Targeted Therapy in Lung Cancer: ASCO and ESMO Updates

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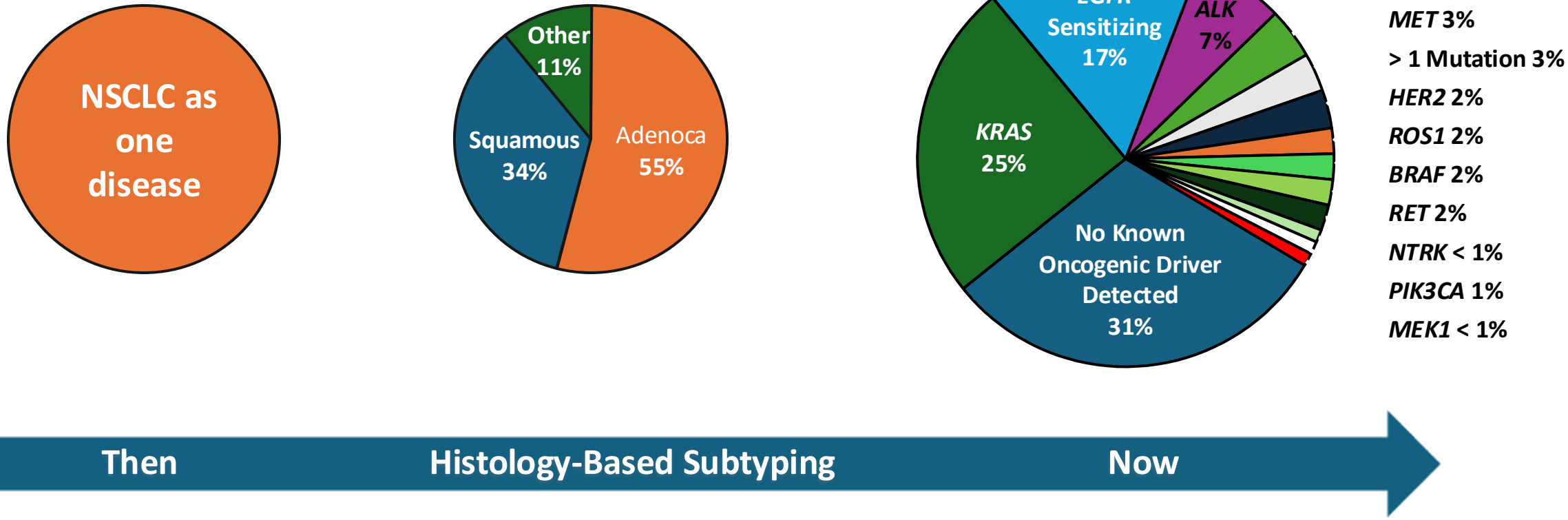
UCDAVIS COMPREHENSIVE CANCER CENTER

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

Evolution of NSCLC Subtyping from Histologic to Molecular-Based



Gandara et al: *J Clin Oncol.* 2013 (adapted from Pao et al)

2024 ASCO® ANNUAL MEETING

Osimertinib after definitive chemoradiotherapy in patients with unresectable stage III epidermal growth factor receptor-mutated (EGFRm) NSCLC: primary results of the Phase 3 LAURA study

Suresh S. Ramalingam,[1] Terufumi Kato, Xiaorong Dong, Myung-Ju Ahn, Le-Van Quang, Nopadol Soparattanapaisarn, Takako Inoue, Chih-Liang Wang, Meijuan Huang, James Chih-Hsin Yang, Manuel Cobo, Mustafa Özgüroğlu, Ignacio Casarini, Dang-Van Khiem, Virote Sriuranpong, Eduardo Cronemberger, Xiangning Huang, Toon van der Gronde, Dana Ghiorghiu, Shun Lu

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Dr Suresh S. Ramalingam

LAURA Phase 3 double-blind study design

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT† treatment

Key inclusion criteria:
- ≥18 years (Japan: ≥20)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomization: 6 weeks

Osimertinib 80 mg, once daily

Randomization 2:1 (N=216)

Stratification by:
Concurrent vs sequential CRT
Stage IIIA vs stage IIIB/IIIC
China vs non-China

Placebo, once daily

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

Open-label osimertinib after BICR-confirmed progression offered to both treatment arms§

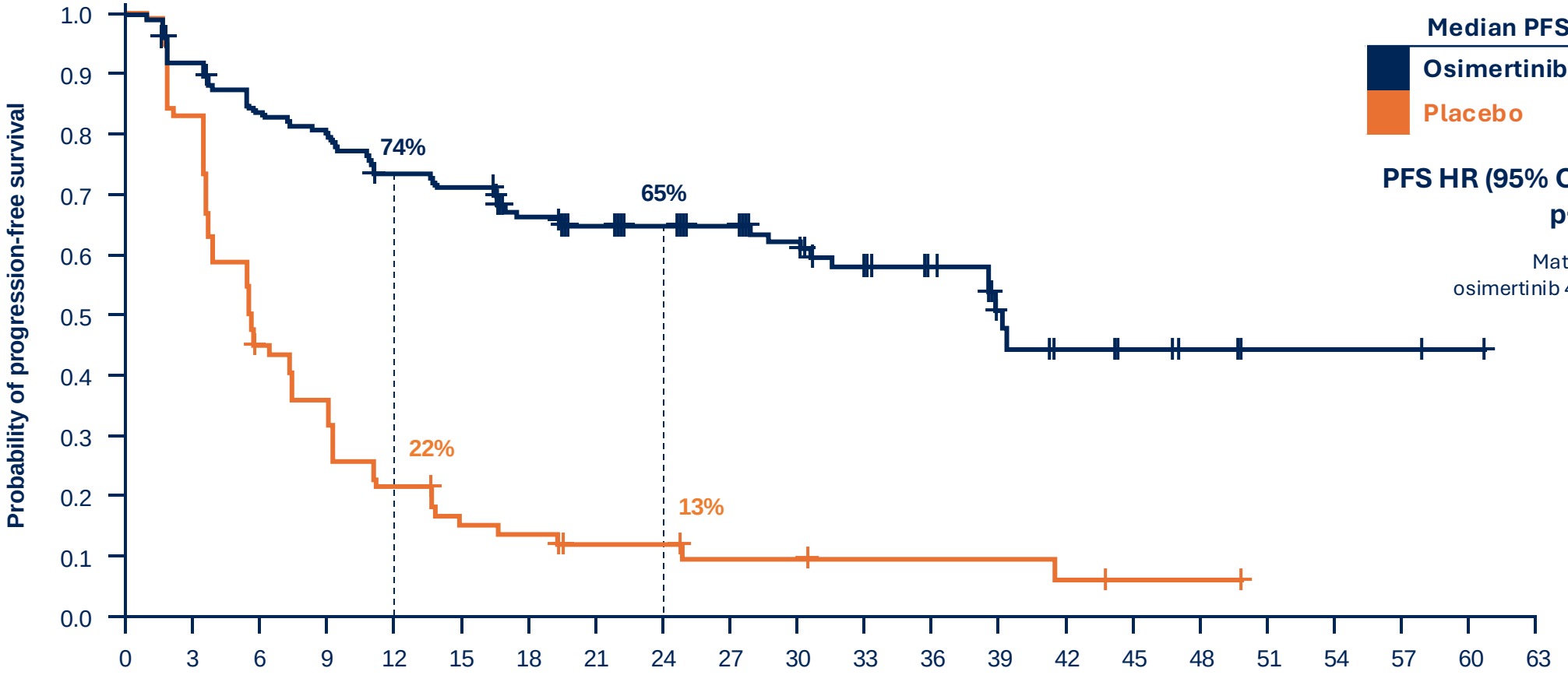
Tumor assessments:
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

Endpoints
- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

*According to AJCC / UICC staging (8th edition);
†Concurrent or sequential CRT comprising ≥2 cycles of platinum-based chemotherapy (or 5 doses of weekly platinum-based chemotherapy) and a total dose of radiation of 60 Gy ±10%;
‡Central or FDA-approved local testing (from a CLIA-approved laboratory, or accredited local laboratory for sites outside of USA) based on tissue;
§If deriving clinical benefit (osimertinib arm); by the judgement of treating physician (placebo arm).

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CLIA, Clinical Laboratory Improvement Amendments; CNS; central nervous system; CRT, chemoradiotherapy; CT, computed tomography; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; FDA, Food and Drug Administration; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; UICC, Union for International Cancer Control; WHO PS, World Health Organization performance status

Progression-free survival by BICR



Median PFS, months (95% CI)

Osimertinib	39.1 (31.5, NC)
Placebo	5.6 (3.7, 7.4)

PFS HR (95% CI): 0.16 (0.10, 0.24), p<0.001

Maturity 56%:
osimertinib 40%, placebo 86%

No. at risk

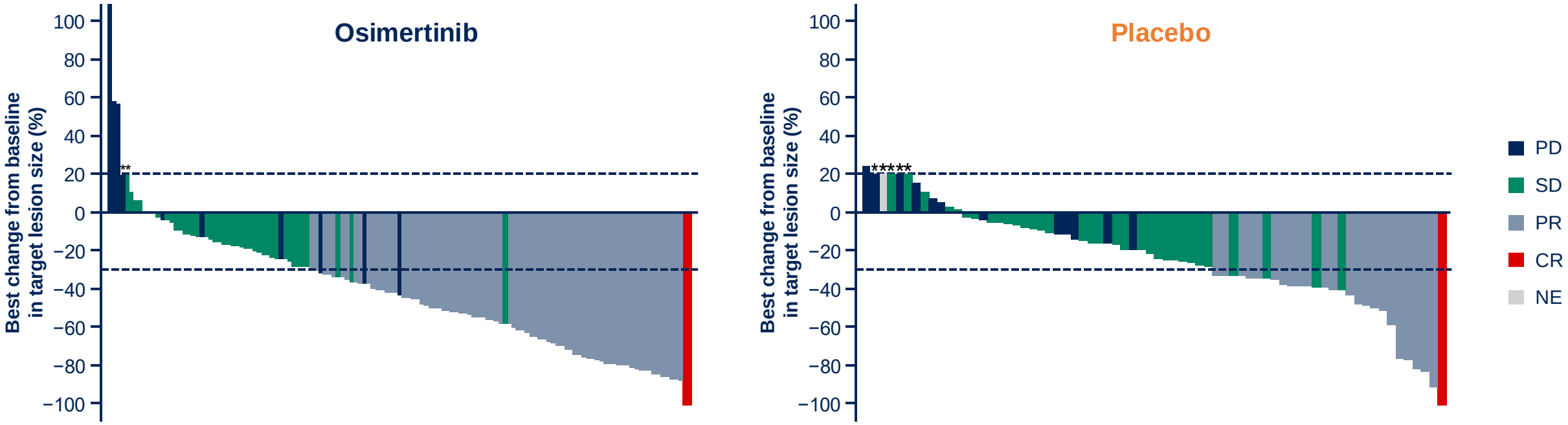
Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Tick marks indicate censored data. Median follow-up for PFS (all patients): osimertinib 22.0 months, placebo 5.6 months. Median follow-up for PFS (censored patients): osimertinib 27.7 months, placebo 19.5 months.

