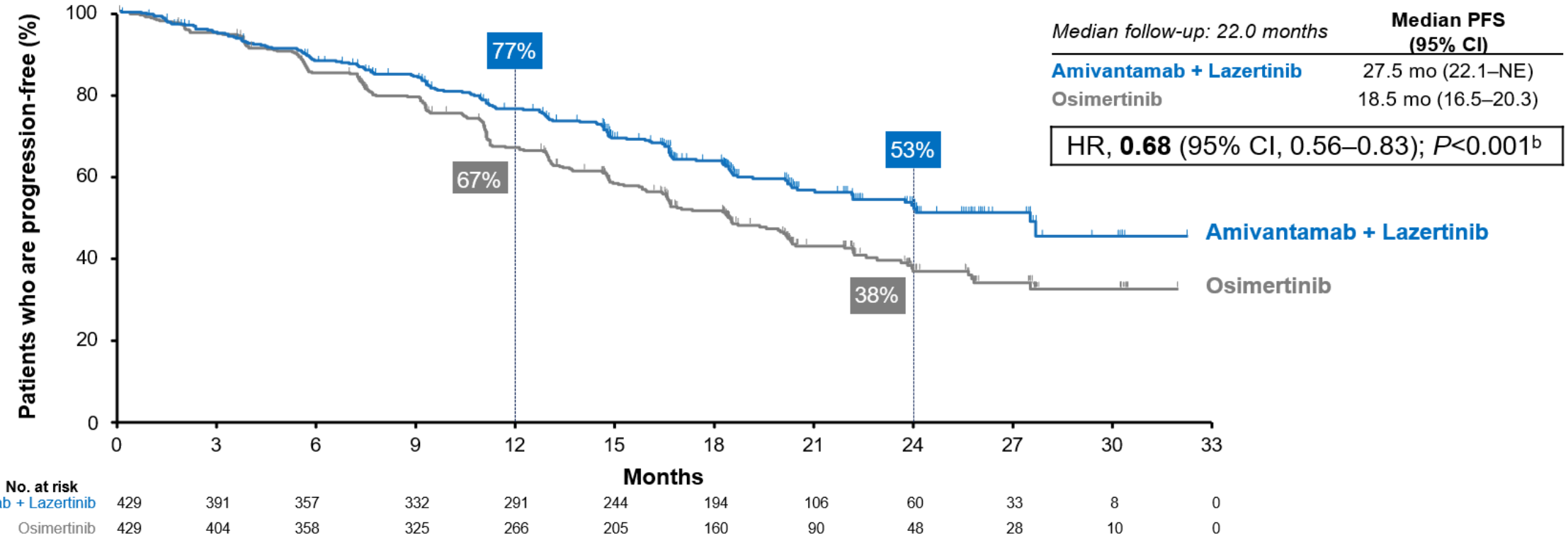
Extracranial Progression-free Survival by BICR[a]

Amivantamab + lazertinib reduced the risk of extracranial progression or death by **32%** and improved median PFS by 9 months

MARIPOSA conducted serial brain MRIs on all patients, which is not routinely done in *EGFR*-mutant NSCLC trials
Both median PFS estimates increase if CNS-only first progressions are censored but a consistent benefit is observed



[a]Extracranial PFS was defined as time from randomization to disease progression (detected by extracranial scans) or death. If first progression was solely detected by CNS, these patients were censored at the time of CNS disease progression.
[b]Nominal *P*-value; endpoint was exploratory and not part of hierarchical hypothesis testing.
BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; mo, months; NE, not estimable; PFS, progression-free survival.

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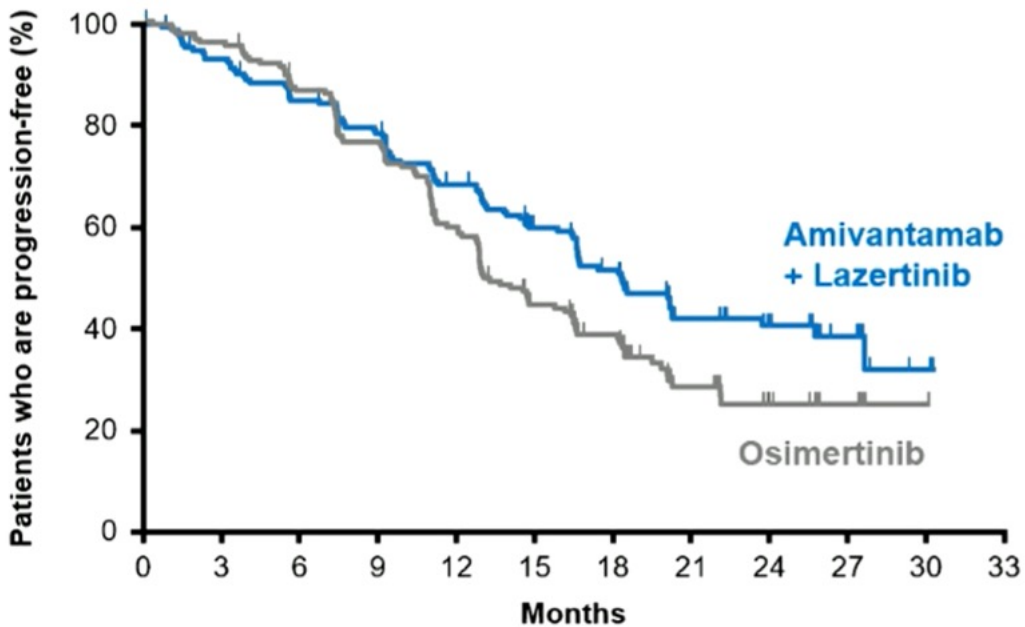
MARIPOSA: PFS by CNS Metastases

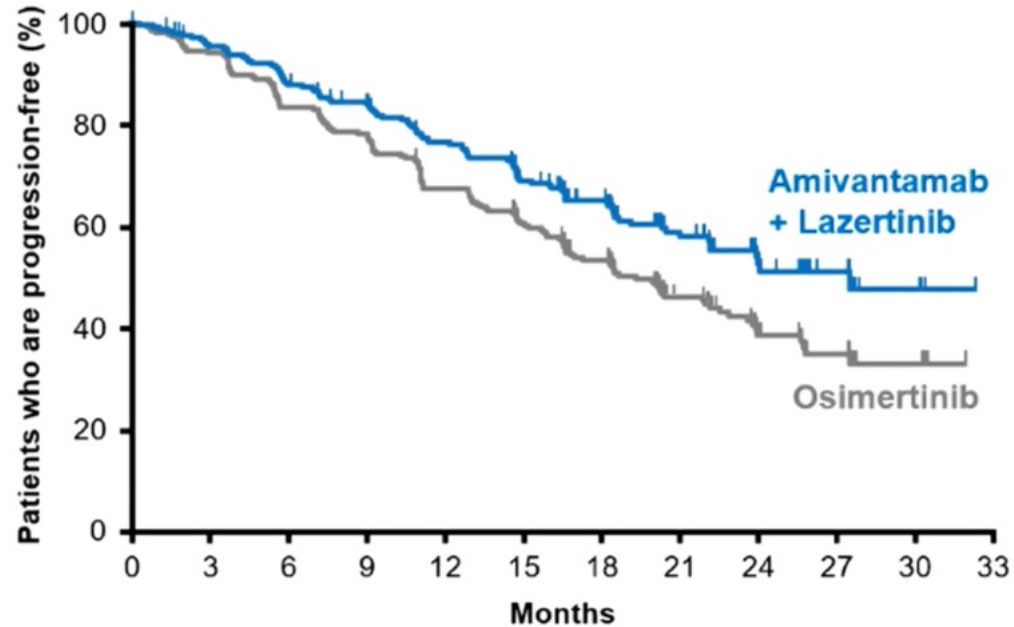
With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

HR, **0.69** (95% CI, 0.53–0.92)



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)



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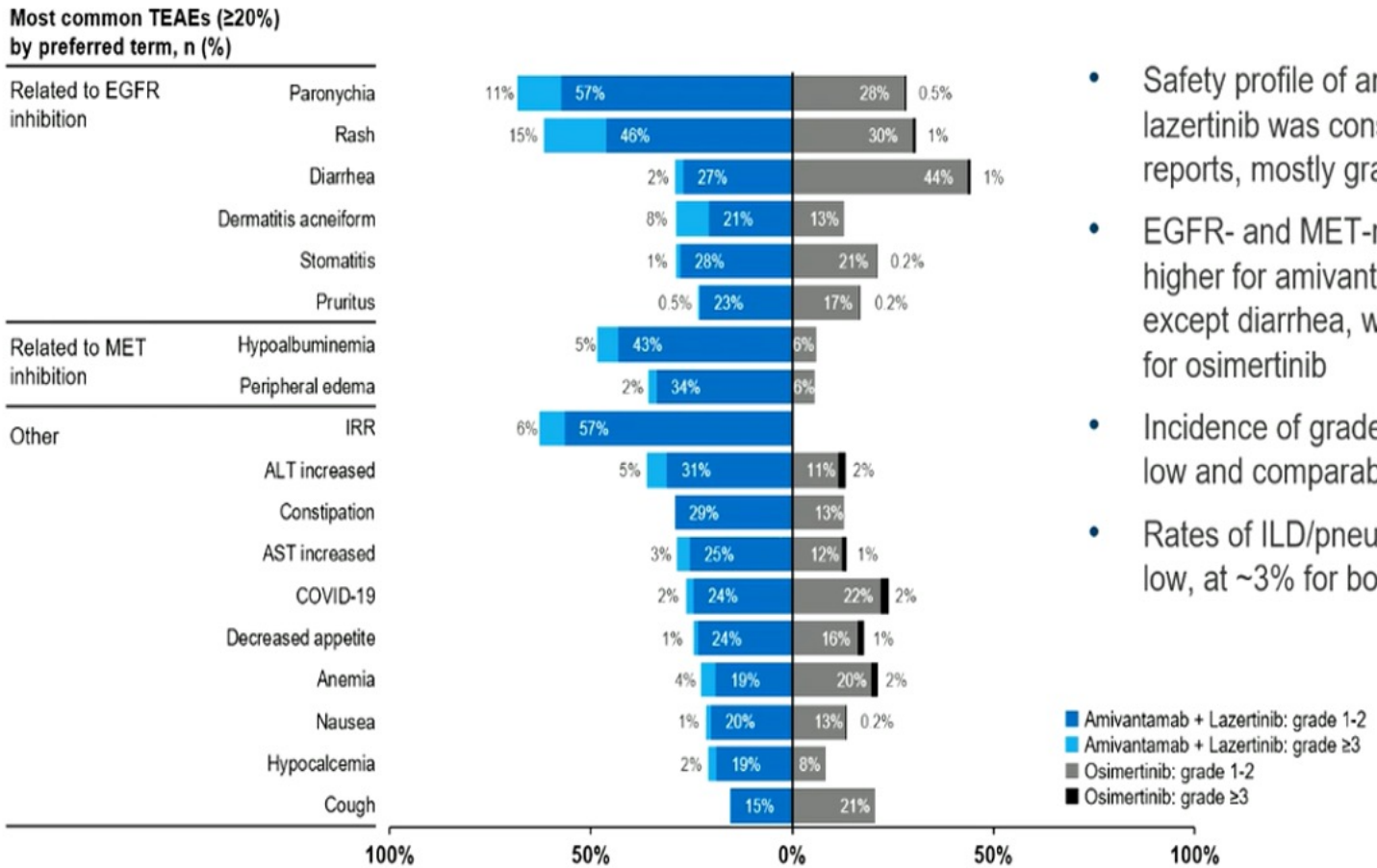
What about toxicity?