Data cut-off: January 5, 2024.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

Tumor response by BICR

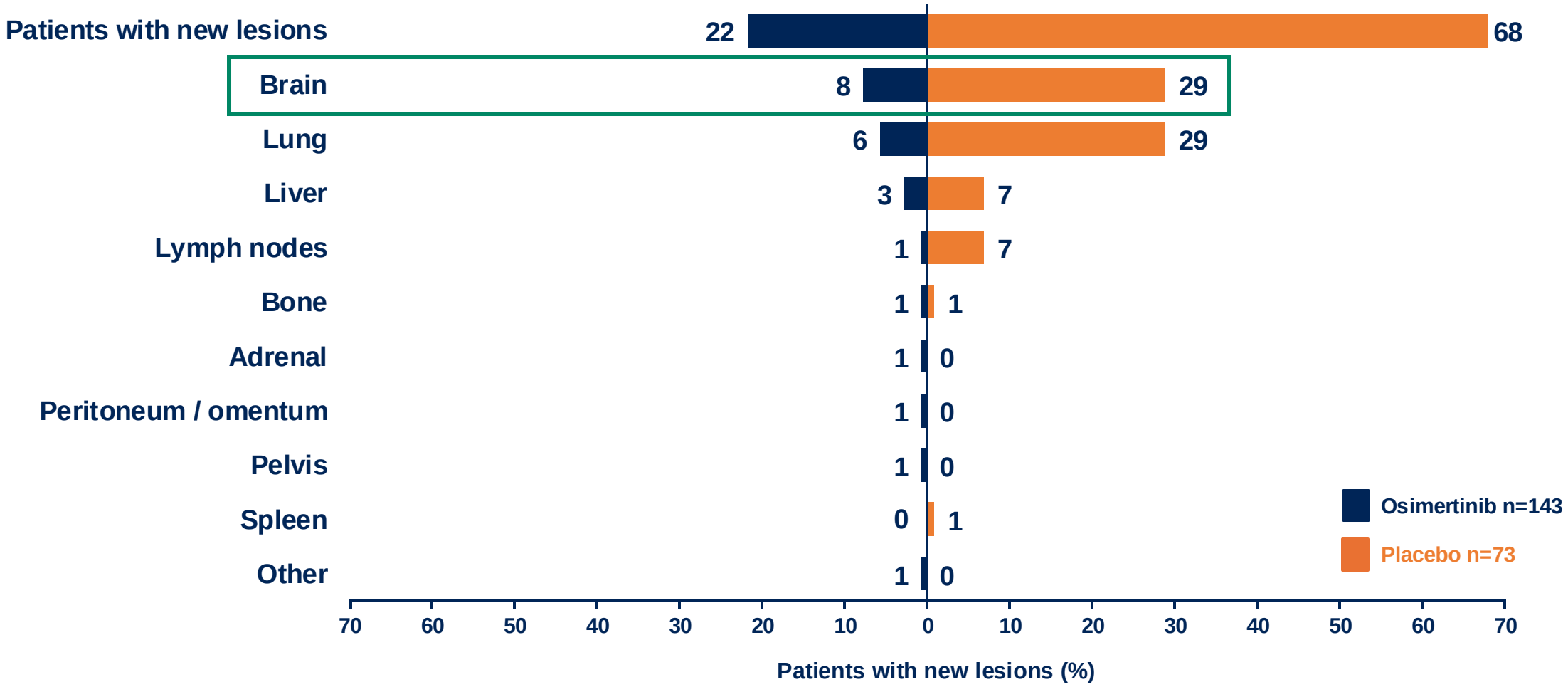


	Osimertinib (n=143)	Placebo (n=73)
Objective response rate, % (95% CI)	57 (49, 66)	33 (22, 45)
Disease control rate, % (95% CI)	89 (83, 94)	79 (68, 88)
Median duration of response, months (95% CI)	36.9 (30.1, NC)	6.5 (3.6, 8.3)

Data cut-off: January 5, 2024.
*Missing data imputed as +20% according to predefined rules.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; NC, not calculable; NE, not evaluable PD, progressive disease; PR, partial response; SD, stable disease

Sites of new lesions by BICR



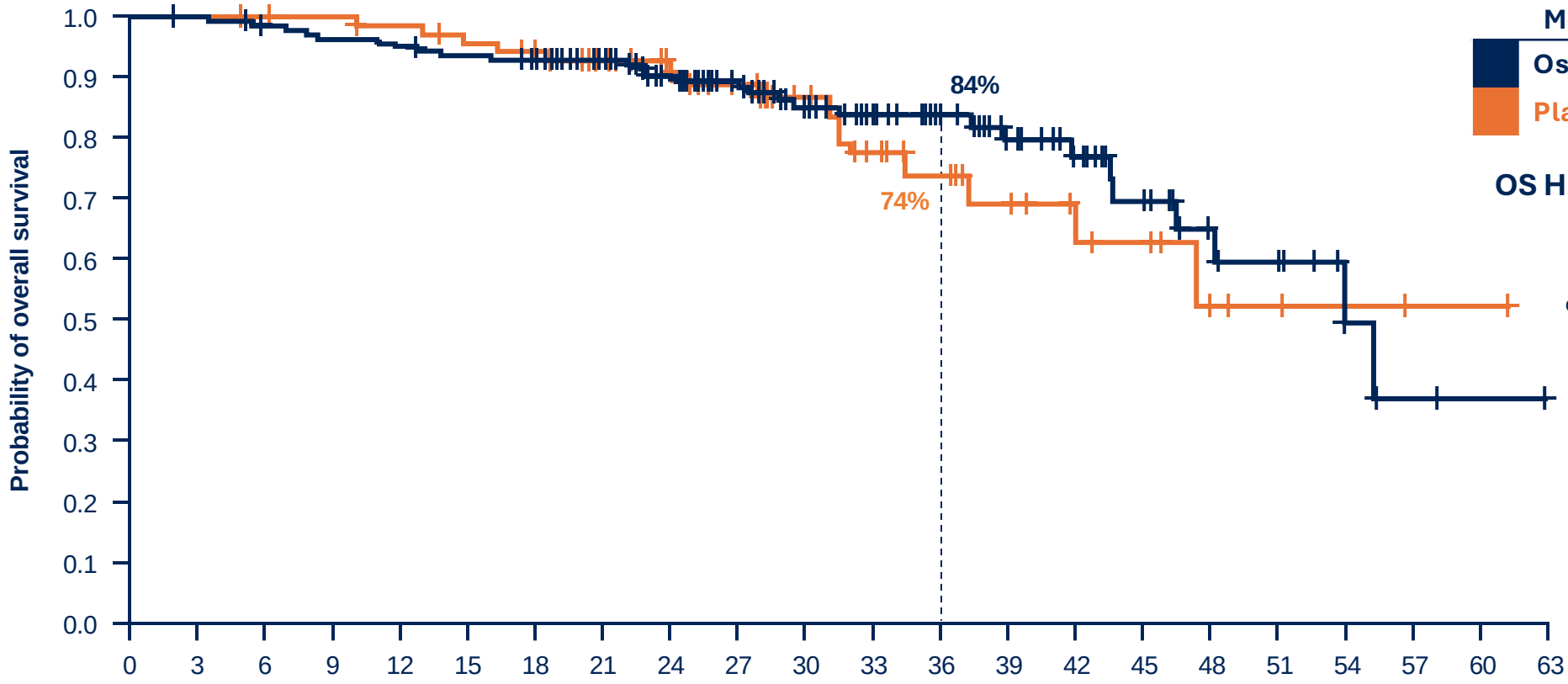
Data cut-off: January 5, 2024.

Percentages based on number of patients in each treatment arm. Patients can have more than one new lesion site. Based on BICR assessments according to RECIST v1.1 and includes all new lesions at any time (including those whose RECIST progression event had been censored).

BICR, blinded independent central review

Interim analysis of overall survival

- In the placebo arm, 81% of patients with BICR-confirmed progression crossed over to osimertinib



Median OS, months (95% CI)

Osimertinib	54.0 (46.5, NC)
Placebo	NR (42.1, NC)

OS HR (95% CI): 0.81 (0.42, 1.56), p=0.530*

Maturity 20%:
osimertinib 20%, placebo 21%

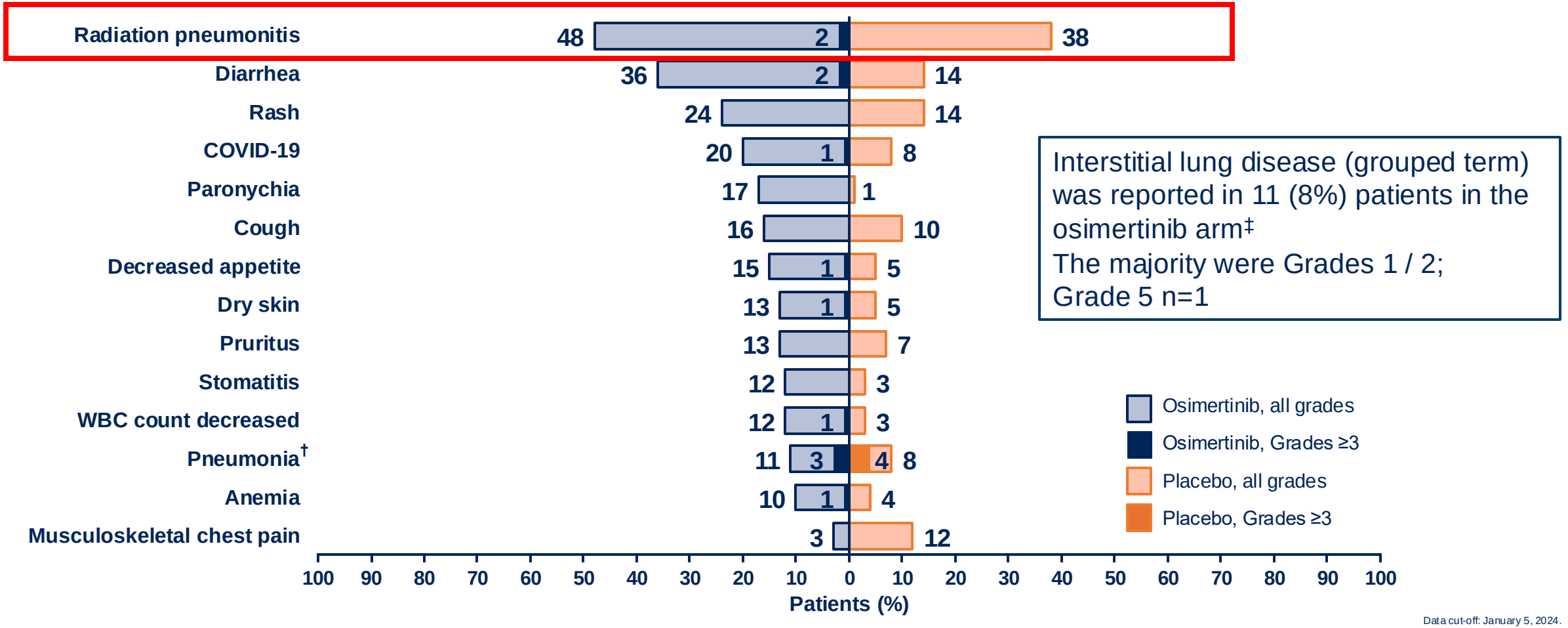
No. at risk																						
Osimertinib	143	142	138	135	133	130	127	115	100	86	71	59	49	37	28	19	12	9	4	2	1	0
Placebo	73	73	71	70	68	65	62	58	48	41	30	23	19	15	11	9	4	3	2	1	1	0

Data cut-off: January 5, 2024.
Tick marks indicate censored data. *For statistical significance at this interim analysis, a p-value of <0.00036 was required;
Median follow-up for OS (all patients): osimertinib 29.5 months, placebo 28.1 months. Median follow-up for OS (censored patients): osimertinib 30.9 months, placebo 28.1 months.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival

All-causality adverse events (≥10%)*

- The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2; Grade 5 n=1

Data cut-off: January 5, 2024.

*AEs with incidence of 10% or more in either treatment arm are shown. Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy; †One grade 5 AE of pneumonia was reported in the osimertinib arm; ‡Interstitial lung disease (grouped term) was reported in 1 patient (1%) in placebo arm; AE was pneumonitis, Grade 1.

AE, adverse event; WBC, white blood cells

Conclusions

- In LAURA, osimertinib demonstrated a statistically significant and clinically meaningful improvement in PFS vs placebo by BICR in unresectable stage III EGFRm NSCLC following definitive chemoradiotherapy
  - **Median PFS** was **39.1 months** (95% CI 31.5, NC) with osimertinib, **5.6 months** (95% CI 3.7, 7.4) with placebo; **HR 0.16** (95% CI 0.10, 0.24), p<0.001
  - PFS benefit was consistent across subgroups
- Interim OS data showed a positive trend in favor of osimertinib, despite a high proportion of patients crossing over to osimertinib in the placebo arm (81%)
- Safety profile of osimertinib post-chemoradiotherapy was as expected and manageable
- EGFR mutation testing is critical in stage III disease to ensure optimal outcomes for patients with EGFRm NSCLC

Osimertinib is the new standard of care for patients with unresectable stage III EGFRm NSCLC who have not progressed after definitive chemoradiotherapy

Data cut-off: January 5, 2024.

BICR, blinded independent central review; CI, confidence interval; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; HR, hazard ratio; NC, not calculable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival

2024 ASCO® ANNUAL MEETING

KRYSTAL-12: phase 3 study of adagrasib versus docetaxel in patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring a *KRAS*^{G12C} mutation

Tony S. K. Mok,[1] Wenxiu Yao,[2] Michaël Duruisseaux,[3–5] Ludovic Doucet,[6] Aitor Azkárate Martínez,[7] Vanesa Gregorc,[8] Oscar Juan-Vidal,[9] Shun Lu,[10] Charlotte De Bondt,[11] Filippo de Marinis,[12] Helena Linardou,[13] Young-Chul Kim,[14] Robert Jotte,[15] Enriqueta Felip,[16] Giuseppe Lo Russo,[17] Martin Reck,[18] Mary F. Michenzie,[19] Wenjing Yang,[19] Julie N. Meade,[19a] Fabrice Barlesi[20]

[1]Chinese University of Hong Kong, Hong Kong Special Administrative Region, China; [2]Sichuan Cancer Hospital & Institute, Chengdu, China; [3]Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute, Lyon, France; [4]Cancer Research Center of Lyon, UMR INSERM 1052, CNRS 5286, Lyon, France; [5]Université Claude Bernard Lyon 1, Université de Lyon, Lyon, France; [6]Institut de Cancérologie de l'Ouest, Nantes, France; [7]Hospital Universitario Son Espases, Mallorca, Spain; [8]Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy; [9]Hospital Universitari i Politècnic La Fe, Valencia, Spain; [10]Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [11]Antwerp University Hospital, University of Antwerp, Antwerp, Belgium; [12]Istituto Europeo di Oncologia, IRCCS, Milan, Italy; [13]Fourth Oncology Department & Comprehensive Clinical Trials Center, Metropolitan Hospital, Athens, Greece; [14]Chonnam National University Medical School and CNU Hwasun Hospital, Hwasun-Gun, Republic of Korea; [15]Rocky Mountain Cancer Center, US Oncology Research, Denver, CO, USA; [16]Vall d'Hebron Institute of Oncology, Vall d'Hebron Barcelona Hospital Campus, Universitat Autonoma de Barcelona, Barcelona, Spain; [17]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [18]Airway Research Center North, German Center for Lung Research, LungenClinic, Grosshansdorf, Germany; [19]Mirati Therapeutics, a Bristol Myers Squibb company, San Diego, CA, USA; [20]Gustave Roussy & Paris Saclay University, Villejuif, France

[a]Affiliation at the time of study

Abstract number LBA8509

KRYSTAL-12[a] study design

Key eligibility criteria

- Locally advanced or metastatic NSCLC with *KRAS*^{G12C} mutation[b]
- Prior treatment with platinum-based chemotherapy and anti-PD-(L)1 therapy[c]
- ECOG PS 0–1
- Stable brain metastases allowed

N = 453

R 2:1

ADA 600 mg BID PO[d]

DOCE 75 mg/m^2 Q3W IV

Crossover from DOCE to ADA was allowed in cases where disease progression per RECIST v1.1 was confirmed by real-time BICR[e]

Stratified by:

- Region (non-Asia-Pacific vs Asia-Pacific)
- Prior treatment (sequential vs concurrent chemotherapy and immunotherapy)

Primary endpoint

- PFS by BICR (RECIST v1.1)

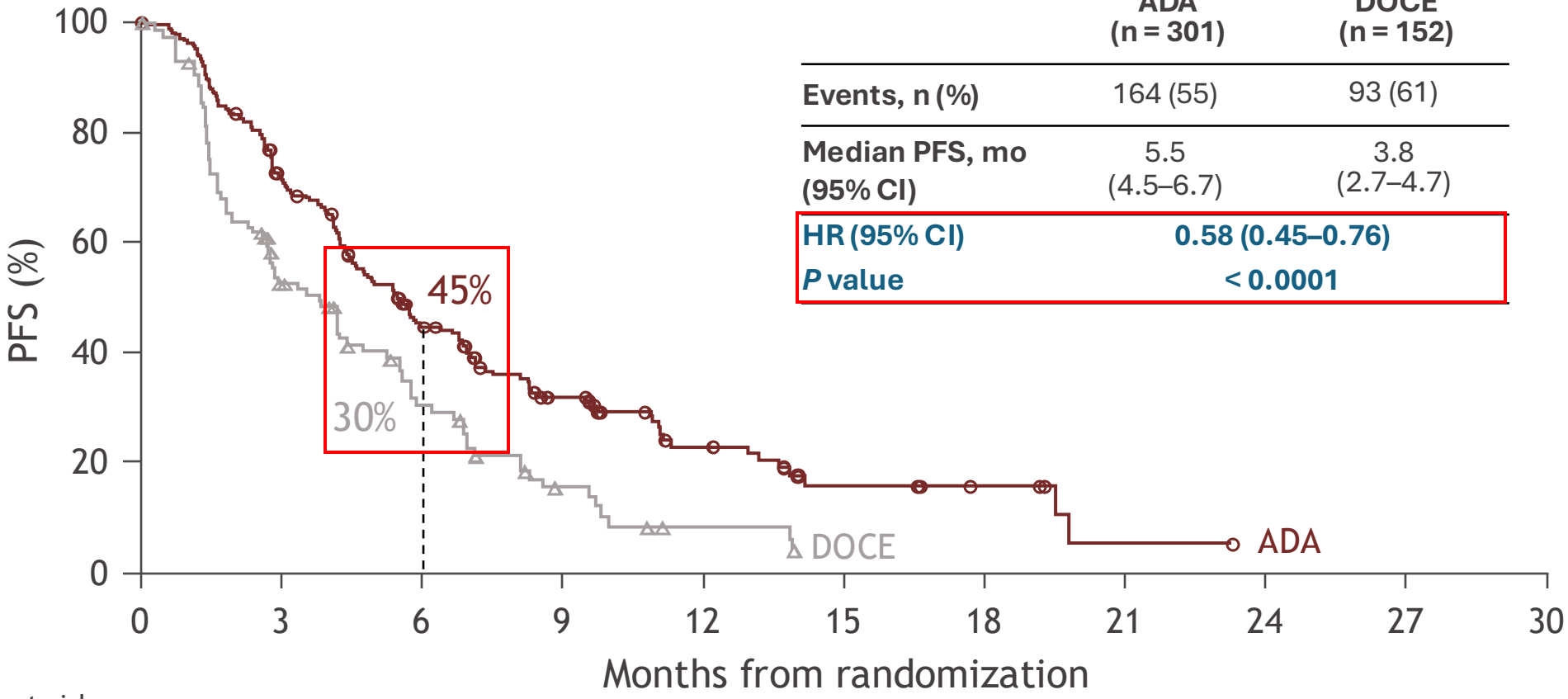
Secondary endpoints

- ORR by BICR (RECIST v1.1)
- DOR
- OS
- Safety
- Patient-reported outcomes

Database lock: March 19, 2024. Data cut-off: December 31, 2023.

[a]NCT04685135. [b]Detected in tumor tissue using sponsor-approved local or central testing. [c]No washout period was required between prior therapy and study treatment. [d]Tablet formulation, except for four patients who initially received the capsule formulation. [e]Other crossover criteria: ECOG PS 0–2, recovery from DOCE-related AEs to grade 1 or baseline (except peripheral neuropathy and alopecia for which grade 2 is acceptable).