- 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

Toxicity
Ami/Laz vs Osimertinib

- IRR: 63% vs 0%
- VTE: 37% vs 9%
- Rash: 61% vs 31%
- Diarrhea: 29% vs 45%
- ILD: 3% vs 3%

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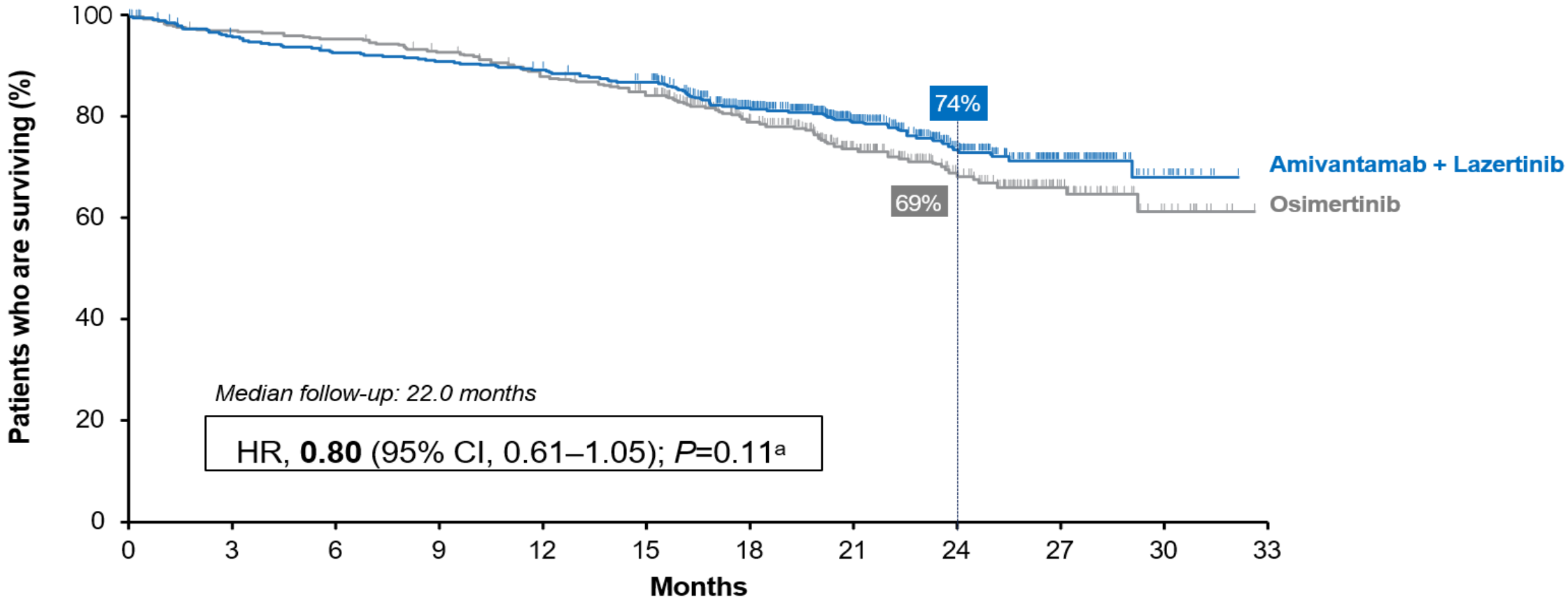
Interim Overall Survival

Early survival data show a trend favoring amivantamab + lazertinib vs osimertinib



No. at risk												
Amivantamab + Lazertinib	429	403	389	382	374	360	293	201	122	58	14	0
Osimertinib	429	416	409	395	372	349	280	186	110	54	13	0

[a]There were a total of 214 deaths in the amivantamab + lazertinib and osimertinib arms at time of the prespecified interim OS analysis, which represents 25% of all randomized patients and 55% of the ~390 projected deaths for the final OS analysis. Medians at this time are not estimable.

CI, confidence interval; HR, hazard ratio; OS, overall survival.

PAPILLON: Phase 3 Study Design

Key Eligibility Criteria

- Treatment-naïve,[a] locally advanced or metastatic NSCLC
- Documented *EGFR* Exon 20 insertion mutations
- ECOG PS 0 or 1

Stratification Factors

- ECOG PS
- History of brain metastases[b]
- Prior EGFR TKI use[a]

1:1 Randomization (N=308)

Amivantamab-Chemotherapy (n=153)

Chemotherapy (n=155)

Dosing (in 21-day cycles)

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

Chemotherapy on the first day of each cycle:

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

Primary endpoint: Progression-free survival (PFS) by BICR according to RECIST v1.1[c]

Secondary endpoints:

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

Optional crossover to 2nd-line amivantamab monotherapy[e]

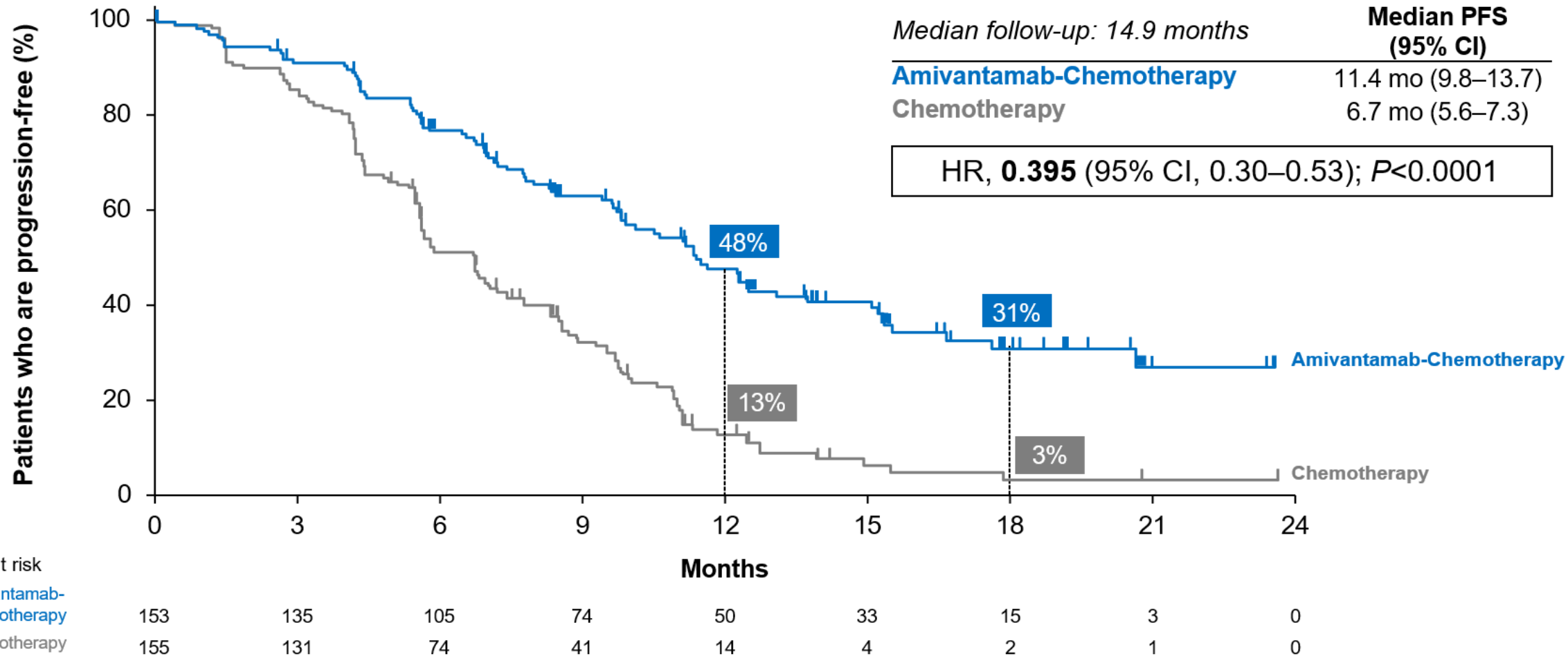
PAPILLON (ClinicalTrials.gov Identifier: NCT04538664) enrollment period: December 2020 to November 2022; data cut-off: 3-May-2023.

[a]Removed as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented).
[b]Patients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomization.
[c]Key statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing.
[d]These secondary endpoints (time to subsequent therapy and symptomatic progression-free survival) will be presented at a future congress.
[e]Crossover was only allowed after BICR confirmation of disease progression; amivantamab monotherapy on Q3W dosing per main study.

AUC, area under the curve; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

Primary Endpoint: Progression-free Survival by BICR

Amivantamab-chemotherapy reduced risk of progression or death by 60%

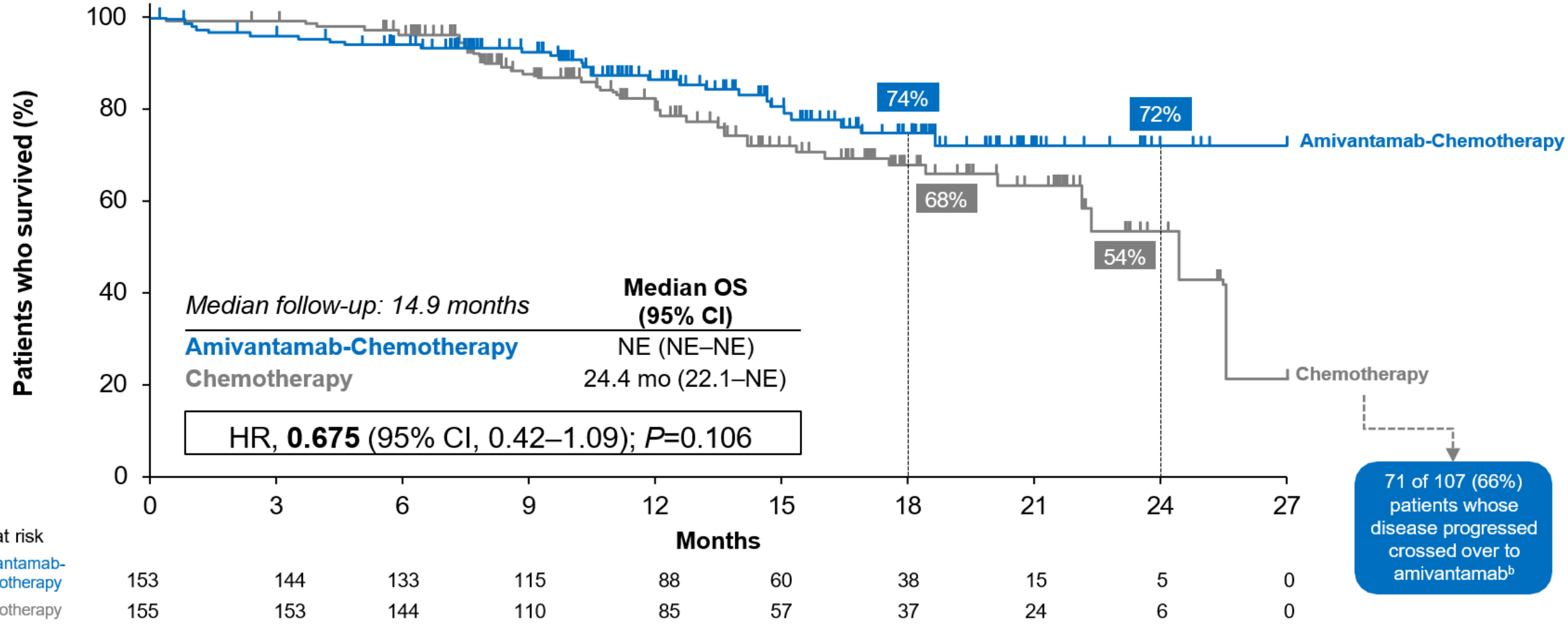


Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001[a])

[a]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Interim Overall Survival[a]

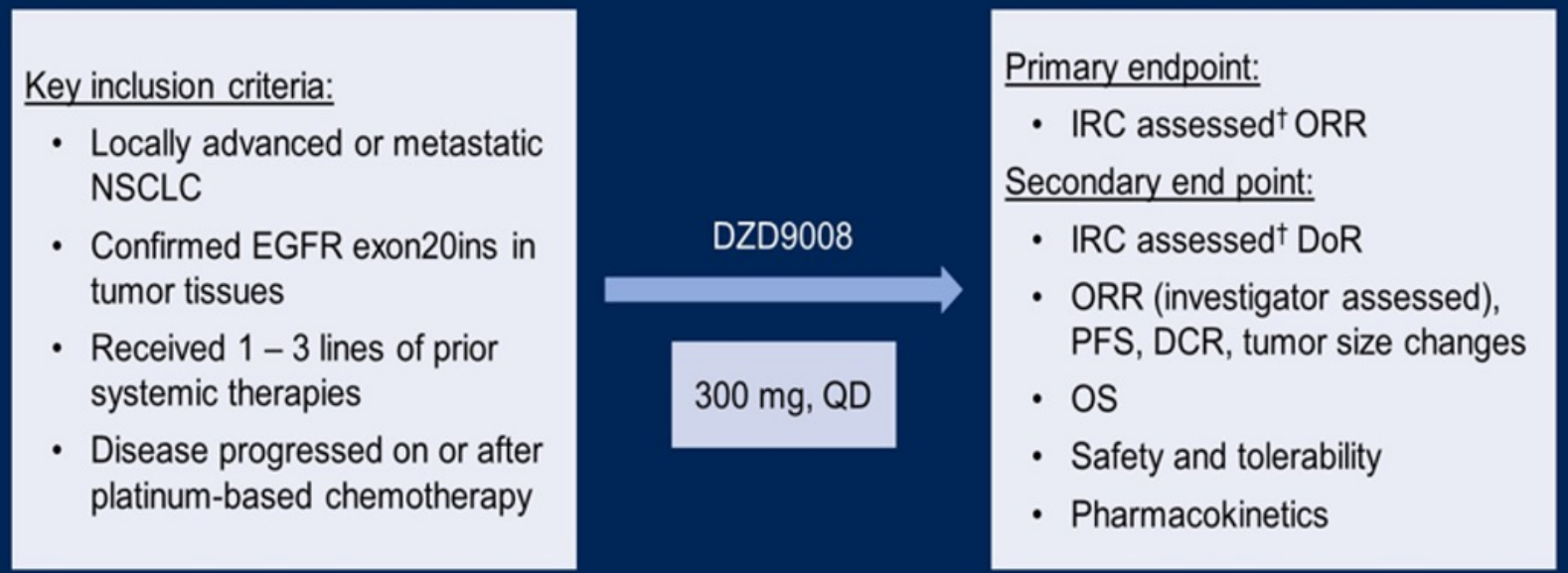
Amivantamab-chemotherapy shows trend in reducing risk of death by over 30%



[a]There were 70 deaths in the study at the time of the prespecified interim OS analysis, which represents 23% of all randomized patients and 33% of the ~210 projected deaths for the final OS analysis.
[b]A total of 71 patients (65 patients as part of the crossover arm plus an additional 6 patients off-protocol) received second-line amivantamab monotherapy out of 107 chemotherapy-randomized patients with disease progression.

CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; OS, overall survival.

WU-KONG6 Study Design



† According to RECIST 1.1. Tumor assessment every 6 weeks

IRC, independent review committee; ORR, objective response rate; DoR, duration of response; PFS, progression free survival; DCR, disease control rate; OS, overall survival.

Data cut-off for analysis: October 17, 2022

Wang M et al. 2023 ASCO

- Sunvozertinib (DZD9008) is a rationally designed, oral, potent EGFR inhibitor targeting EGFR exon20ins as well as other EGFR mutations, with selectivity against WT EGFR.
- Sunvozertinib showed significant antitumor activities in earlier clinical studies and was granted breakthrough therapy designation by US FDA and China CDE.
- Based on these results, two singles arm pivotal studies have been conducted in patients who have failed at least one line of systemic therapy; one in China (WU-KONG6) presented here.
- Sunvozertinib has shown impressive anti-tumor activities in treatment-naïve NSCLC patients with EGFR exon20ins (poster 9037) and in patient with EGFR sensitizing mutations after EGFR TKI failures (poster 9013).

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Components of a Successful EGFR exon20ins TKI (Sunvozertinib):

■ Inhibit wide range of EGFR exon20ins (C-Helix, Near & Far Loop)	**YES**
■ EGFR Wild-type sparing (comparatively)	**YES**
■ CNS activity	**YES**
■ Suppression of resistance mechanisms of EGFR exon20ins TKI	**?** (preclinical T790M)

Riess JW. 2023 ASCO; Santos ES. 2023 ILCC

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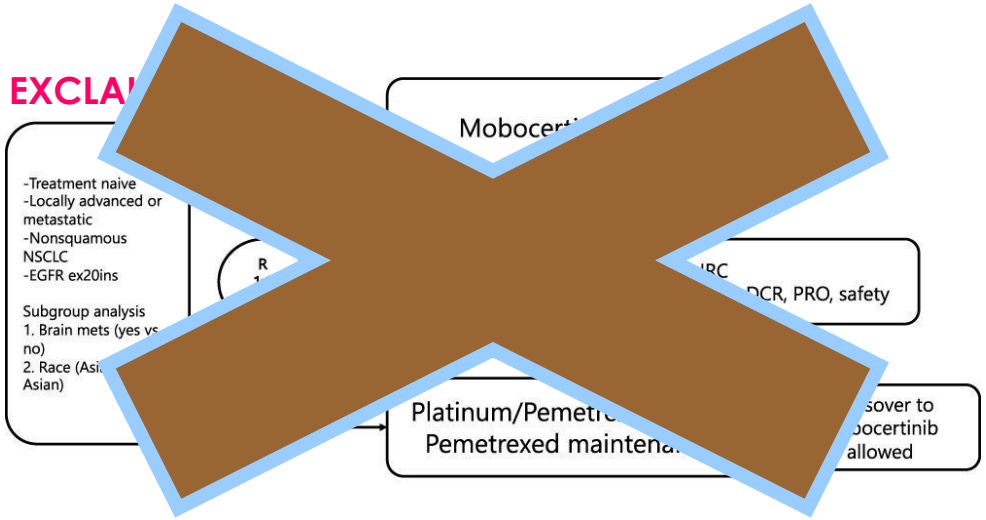
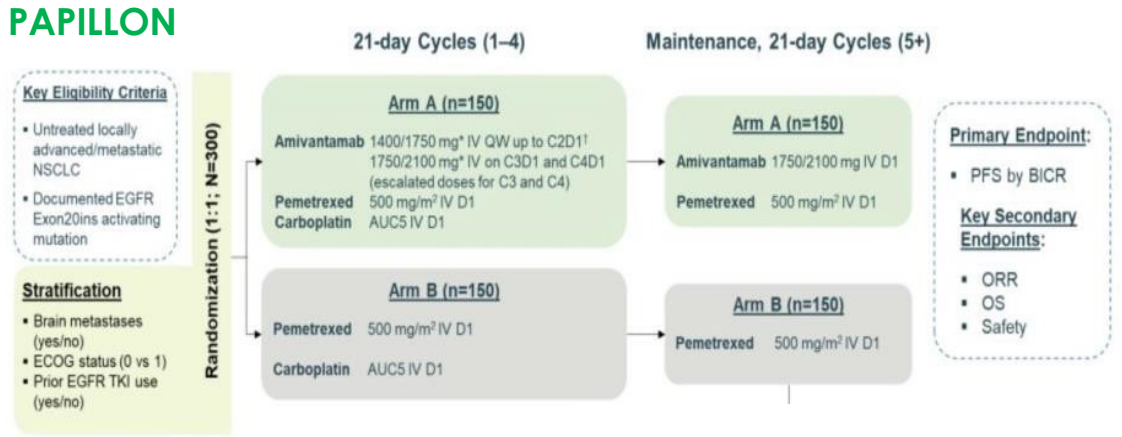
After ESMO 2023, there are still unanswered questions in EGFRex20ins:

- **Optimal First-Line Treatment Strategies**
  - PAPILLON: positive (Category 2A, NCCN v1.2024, 12/21/23)
  - EXCLAIM-2: negative; Mobo was withdraw from US market.
- **How should currently available therapies be sequenced?**
  Chemo/Amivantamab → u n m e t n e e d
- **Management of CNS Metastases**
  - Novel agents (ORIC 114) may have a role.
  - BLU-451: discontinue development recently.
- **Personalization of therapy by EGFR exon20ins by location of insertion? Should treatment be tailored.** (Sunvozertinib showed promising activity across a broad spectrum of EGFR exon20ins)
- **Overcoming acquired resistance** (Acquired resistance to mobocertinib and poziotinib associated with acquired EGFR T790M and secondary mutations in exon 20)