Primary endpoint: PFS[a] per BICR

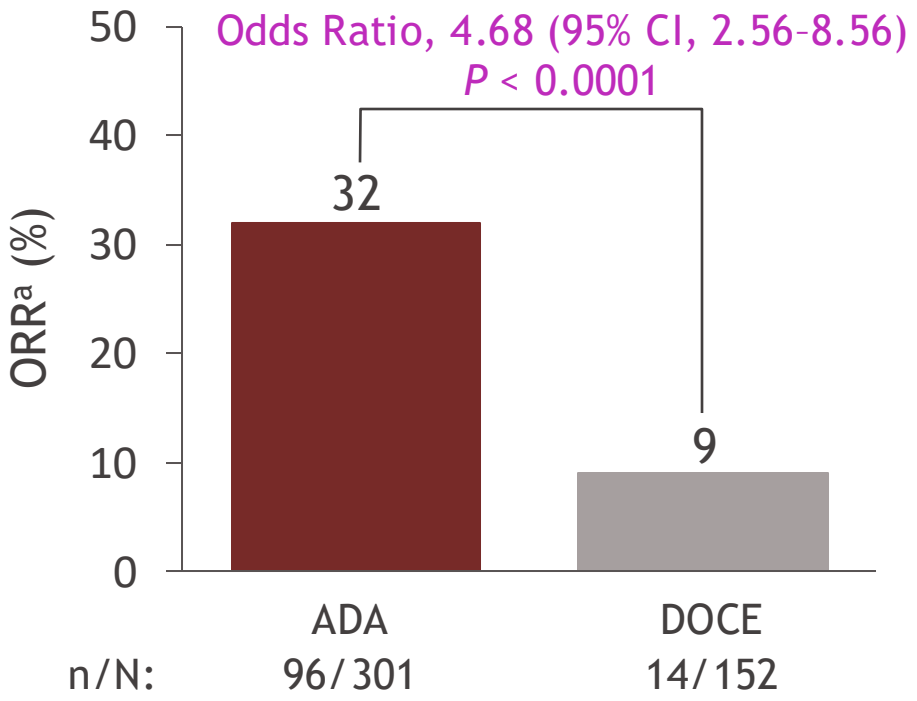


	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5–6.7)	3.8 (2.7–4.7)
HR (95% CI)	**0.58 (0.45–0.76)**	
***P* value**	**< 0.0001**	

Median follow-up: 7.2 months.

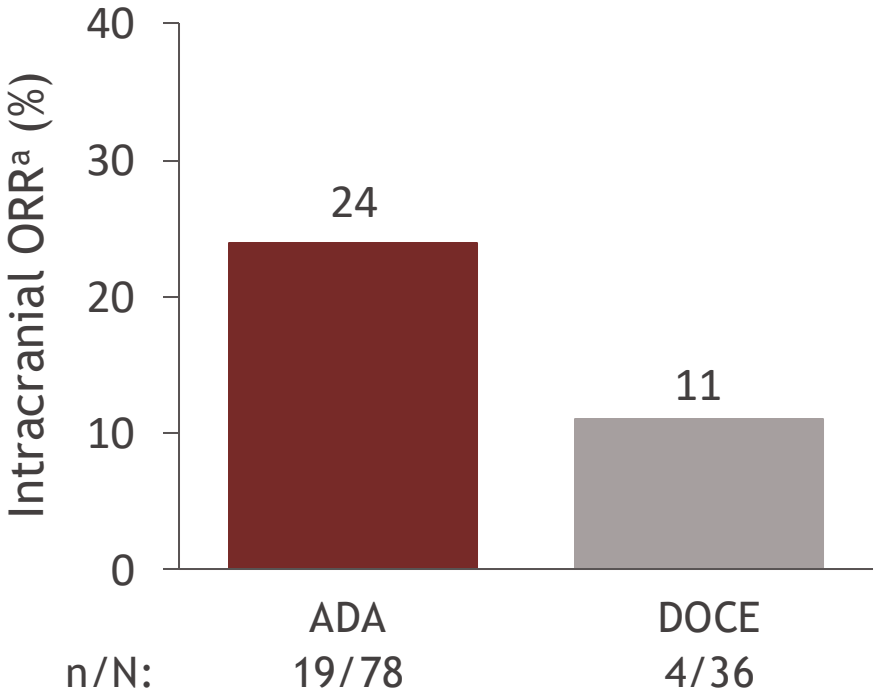
[a]Time from randomization to the date of disease progression per BICR or death due to any cause, whichever occurs first. For patients who started a subsequent anticancer therapy prior to disease progression or death, PFS was censored at the date of the last tumor assessment prior to the start of the new therapy.

Tumor and Intracranial response per BICR



Tumor response	ADA (n = 301)	DOCE (n = 152)
DCR,[b] n (%)	236 (78)	89 (59)
Median DOR,[c] mo (95% CI)	8.3 (6.1–10.4)	5.4 (2.9–8.5)
Remaining in response at 6 mo, %	64	39

All patients with baseline CNS metastases[a]



Intracranial response[a]	ADA (n = 78)	DOCE (n = 36)
Intracranial DCR, n (%)	64 (82)	20 (56)

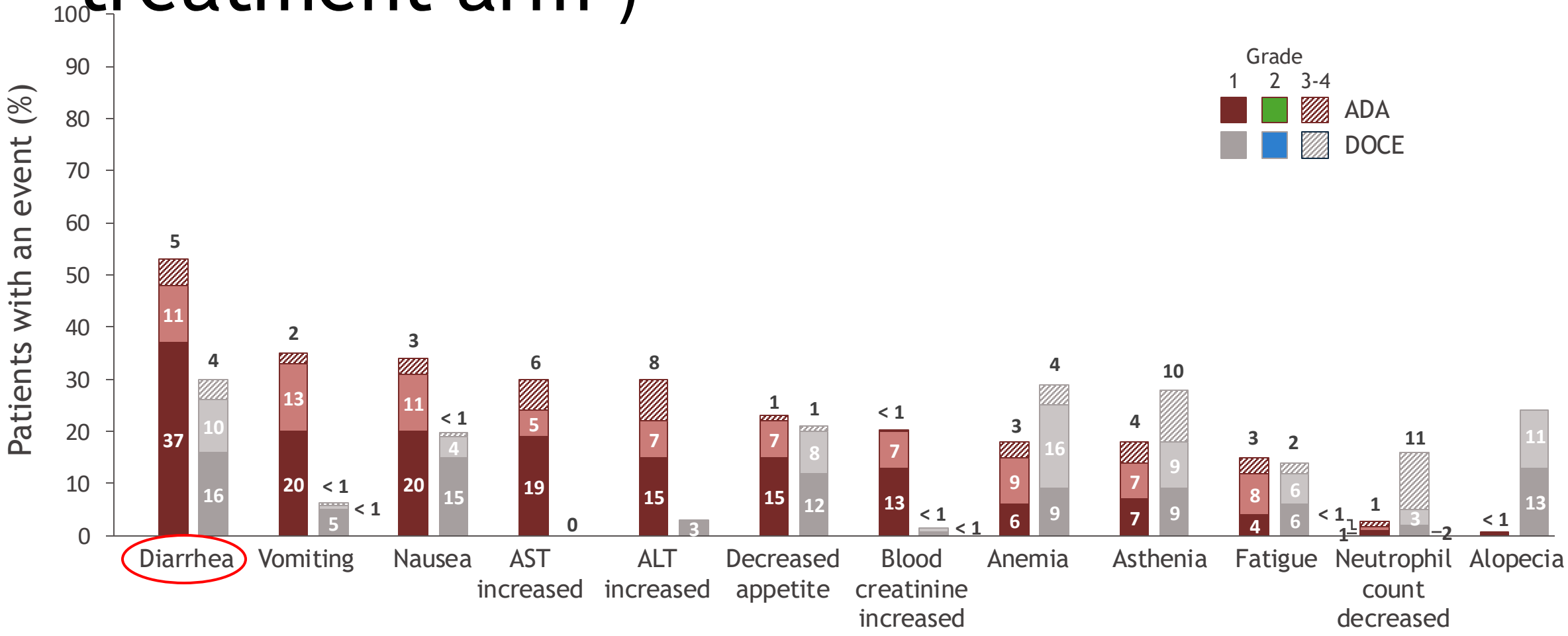
[a]ORR is defined as the percent of patients documented to have a confirmed CR/PR by BICR (per RECIST v1.1). [b]Disease control rate (DCR) is defined as the percent of patients documented to have a confirmed CR/PR/SD by BICR (per RECIST v1.1). [c]DOR is defined as the time from the date of first documentation of CR/PR to the first documentation of PD or death due to any cause in the absence of documented PD. DOR is only calculated for patients with confirmed CR/PR. [d]Waterfall plots include patients with at least one target lesion at baseline and at least one post-baseline tumor assessment.

Safety summary[a]

Patients, %	ADA (n = 298)	DOCE (n = 140)
TRAEs	94	86
Grade ≥ 3 TRAEs	47	46
TRAEs leading to discontinuation[b]	8	14
TRAEs leading to dose reduction	48	24
TRAEs leading to dose interruption	59	19
Treatment-related SAEs	21	16
Treatment-related deaths[c]	1	< 1

[a]AEs per CTCAE v5.0 and MedDRA v26.0. Includes events reported between the first dose and 28 days after the last dose, and prior to the initiation of subsequent anticancer therapy. For each category, patients are included only once, even if they experienced multiple events in that category. [b]Most common TRAEs leading to treatment discontinuation were ALT increased (n = 3), neutropenia, diarrhea, and pneumonitis (n = 2 each) with ADA, and asthenia, fatigue, and peripheral neuropathy (n = 3 each) with DOCE. [c]Treatment-related deaths were due to epilepsy, hepatic failure, hepatic ischemia, and unknown cause with ADA, and sepsis with DOCE (n = 1 each).

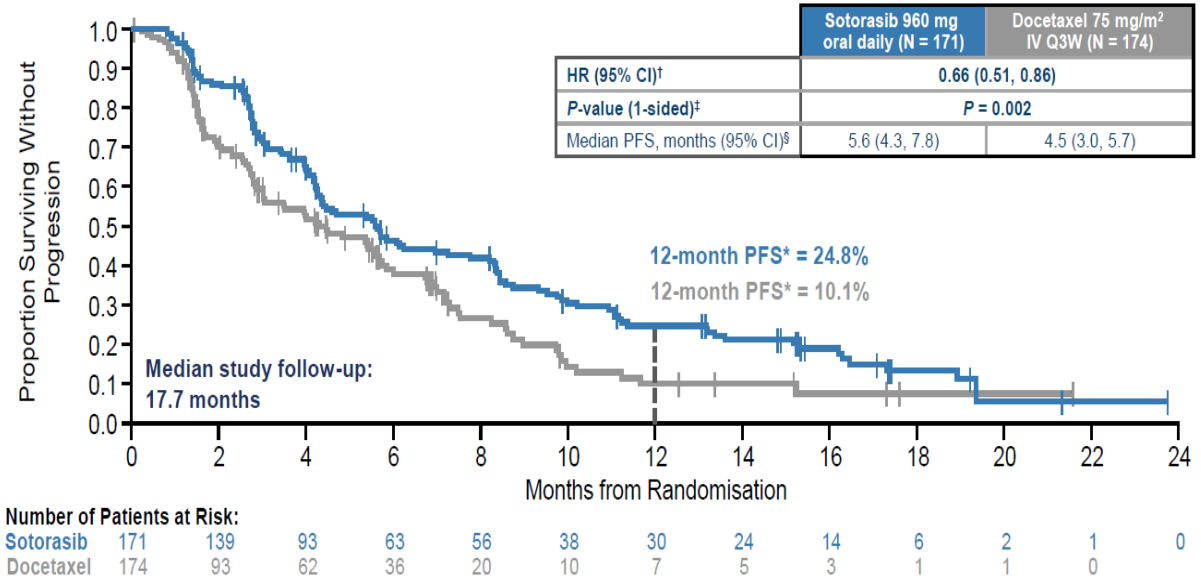
Most frequent TRAEs (> 15% in either treatment arm[a])



[a]For each TRAE, patients are included only once at the maximum severity.

CodeBreaK 200: Sotorasib vs Docetaxel

Primary Endpoint: PFS by BICR

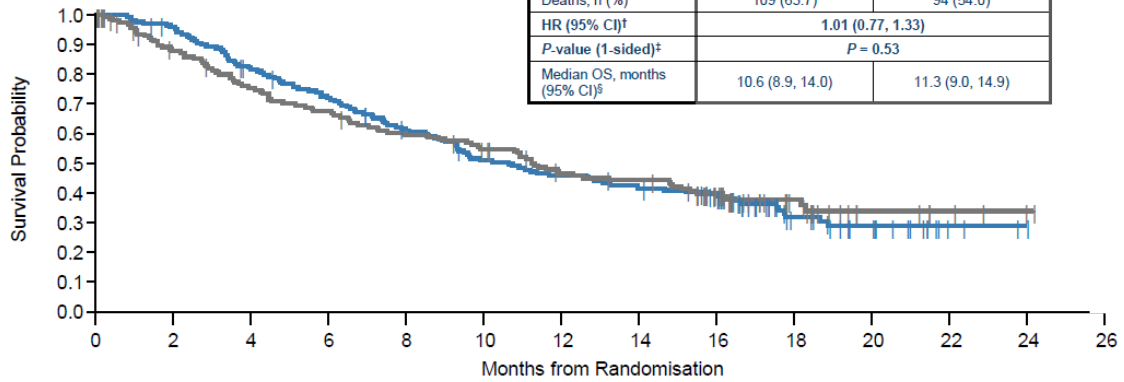


	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

OS: Sotorasib vs Docetaxel



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

Number of Patients at Risk:

Sotorasib	171	162	137	119	98	81	73	66	56	25	15	3	0
Docetaxel	174	135	115	103	90	81	65	61	44	20	7	4	1	0

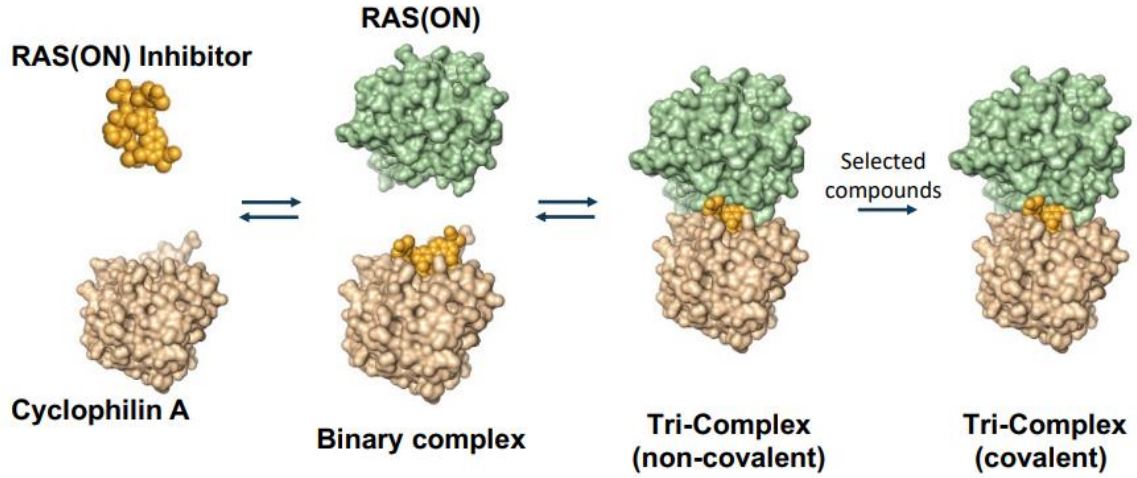
Johnson ML, et al. ESMO 2022. Abstract LBA10

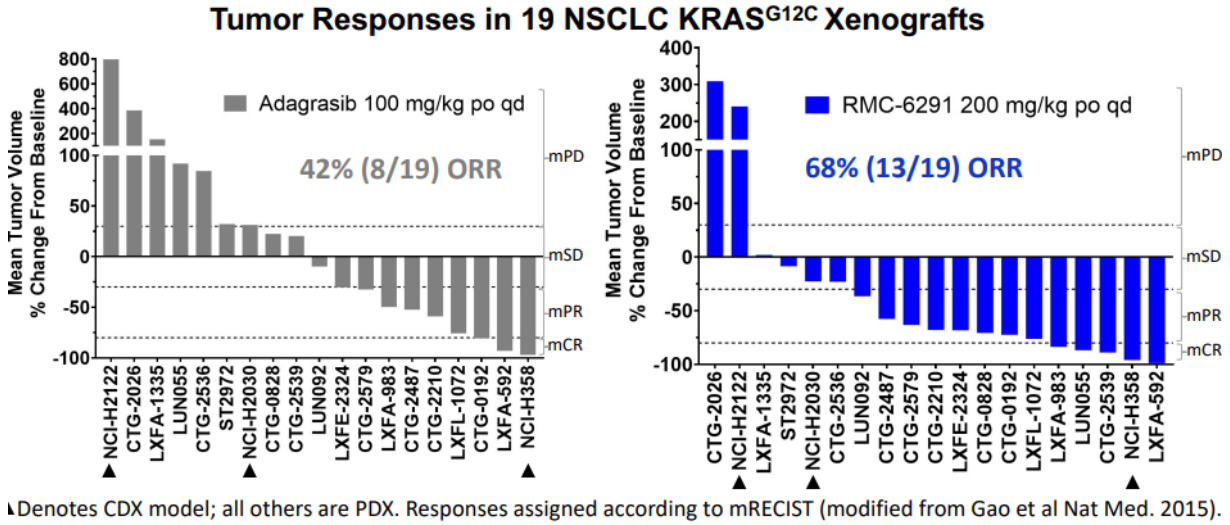
Next Generation RAS Inhibitors

- Less susceptible to adaptive resistance compared to GDP bound RAS

- RMC-6291 KRAS G12C (ON) inhibitor
- RMC-9805 KRAS G12D (ON) inhibitor
- RMC-6236-Pan RAS (ON)

- Divarasib – Single arm study
  ORR = 53.4% (95% CI, 39.9 to 66.7), and mPFS was 13.1 months (95% CI, 8.8 to, could not be estimated)





Sacher et al N Engl J Med 2023;389:710-721.

2024 ASCO® ANNUAL MEETING

Lorlatinib vs Crizotinib in Treatment-Naive Patients With Advanced *ALK*+ Non-Small Cell Lung Cancer: 5-Year Progression-Free Survival and Safety From the CROWN Study

Benjamin J. Solomon,[1] Geoffrey Liu,[2] Enriqueta Felip,[3] Tony S. K. Mok,[4] Ross A. Soo,[5] Julien Mazieres,[6] Alice T. Shaw,[7] Filippo de Marinis,[8] Yasushi Goto,[9] Yi-Long Wu,[10] Dong-Wan Kim,[11] Jean-François Martini,[12] Rossella Messina,[13] Jolanda Paolini,[13] Anna Polli,[13] Despina Thomaidou,[14] Francesca Toffalorio,[13] Todd M. Bauer[15]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong; [5]National University Cancer Institute, Singapore; [6]Toulouse University Hospital and Centre de Recherche Cancérologie Toulouse CRCT, INSERM, France; [7]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [8]European Institute of Oncology, IRCCS, Milan, Italy; [9]National Cancer Center Hospital, Tokyo, Japan; [10]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangdong, China; [11]Seoul National University College of Medicine and Seoul National University Hospital, Seoul, South Korea; [12]Pfizer, La Jolla, CA, USA; [13]Pfizer, Milan, Italy; [14]Pfizer, Athens, Greece; [15]Greco-Hainsworth Centers for Research/Tennessee Oncology, Nashville, TN, USA

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Current Post Hoc Analyses at 5 Years

Endpoint evaluation by BICR stopped after the 3-year analysis

Key eligibility criteria

- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1 N=296

Lorlatinib 100 mg once daily n=149

Stratified by:

- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

Crizotinib 250 mg twice daily n=147

No crossover between treatment arms was permitted

Current analyses

Data cutoff: October 31, 2023

- **Investigator Assessed**
  - PFS[a]
  - ORR and IC ORR
  - DOR and IC DOR
  - IC TTP
- Safety
- Biomarker analyses