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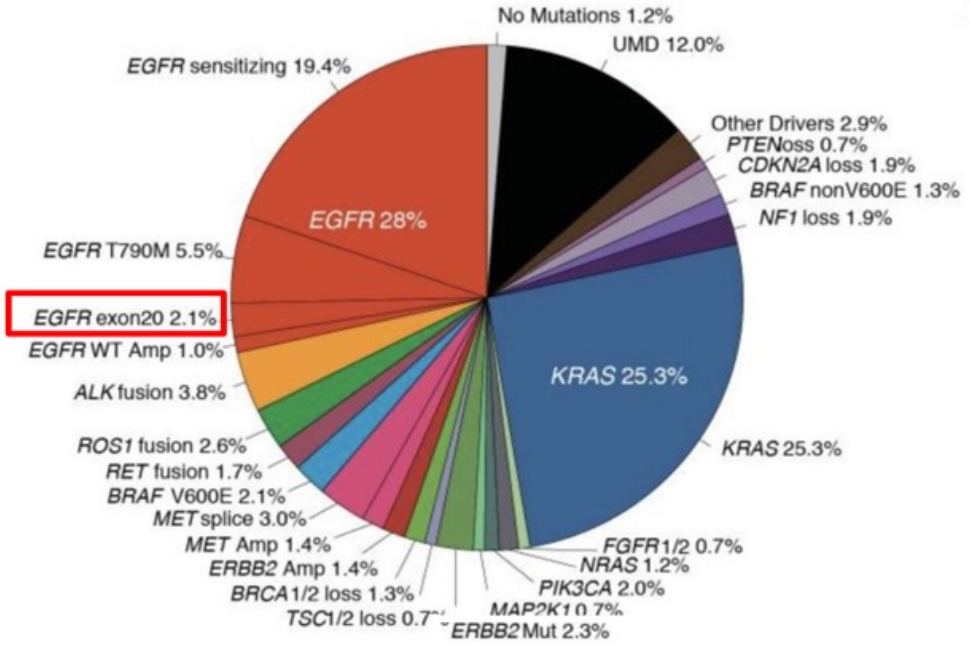
Fostering Multidisciplinary Care in the Era of Complex Cancer Treatments

ALK Pathway



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ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R
1:1

N=257

Alectinib 600 mg BID
2 years

Platinum-based chemotherapy†
Q3W; 4 cycles

Recurrence

Recurrence

Further treatments at investigator's choice and survival follow-up

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

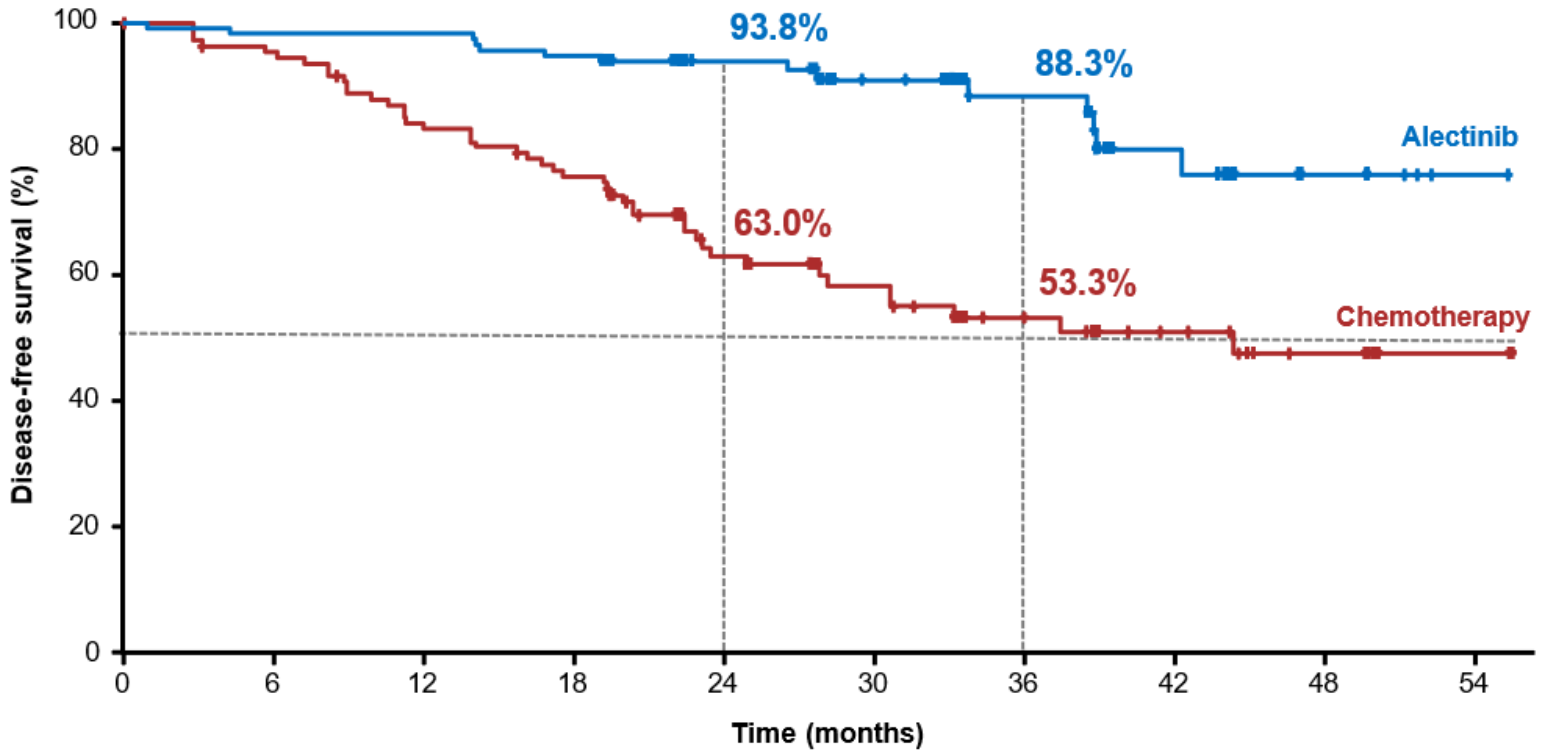
Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

MADRID 2023 ESMO congress

Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

Disease-free survival: stage II–IIIA*



No. at risk

Alectinib	116	111	111	107	67	49	35	21	10	3
Chemo	115	102	88	79	48	35	23	17	10	2

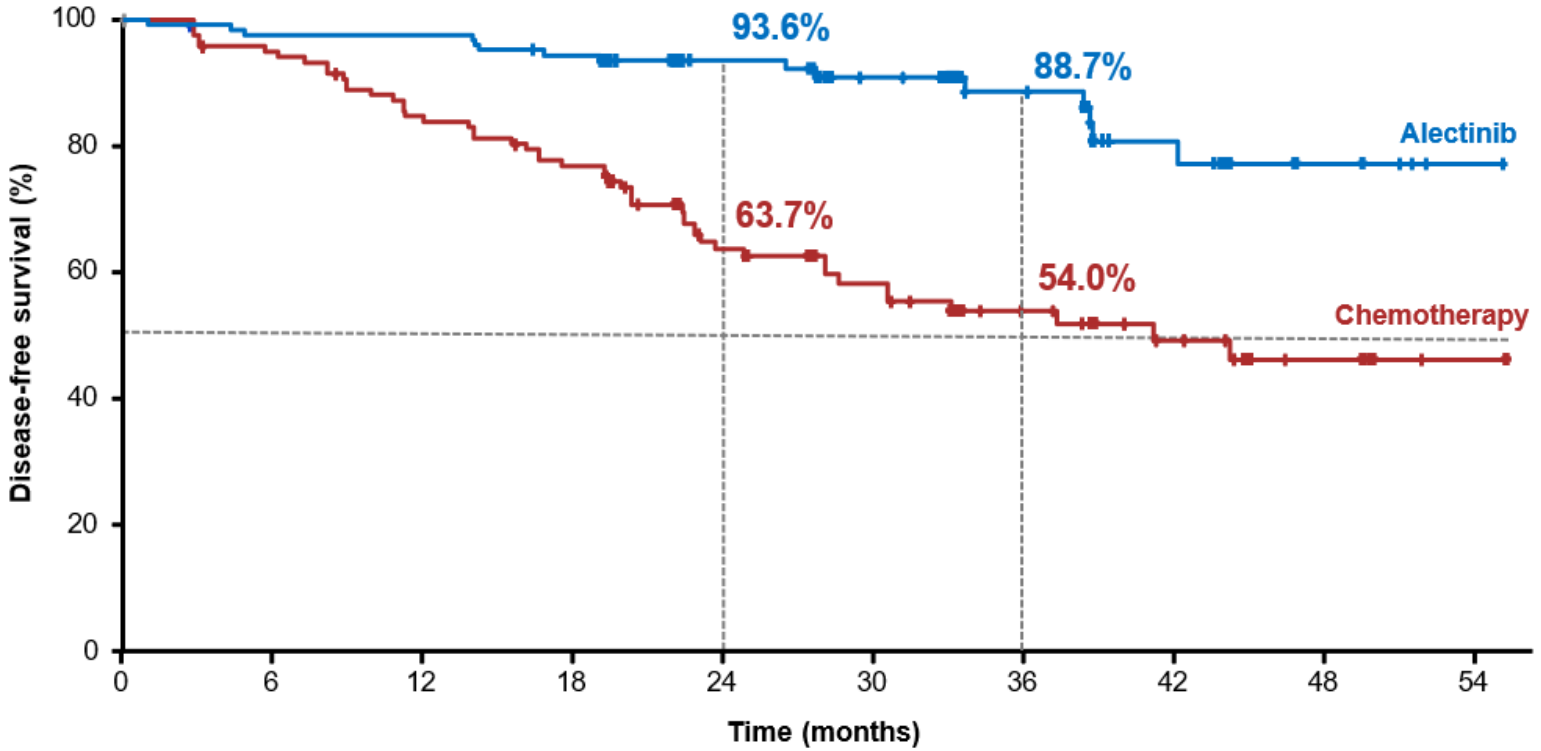
	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months

*Per UICC/AJCC 7th edition; †Stratified log rank; DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

Disease-free survival: ITT (stage IB–IIIA)*



No. at risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemo	127	112	98	89	55	41	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