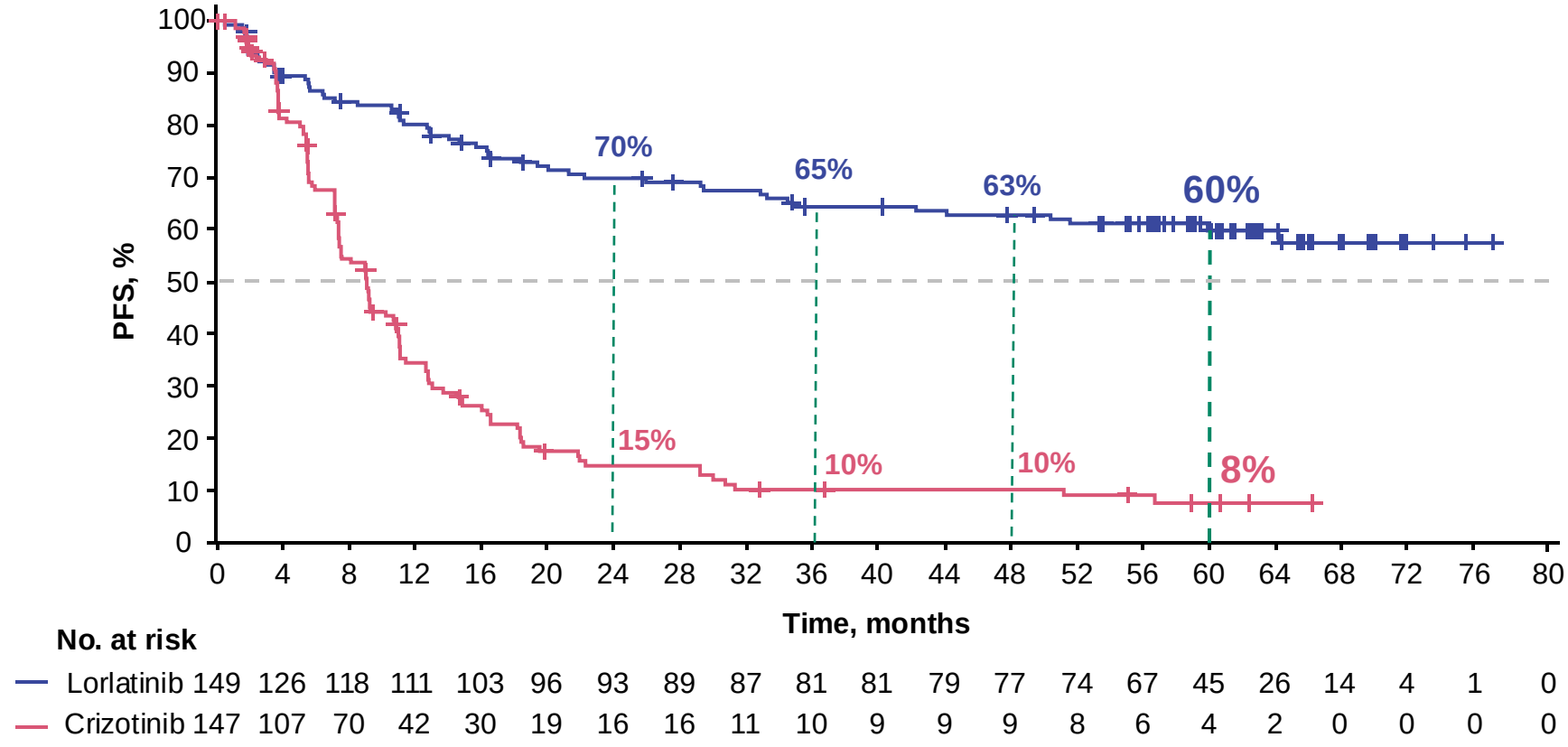
- The median duration of follow-up for PFS was 60.2 months (95% CI, 57.4-61.6) in the lorlatinib arm and 55.1 months (95% CI, 36.8-62.5) in the crizotinib arm

CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; ORR, objective response rate; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression.

[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.

Benjamin J. Solomon (Ben.Solomon@petermac.org)

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

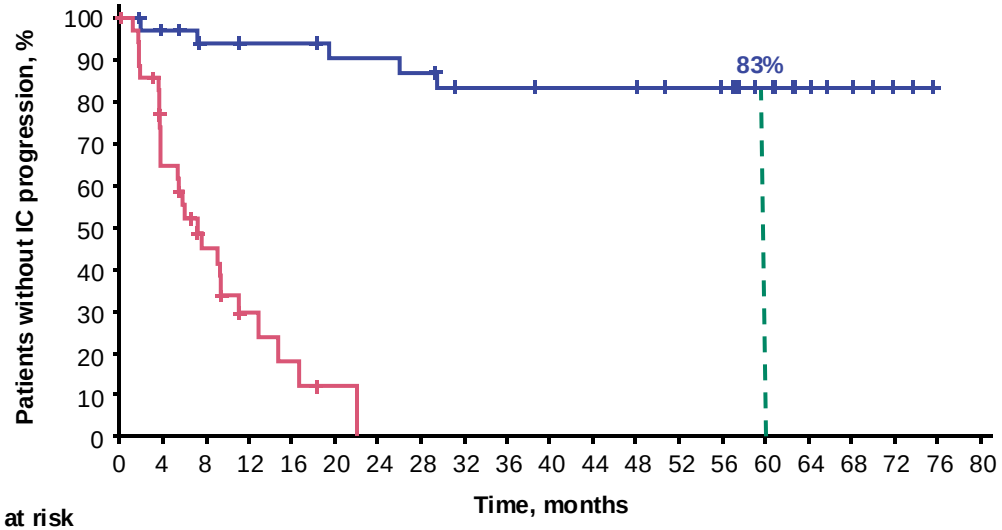
HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

Benjamin J. Solomon (Ben.Solomon@petermac.org)

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)**	

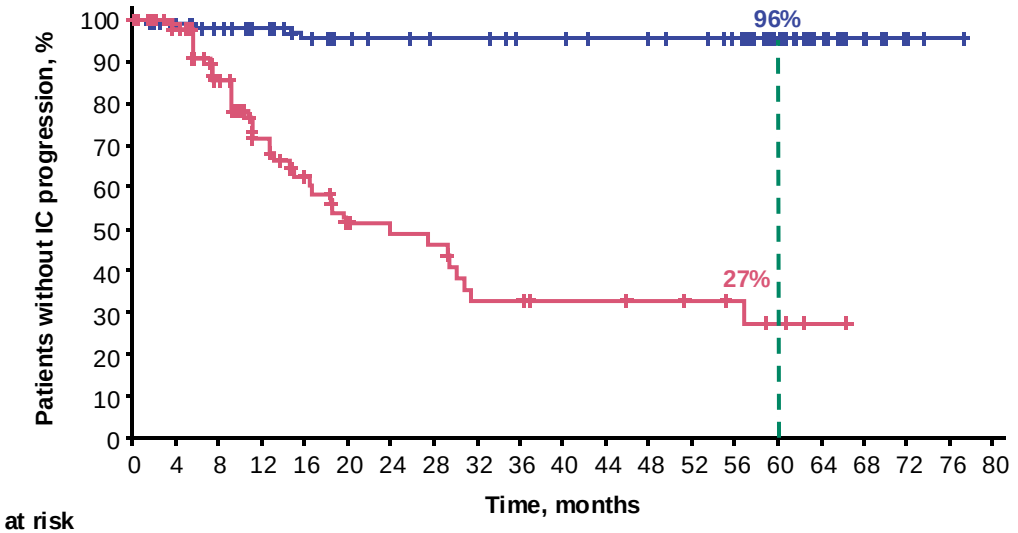


No. at risk

Lorlatinib	35	32	29	28	28	26	26	25	22	22	20	20	19	18	17	12	7	5	2	0	-
Crizotinib	38	21	12	5	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-

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)**	



No. at risk

Lorlatinib	114	96	90	84	77	72	70	67	67	64	64	61	60	59	55	38	22	9	3	1	0
Crizotinib	109	86	63	41	31	21	19	18	12	12	10	10	9	8	6	4	2	0	0	0	0

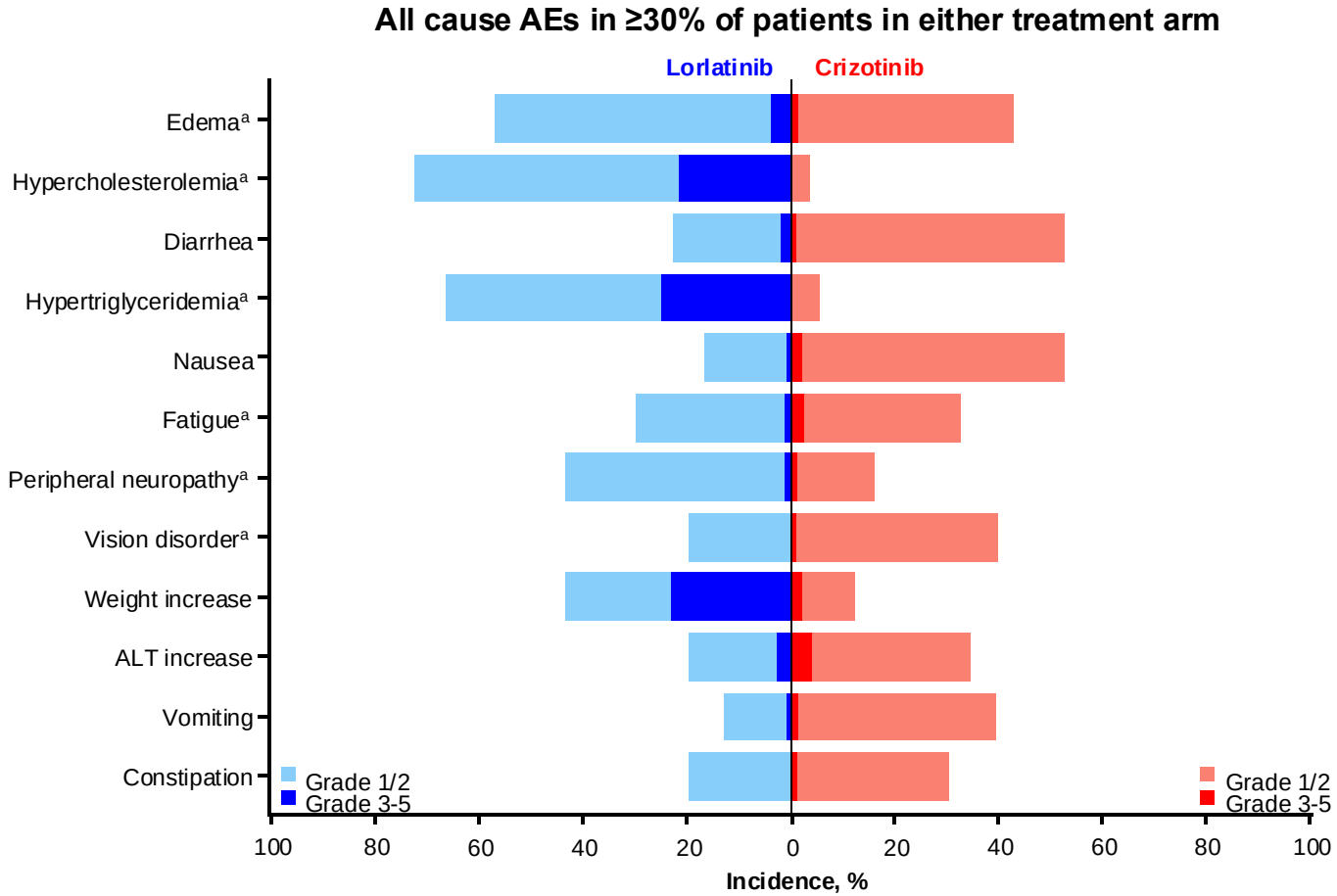
HR, hazard ratio; IC, intracranial; NR, not reached.