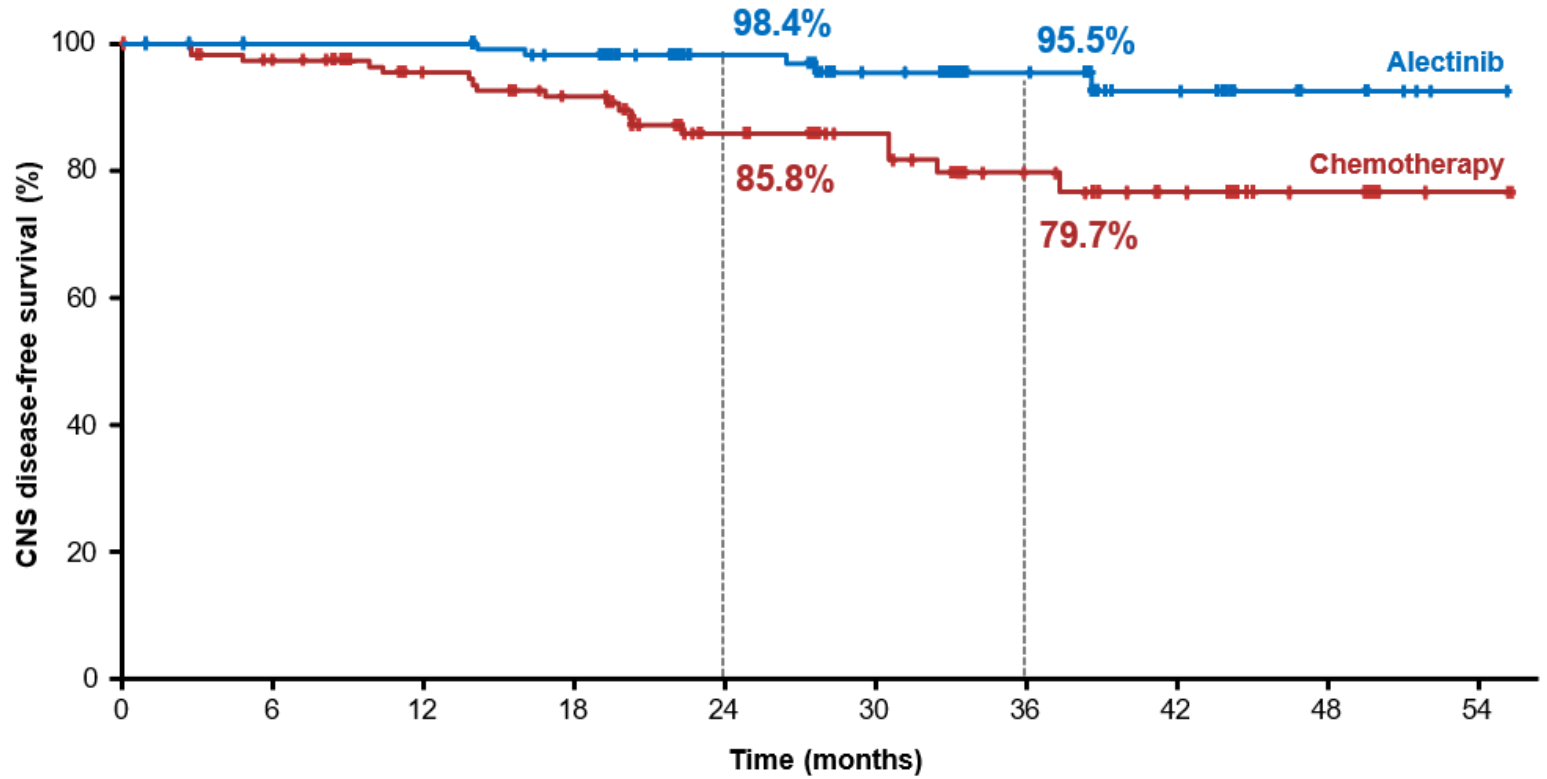
At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported‡

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months

*Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

CNS disease-free survival in the ITT population



No. at risk

Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	**0.22** (0.08, 0.58)	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023

*Stratified analysis with race and stage as stratification factors

CNS-DFS defined as time from randomisation to the first documented recurrence of disease in the CNS or death from any cause

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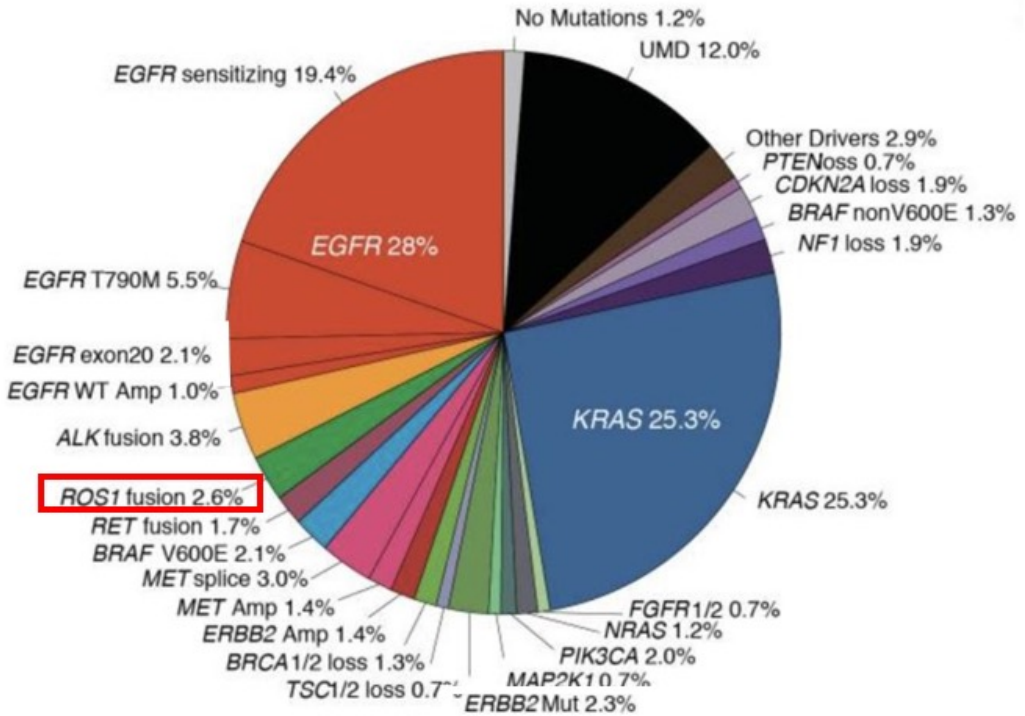
ROS1 Pathway



FDA approves repotrectinib for ROS1-positive non-small cell lung cancer

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On November 15, 2023, the Food and Drug Administration approved repotrectinib for locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC).

This is the first FDA approval that includes patients with ROS1-positive NSCLC who have previously received a ROS1 tyrosine kinase inhibitor (TKI), in addition to patients who are TKI naïve.

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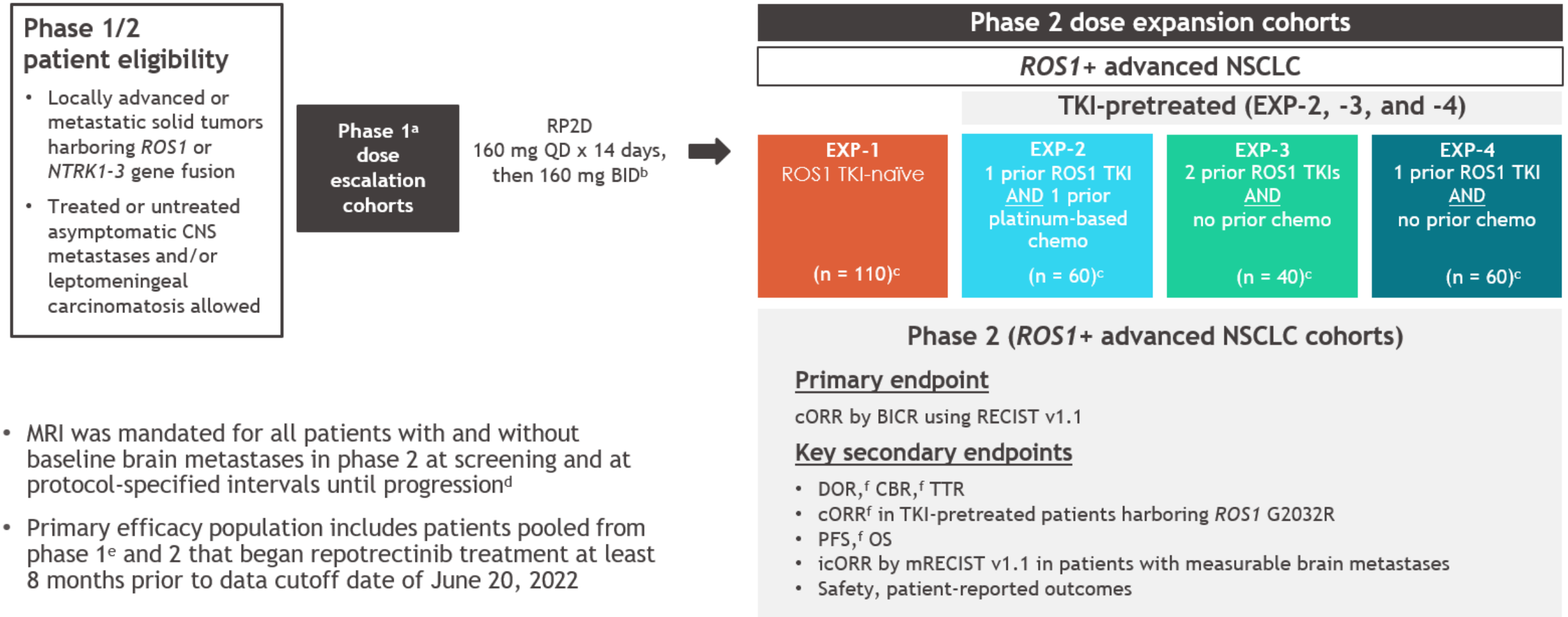
Figure 1. Efficacy analysis of the phase 1/2 TRIDENT-1 study design



- MRI was mandated for all patients with and without baseline brain metastases in phase 2 at screening and at protocol-specified intervals until progression[d]
- Primary efficacy population includes patients pooled from phase 1[e] and 2 that began repotrectinib treatment at least 8 months prior to data cutoff date of June 20, 2022