Benjamin J. Solomon (Ben.Solomon@petermac.org)

Safety Profile of Lorlatinib Was Consistent With That Observed in Prior Analyses

All-causality AEs observed in the lorlatinib arm:

- AEs of any-grade, grade 3/4, and serious occurred in 100%, 77%, and 44% of patients
- The higher incidence of grade 3/4 AEs was largely due to hypertriglyceridemia (25%), weight increase (23%), hypercholesterolemia (21%), and hypertension (12%)
- CNS AEs[b] occurred in 42% of patients in the lorlatinib arm, 86% of which were grade 1/2
- AEs led to dose reduction in 23% of patients, temporary treatment discontinuation in 62%, and permanent discontinuation in 11%; of which 5% were due to treatment-related AEs, all reported during the first 26 months



AE, adverse event; CNS, central nervous system.

[a]This category comprised a cluster of AEs that may represent similar clinical symptoms or syndromes. [b]Includes cognitive effects (28%), mood effects (21%), speech effects (6%), and psychotic effects (5%),

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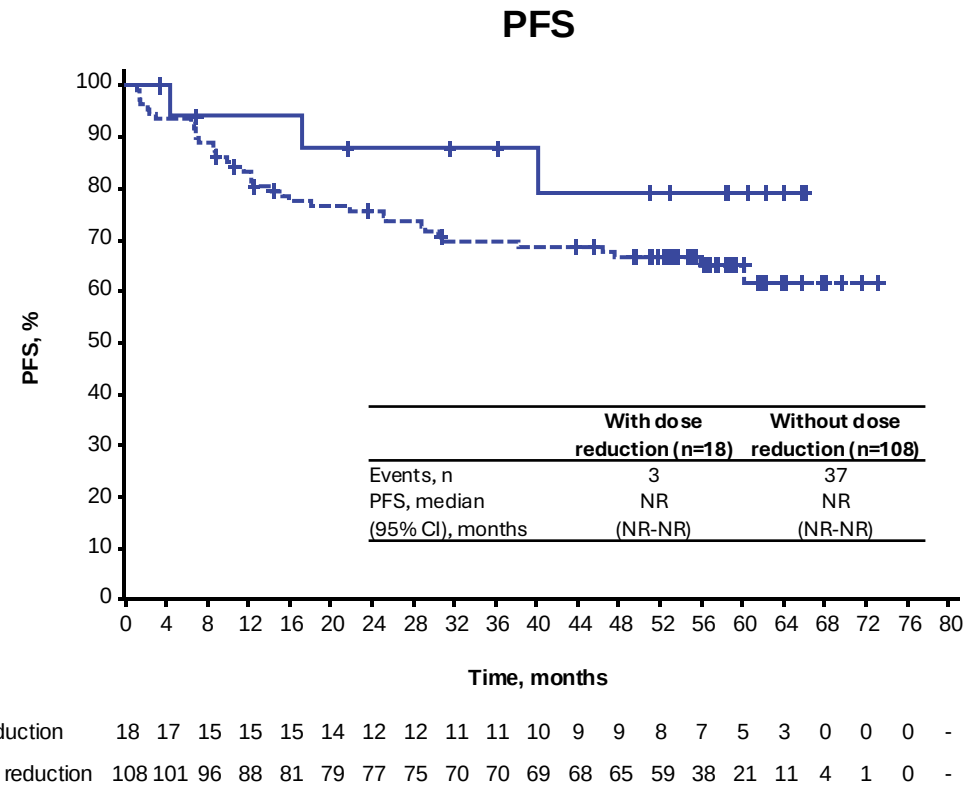
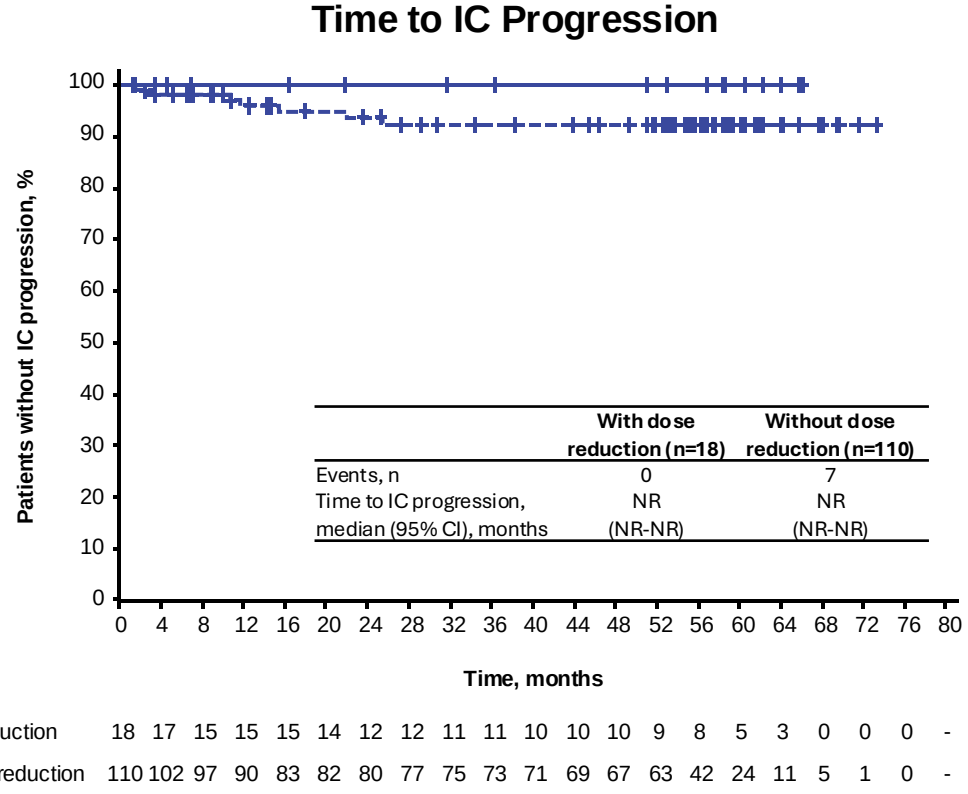
Dose Reduction Did Not Impact Efficacy of Lorlatinib in Patients Who Had Dose Reduction in the First 16 Weeks





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

Benjamin J. Solomon (Ben.Solomon@petermac.org)

Emerging New *ALK* Mutations Were Not Detected in ctDNA Collected at the End of Lorlatinib Treatment

	Lorlatinib (n=31) n (%)	**Crizotinib (n=89)** n (%)
Resistance mechanisms		
New single ALK mutation	0	8 (9)
ALK compound mutation	0	2 (2)
Bypass mechanism	9 (29)	10 (11)
MAPK pathway aberration	3 (10)	1 (1)
PI3K/MTOR/PTEN pathway aberration	2 (6)	0
RTK pathway aberration	4 (13)	5 (6)
Cell cycle pathway aberration	2 (6)	5 (6)
Other gene aberration	11 (35)	19 (21)
Unknown	13 (42)	56 (63)

ctDNA from plasma collected at screening was analyzed with a validated, commercially available, 74-gene ctDNA next-generation sequencing assay (Guardant360 panel version 2.11; bioinformatics pipeline version 3.5.3; Guardant Health, Inc., Redwood City, CA).
ctDNA, circulating tumor DNA.

Benjamin J. Solomon (Ben.Solomon@petermac.org)

How to Choose? FDA Approved Next Generation ALK inhibitors for 1L Therapy: Efficacy and Toxicity

	Alectinib	Brigatinib	Lorlatinib
ORR	79%	71%	76%
Med PFS by ICR	25.7 mo	24 mo	NR (3yr follow-up)
Med PFS by IR	34.8	30.8	NR (5-yr PFS=60%)
Med OS	>5 yr	NR	NR
Toxicity	Fatigue, constipation, myalgia (CPK), edema, transaminitis (moderate) Weight gain	Nausea, diarrhea, fatigue, HA, HTN, pulmonary tox, transaminitis	Edema, neuropathy, cognitive changes (mood), lipids, weight gain

- **1L, first-line**

BARCELONA 2024 ESMO congress

Phase 1/2 ALKOVE-1 study of NVL-655 in ALK-positive (ALK+) solid tumors

A. Drilon[1], J. J. Lin[2], M. L. Johnson[3], C. S. Baik[4], L. Paz-Ares[5], B. Besse[6], J. Mazieres[7], A. Swalduz[8], A. Minchom[9], J. E. Reuss[10], S. Gadgeel[11], J. W. Riess[12], G. Liu[13], B. J. Solomon[14], D. R. Camidge[15], W. Swe[16], Y. Sun[16], J. Shen[16], V. W. Zhu[16], E. Felip[17]

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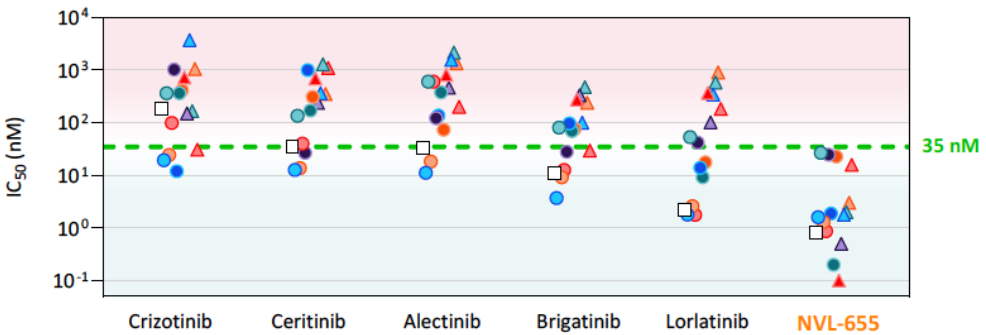
Presented at the European Society For Medical Oncology (ESMO) Congress 2024 | Barcelona, Spain | September 14, 2024