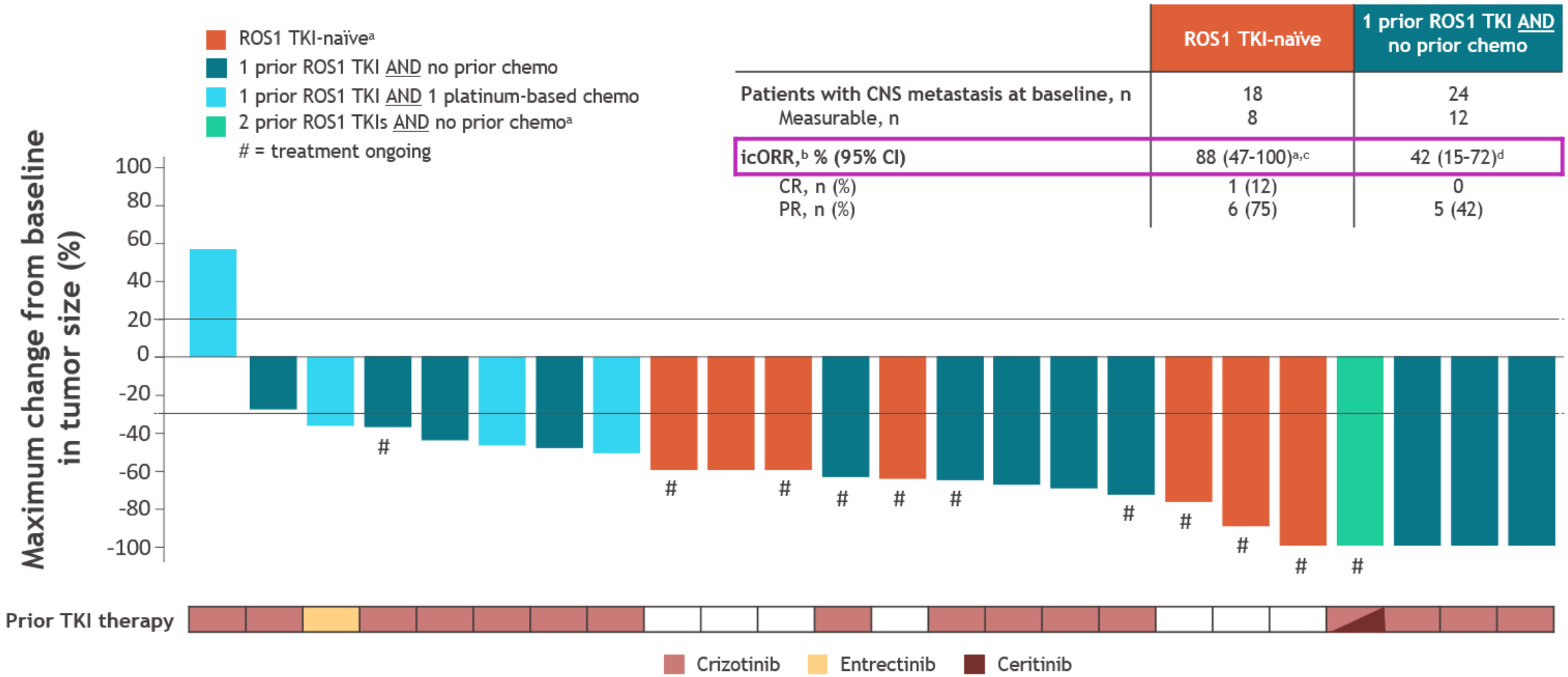
Data cutoff date: June 20, 2022.
[a]Phase 1 primary endpoints: DLT, MTD, RP2D. [b]Based on tolerability. [c]N's for expansion cohorts indicate enrollment targets. [d]MRI brain scans performed at Cycle 3 day 1 (± 7 days), every 2 cycles (± 7 days) up to Cycle 19 and then every 3 cycles (± 7 days) up to Cycle 37 and then every 4 cycles (± 7 days); brain CT was acceptable if brain MRI was contraindicated. [e]Patients from phase 1 received 40 mg QD to 160 mg QD and 160 mg BID. [f]By RECIST v1.1. BICR, blinded independent central review; BID, twice daily; CBR, clinical benefit rate; chemo, chemotherapy; cORR, confirmed objective response rate; CT, computed tomography; DLT, dose-limiting toxicity; DOR, duration of response; icORR, intracranial objective response rate; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MRI, magnetic resonance imaging; MTD, maximum-tolerated dose; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; TTR, time to response.

Table 2. Systemic efficacy in patients with *ROS1*+ NSCLC with baseline CNS metastases per BICR

	ROS1 TKI-naïve (n = 71)	1 prior ROS1 TKI AND no prior chemo (n = 56)	1 prior ROS1 TKI AND 1 prior platinum-based chemo (n = 26)	2 prior ROS1 TKIs AND no prior chemo (n = 18)
Median follow-up, months	18.1	15.5	21.3	14.1
Patients with CNS mets,[a] n (%)	18 (25)	24 (43)	10 (38)	8 (44)
cORR,[b] % (95% CI)	89 (65-99)	33 (16-55)	40 (12-74)	12 (0.3-53)
CR, n (%)	1 (6)	0 (0)	0 (0)	1 (12)
PR, n (%)	15 (83)	8 (33)	4 (40)	0 (0)
SD,[b] n (%)	1 (6)	11 (46)	3 (30)	1 (12)
DOR,[c] % (95% CI)				
≥ 6 months	100 (100-100)	62 (29-96)	50 (1-99)	100 (100-100)
≥ 12 months[d]	93 (79-100)	–	–	–
PFS,[c] % (95% CI)				
≥ 6 months	94 (83-100)	57 (35-78)	40 (10-70)	12 (0-35)
≥ 12 months[d]	87 (71-100)	–	–	–
Patients without CNS mets, n (%)	53 (75)	32 (57)	16 (62)	10 (56)
cORR,[b] % (95% CI)	75 (62-86)	41 (24-59)	44 (20-70)	40 (12-74)
CR, n (%)	3 (6)	3 (9)	1 (6)	0 (0)
PR, n (%)	37 (70)	10 (31)	6 (38)	4 (40)
SD,[b] n (%)	10 (19)	14 (44)	5 (31)	2 (20)
DOR,[c] % (95% CI)				
≥ 6 months	87 (77-98)	92 (76-100)	71 (38-100)	50 (1-99)
≥ 12 months[d]	84 (72-96)	–	–	–
PFS,[c] % (95% CI)				
≥ 6 months	90 (81-98)	75 (59-91)	38 (12-63)	30 (2-58)
≥ 12 months[d]	77 (65-89)	–	–	–

[a]Including patients with measurable and non-measurable lesions. [b]By RECIST v1.1. [c]DOR and PFS were calculated by Kaplan-Meier estimates. [d]Not reported for TKI-pretreated cohorts due to small number of patients at risk. CR, complete response; mets, metastases; PR, partial response; SD, stable disease.

Figure 3. icORR and reduction in intracranial tumor burden in TKI-naïve and TKI-pretreated patients with *ROS1*+ advanced NSCLC and measurable baseline CNS metastases



	ROS1 TKI-naïve	1 prior ROS1 TKI AND no prior chemo
Patients with CNS metastasis at baseline, n	18	24
Measurable, n	8	12
icORR,[b] % (95% CI)	88 (47-100)[a,c]	42 (15-72)[d]
CR, n (%)	1 (12)	0
PR, n (%)	6 (75)	5 (42)

[a]One patient discontinued from study treatment before completing any post-baseline scans. [b]icORR assessed by mRECIST v1.1 in evaluable patients in phase 2 portion of study. [c]No patients had an intracranial best response of SD or PD; icORR in ROS1 TKI-naïve patients with prior intervention for CNS lesion within 60 days before starting repotrectinib treatment (n = 2) was 100% (95% CI, 16-100). [d]50% (n = 6) and 8% (n = 1) of patients had intracranial best response of SD and PD, respectively; icORR in patients pretreated with 1 prior ROS1 TKI and no prior chemo with prior intervention for CNS lesion within 60 days before starting repotrectinib treatment (n = 6) was 38% (95% CI, 9-76).

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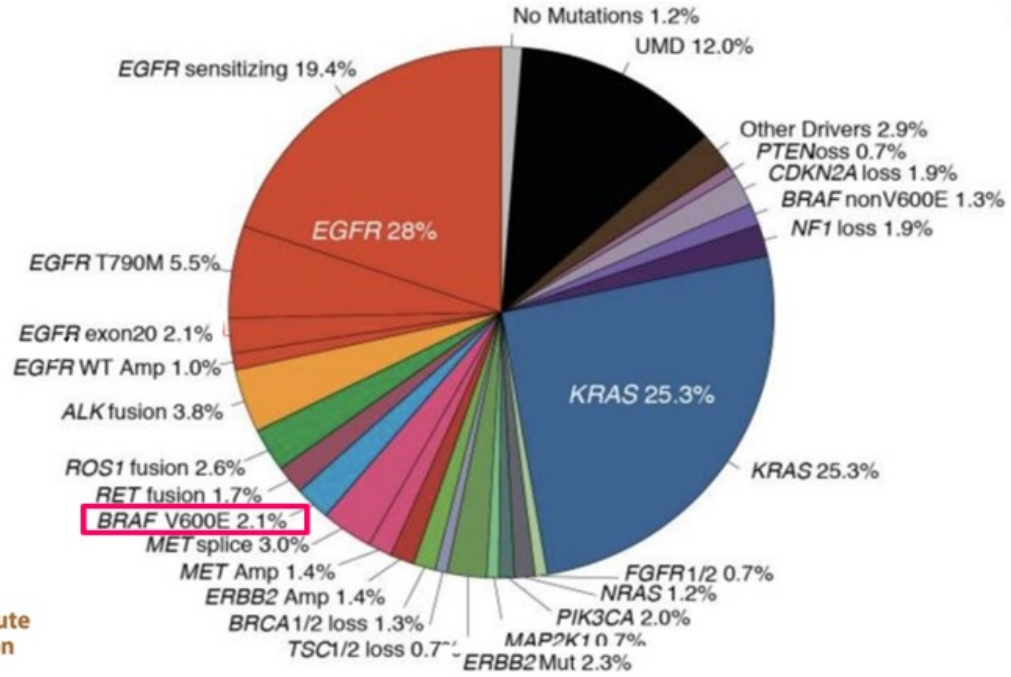
B-RAF Pathway



FDA approves encorafenib with binimetinib for metastatic non-small cell lung cancer with a BRAF V600E mutation

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On October 11, 2023, the Food and Drug Administration approved encorafenib with binimetinib for adult patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, as detected by an FDA-approved test.

FDA also approved the FoundationOne CDx (tissue) and FoundationOne Liquid CDx (plasma) as companion diagnostics for encorafenib with binimetinib. If no mutation is detected in a plasma specimen, the tumor tissue should be tested.

Efficacy was evaluated in 98 patients with metastatic NSCLC with BRAF V600E mutation enrolled in PHAROS (NCT03915951), an open-label, multicenter, single-arm study. Prior BRAF or MEK inhibitors was not allowed. Patients received encorafenib and binimetinib until disease progression or unacceptable toxicity.

Encorafenib plus binimetinib in patients with metastatic BRAF V600E NSCLC

- The combination of encorafenib (BRAF inhibitor) plus binimetinib (MEK inhibitor) has demonstrated clinical efficacy with an acceptable safety profile in patients with metastatic BRAF V600E/K–mutant melanoma[1]
- For patients with metastatic BRAF V600E–mutant NSCLC the combination of dabrafenib and trametinib was approved by the US FDA and is a current standard of care [2]
  - This approval was based on the results of a single-arm, phase 2 study that showed meaningful antitumor activity and a manageable safety profile[3,4]
    - In treatment-naïve and previously treated patients, the ORR by IRR was 64% and 63%, respectively
    - The median DOR by IRR was 15.2 months and 9.0 months, respectively
- Given the observed efficacy and safety profile of encorafenib plus binimetinib in patients with BRAF V600E/K–mutant metastatic melanoma, this combination therapy was assessed in patients with metastatic BRAF V600E–mutant NSCLC

PHAROS (NCT03915951):
A single-arm, open-label, multicenter, phase 2 study

Key eligibility criteria

- Metastatic BRAF V600E–mutant NSCLC
- ECOG performance status 0 or 1
- No *EGFR* mutation, *ALK* fusion, or *ROS1* rearrangement
- No more than 1 prior line of treatment in the advanced setting
- No prior treatment with BRAF or MEK inhibitor
- No symptomatic brain metastases

BRAF mutation testing

- Determined locally by PCR- or NGS-based assay; sent to central laboratory[a]
- Pleural fluid, fresh and archived tissue, and fine needle aspiration were acceptable

Patients enrolled

- Treatment naïve n=59
- Previously treated n=39

Encorafenib: 450 mg QD
Binimetinib: 45 mg BID
28-day cycles
Treat until progression or unacceptable toxicity

Primary endpoint

- ORR[b] by IRR

Secondary endpoints

- ORR by investigator
- DOR, DCR, PFS, and TTR (all by IRR and investigator)
- OS
- Safety

Exploratory endpoints

- Biomarker and pharmacokinetic analyses

BID, twice daily; **DCR**, disease control rate; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **IRR**, independent radiology review; **ORR**, objective response rate; **NGS**, next-generation sequencing; **OS**, overall survival; **PCR**, polymerase chain reaction; **PFS**, progression-free survival; **QD**, once daily; **TTR**, time to response.

[a]BRAF V600 mutations were retrospectively confirmed by FoundationOne CDx (Foundation Medicine, Cambridge, MA). [b]According to RECIST 1.1.

1. Dummer R, et al. *Lancet Oncol*. 2018;19(5):603-615. 2. Dabrafenib prescribing information. June 2022. 3. Planchard D, et al. *Lancet Oncol*. 2016;17(7):984-993. 4. Planchard D, et al. *Lancet Oncol*. 2017;18(10):1307-1316.

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC

Antitumor activity endpoints by IRR

	Treatment naïve (n=59)	Previously treated (n=39)
Objective response rate (95% CI), %[a]	75 (62, 85)	46 (30, 63)
Complete response	9 (15)	4 (10)
Partial response	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	41 (26, 58)
Duration of response, median (95% CI), months	NE (23.1, NE)	16.7 (7.4, NE)
Duration of response ≥12 months, n/N (%)	26/44 (59)	6/18 (33)
Time to response, median (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)

IRR, independent radiology review; **NE**, not estimable.

[a]Response of 3 patients were not evaluable in the treatment-naïve group, and 5 were not evaluable in the previously treated group.

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Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC
Incidence of TRAEs of any grade >10% in all patients

	Overall (N=98)		
	Any grade	Grade 3	Grade 4
Any TRAEs, n (%)[a]	92 (94)	37 (38)	3 (3)[b]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Edema peripheral	11 (11)	0	0

Note: Any-grade abdominal pain, alopecia, asthenia, and dry skin occurred in 10% of patients; any-grade pyrexia occurred in 8% of patients.
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **TRAE**, treatment-related adverse event.
[a]One patient died due to intracranial hemorrhage, which was assessed as treatment related by the investigator. [b]Grade 4 TRAEs were colitis, disseminated intravascular coagulation, increased γ-glutamyl transferase, and hyponatremia.

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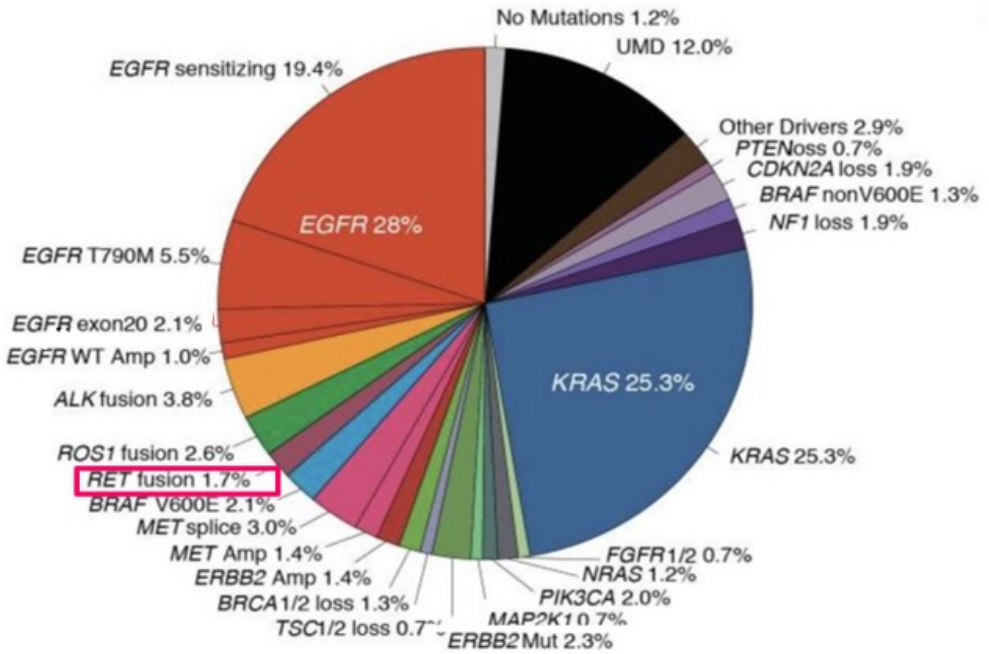
RET Pathway


No Mutations 1.2%
UMD 12.0%
EGFR sensitizing 19.4%
Other Drivers 2.9%
PTENloss 0.7%
CDKN2A loss 1.9%
BRAF nonV600E 1.3%
NF1 loss 1.9%
EGFR 28%
EGFR T790M 5.5%
EGFR exon20 2.1%
EGFR WT Amp 1.0%
ALK fusion 3.8%
KRAS 25.3%
ROS1 fusion 2.6%
RET fusion 1.7%
BRAF V600E 2.1%
MET splice 3.0%
MET Amp 1.4%
ERBB2 Amp 1.4%
BRCA1/2 loss 1.3%
TSC1/2 loss 0.7%
ERBB2 Mut 2.3%
KRAS 25.3%
FGFR1/2 0.7%
NRAS 1.2%
PIK3CA 2.0%

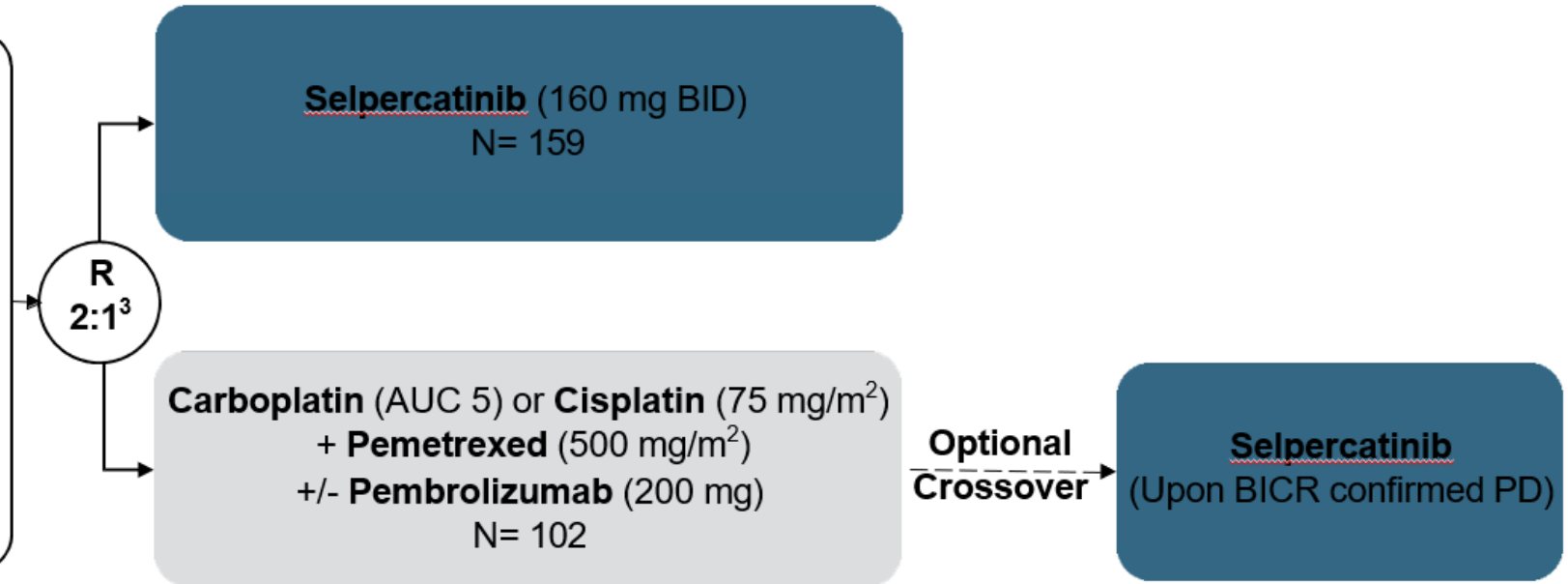
LIBRETTO-431 phase 3 open-label study design

Key Eligibility Criteria

- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

Stratification factors:

- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator s choice of treatment with pembrolizumab



Gated Primary Endpoints: PFS by blinded independent central review (BICR) in ITT-Pembrolizumab[4] and ITT population

Secondary Endpoints:

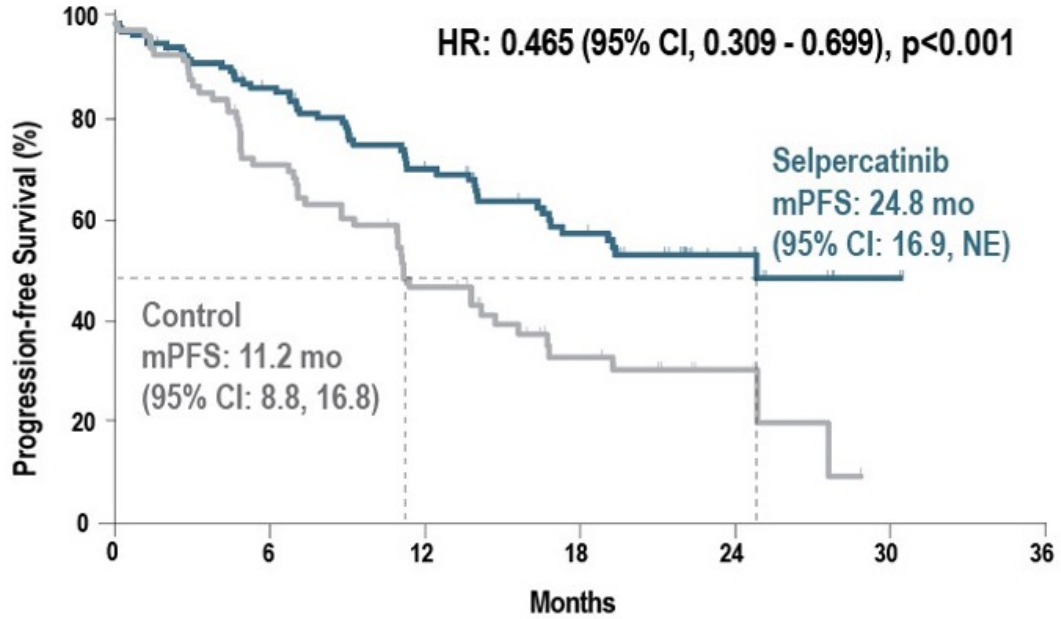
- **Efficacy** ([OS, ORR, DOR], CNS [ORR, DOR, time to progression][5])
- **Safety**
- **Patient Reported Outcomes** (NSCLC-SAQ [tertiary endpoint EORTC QLQ-C30])

[1] Not suitable for radical surgery or radiation therapy
[2] Investigator assessed
[3] The initial randomization ratio was 1:1, but amended to 2:1
[4] ITT-Pembrolizumab are patients stratified with investigator intent to receive chemotherapy with pembrolizumab and per protocol had to be at least 80% of the ITT population
[5] Baseline and longitudinal intracranial scans were required for all patients following an amendment. Prior to the amendment, longitudinal intracranial scans were required if patients had known CNS metastases at baseline

Progression-free survival (PFS) assessed by BICR

ITT-Pembrolizumab Population

(Median follow-up of ~19 mo)

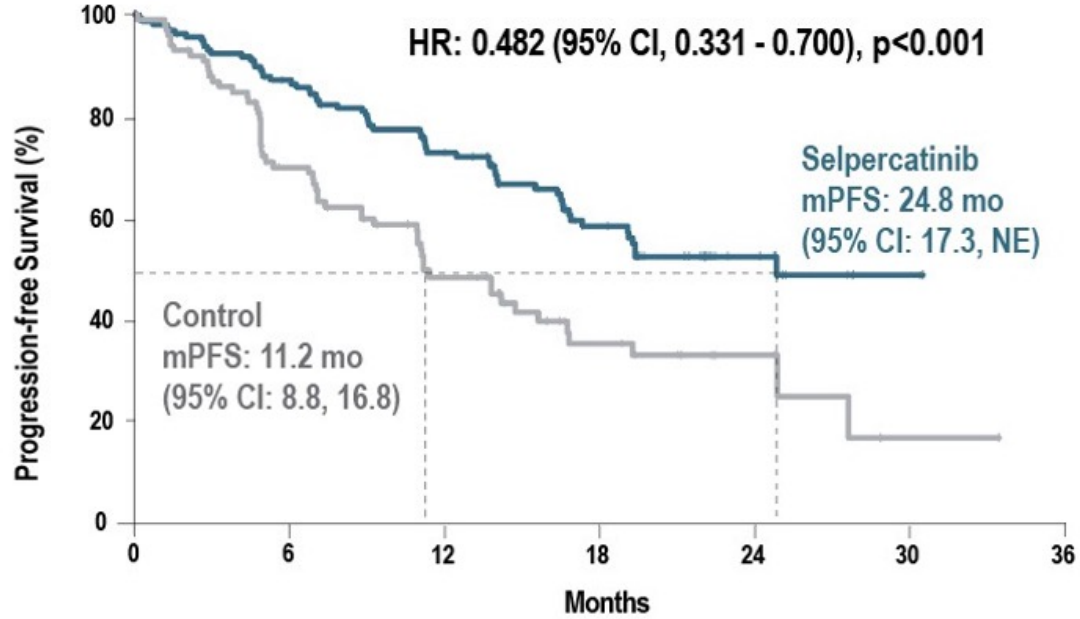


No. at Risk

Selpercatinib	129	105	72	44	16	2	0
Control	83	55	29	15	6	0	0

ITT Population

(Median follow-up of ~18 mo)



No. at Risk

Selpercatinib	159	130	90	52	18	3	0
Control	102	63	33	16	7	1	0

The primary endpoints were met, as selpercatinib resulted in a statistically significant improvement in PFS in both pre-specified populations

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Systemic ORR, DOR, OS and Intracranial ORR and DOR

Systemic Outcomes

	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)

Overall response rate by RECIST 1.1 was higher and responses were more durable with selpercatinib

In patients with measurable CNS disease at baseline, selpercatinib demonstrated improved outcomes in:

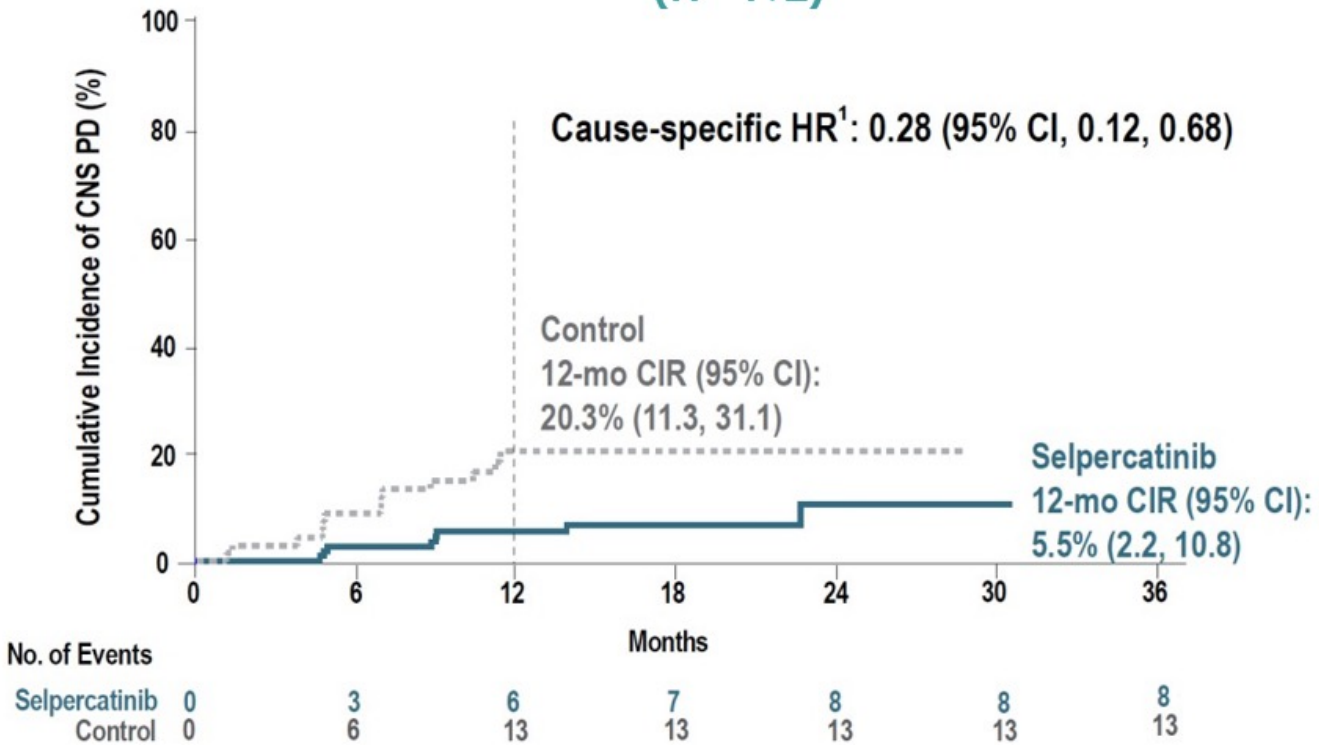
- **intracranial response rate by RECIST 1.1 including complete responses, and DOR**
- **intracranial PFS**

[1] Effective crossover rate: patients who discontinued from control treatment and received a selective RET inhibitor on or off study

[2] In patients with measurable CNS disease at baseline.

Cumulative incidence rate of CNS progression

Patients with and without Baseline CNS Metastases (N= 192)



Time to CNS progression was delayed with selpercatinib

Risk of CNS Progression

Without CNS Metastases at Baseline	Selpercatinib (N= 99)	Control (N= 51)
12-month CIR, % (95% CI)	1.1% (0.1, 5.2)	14.7% (5.7, 27.6)
Cause-specific HR[1] (95% CI)	0.17 (0.04, 0.69)	

With CNS Metastases at Baseline	Selpercatinib (N= 21)	Control (N= 21)
12-month CIR, % (95% CI)	25.7% (8.8, 46.7)	33.3% (14.3, 53.8)
Cause-specific HR[1] (95% CI)	0.61 (0.19, 1.92)	

[1] Cause-specific HR for CNS progression, accounting for the competing risks of non-CNS PD and death
CIR: Cumulative incidence rate

Data shown are from the ITT-Pembrolizumab population

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Conclusions

- ADAURA and ALINA trials have established new standard of care for patients whose tumors harbor EGFR exon 19 or L858R mutations and ALK rearrangement, respectively (in the adjuvant setting; pathological stage IB-IIIA).
- FLAURA 2 and MARIPOSA results are challenging Osimertinib as sole 1st line therapy for patients with EGFRex19del or L858R mutations.
- For patients with CNS disease and L858R, Osi plus chemotherapy represents a better option than Osi alone (FLAURA 2).
- MARIPOSA study also showed that Ami/Chemo combination has CNS protectant effect.
- Amivantamab-chemotherapy is the new standard of care for EGFRex20in as it significantly improved PFS (HR, 0.395); OS trends in favor of Ami/Chemo despite high crossover (PAPILLON study).
- Repotrectinib (for ROS-1+) and Encorafenib/Binimetinib (B-RAF^{V600E}+) have been added to therapeutic armamentarium in 2023.
- Selpercatinib beat chemotherapy +/- immunotherapy as frontline for patients whose tumors harbor RET rearrangement in a Phase 3 trial.

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