NVL-655: A Rationally Designed ALK-selective, TRK-sparing TKI

ALK Fusion and ALK Single/Compound Mutation Activity

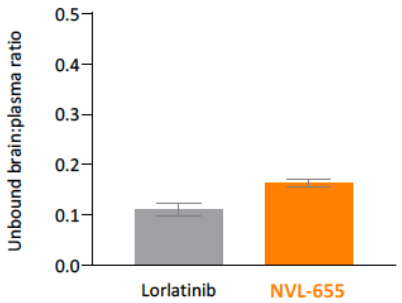
Potent activity (IC_{50} = 0.1 – 30 nM) against ALK-driven cell lines, including ALK single and compound mutants



Cell lines harboring EML4-ALK fusion
3-day cell viability assay

Brain Penetrance

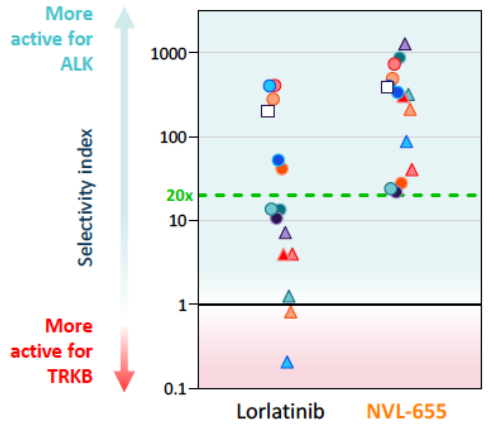
Preclinical pharmacokinetic data similar to lorlatinib



Wistar Han rats
10 mg/kg, single dose PO
1-hour timepoint

Avoidance of TRK Inhibition

Selective inhibition of ALK and ALK mutants over TRK



$$\text{Selectivity index} = \frac{IC_{50}\ (\text{pTRKB})}{IC_{50}\ (\text{Ba/F3 EML4-ALK})}$$

□ No resistance mutations | MGH048-1 (v1)

Single ALK mutations

- T1151M | Ba/F3 (v3)
- I1171N | Ba/F3 (v1)
- F1174L | Ba/F3 (v3)
- V1180L | Ba/F3 (v1)
- L1196M | MGH045-1 (v1)
- L1198F | Ba/F3 (v1)
- G1202R | YU-1077 (v3)
- D1203N | Ba/F3 (v1)

Compound ALK mutations

- G1202R/T1151M | MR448re (v3)
- G1202R/F1174L | Ba/F3 (v3)
- G1202R/L1196M | MGH953-7 (v3)
- G1202R/L1198F | Ba/F3 (v1)
- G1202R/G1269A | Ba/F3 (v1)
- I1171N/L1198F | Ba/F3 (v1)

Lin J.J. et al. (2024). NVL-655 Is a Selective and Brain-Penetrant Inhibitor of Diverse ALK Mutant Oncoproteins, Including Lorlatinib-Resistant Compound Mutations. *Cancer Discovery*. Advance Online Publication.

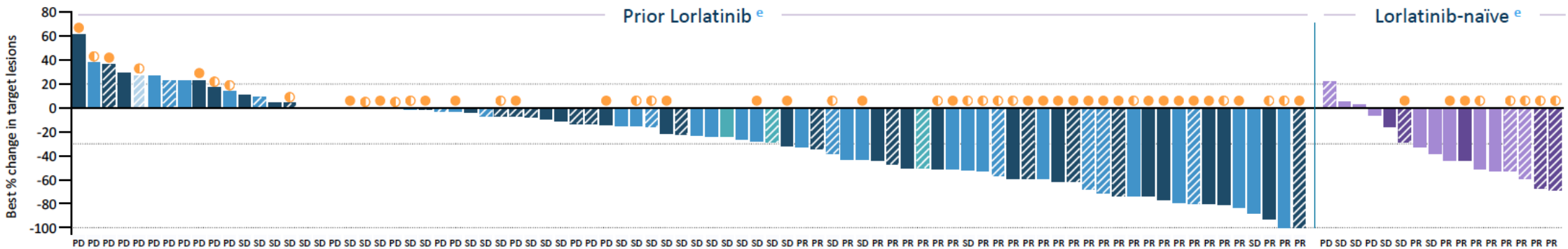
Head-to-head clinical studies comparing NVL-655 with currently approved or investigational therapies have not been conducted.

IC_{50}, half-maximal inhibitory concentration; PO, orally; v, EML4 breakpoint variant.

Sources: Lin J.J. et al., Cancer Discovery 2024; Lin J.J. et al., AACR-NCI-EORTC 2023; Lee, J. *et al.* AACR 2023; Fujino, T. *et al.* EORTC-NCI-AACR 2022; Mizuta, H. *et al.* WCLC-IASLC 2022; Tangpeerachaikul, A. *et al.* AACR 2022; Tangpeerachaikul, A. *et al.* AACR-NCI-EORTC 2021; Pelish, H. *et al.* AACR 2021. Data also reflect additional repeat testing and models.

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.

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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**

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Phase 1/2 ARROS-1 study of zidesamtinib (NVL-520) in ROS1 fusion-positive solid tumors

B. Besse[1], A. Drilon[2], B. C. Cho[3], D. R. Camidge[4], J. Neal[5], C. C. Lin[6], S. V. Liu[7], M. Nagasaka[8], S. Kao[9], E. Felip[10], A. J. van der Wekken[11], C. C. Lin[12], J. Bauman[13], S. Gadgeel[14], M. Samant[15], J. Shen[15], Y. Sun[15], V. W. Zhu[15], V. A. Upadhyay[15], J. J. Lin[16]

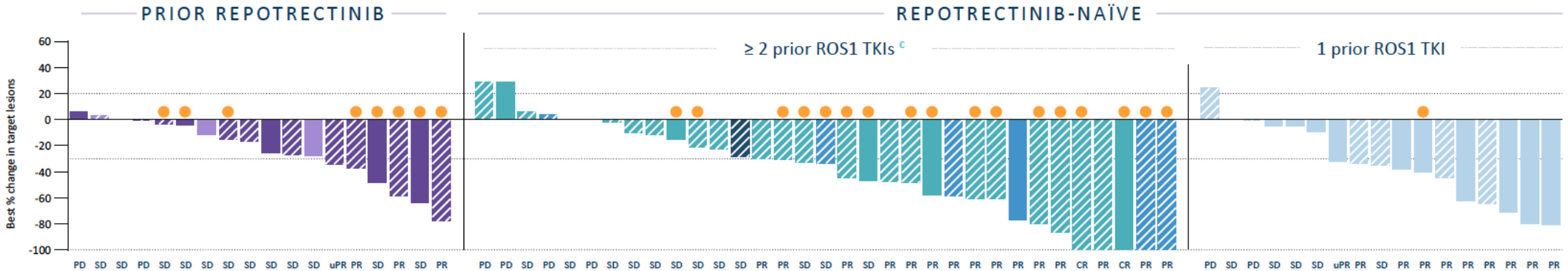
[1]Institut Gustav Roussy, Villejuif, France; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center, New York, NY, United States; [3]Yonsei Cancer Center, Seoul, Republic of Korea; [4]University of Colorado Cancer Center, Aurora, Colorado, United States; [5]Stanford Cancer Institute, Palo Alto, California, United States; [6]National Taiwan University Hospital, Taipei, Taiwan; [7]Georgetown Lombardi Comprehensive Cancer Center, Washington, District of Columbia, United States; [8]University of California Irvine, Orange, California, United States; [9]Chris O'Brien Lifehouse, Camperdown, Australia; [10]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [11]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [12]National Cheng Kung University Hospital, Tainan, Taiwan; [13]Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States [14]Henry Ford Cancer Center, Detroit, Michigan, United States; [15]Nuvalent, Cambridge, Massachusetts, United States; [16]Massachusetts General Hospital, Boston, MA, United States

Presented at the European Society For Medical Oncology (ESMO) Congress 2024 | Barcelona, Spain | September 14, 2024

Preliminary Activity: Radiographic Tumor Response Across Previously Treated Patients with ROS1+ NSCLC

All NSCLC Response Evaluable Patients *± chemotherapy*	Any Prior ROS1 TKI (range 1-4)				≥ 2 prior ROS1 TKIs			1 prior ROS1 TKI (crizotinib)
	All	Repotrectinib-naive	ROS1 G2032R Resistance Mutation [b]		All	Prior Lorlatinib	Repotrectinib-naive	
			Prior Repotrectinib	Repotrectinib-naive				
RECIST 1.1 ORR % (n/n) [a]	**44%** (31/71)	**51%** (27/53)	**38%** (3/8)	**72%** (13/18)	**41%** (21/51)	**44%** (17/39)	**47%** (17/36)	**73%** (8/11)
CR *	2	2	-	2	2	2	2	-

* 2 confirmed CRs ongoing with DOR 19.3+ and 26.3+ months. 5 additional CRs observed among patients without measurable disease (2 prior ROS1 TKIs [n=2], 1 prior ROS1 TKI (crizotinib [n=1], entrectinib [n=2])), all ongoing with DOR 3.6+, 3.7+, 13.8+, 13.9+, and 18.5+ months.



Data cut-off: 1 July 2024. Response-evaluable patients with ROS1+ NSCLC.

CR, complete response; **DOR**, duration of response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **SD**, stable disease; **TKI**, tyrosine kinase inhibitor; **uPR**, unconfirmed partial response.

[a] Includes two ongoing partial responses pending confirmation.

[b] ROS1 mutations as per local or central testing of blood (ctDNA) or tissue. Responses also observed in patients with ROS1 resistance mutations other than G2032R (S1986F, D2033N).

[c] Three response-evaluable patients not shown due to incomplete or missing post-baseline tumor assessments in the setting of symptomatic deterioration.

KEY: PATIENT DETAILS

Prior Repotrectinib:
- ≥ 2 prior ROS1 TKIs
- 1 prior ROS1 TKI

Repotrectinib-naive:
- 4 prior ROS1 TKIs
- 3 prior ROS1 TKIs
- 2 prior ROS1 TKIs
- 1 prior ROS1 TKI

+ chemotherapy

ROS1 G2032R mutation

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Summary of ROS1 TKIs in TKI-Naïve ROS1+ NSCLC

	Crizotinib* (PROFILE 1001)	Entrectinib* (ALKA-372-001, STARTRK-1, STARTRK-2)	Ceritinib (Korean Phase 2)	Taletrectinib (Chinese Phase 2)	Lorlatinib (Phase 1/2)	Repotrectinib# (TRIDENT-1 Phase 1/2)
N	53	161	20	106	21	71
ORR	72%	67% (n=108)	67%	90.6%	62%	79%
Median PFS	19.3 months	15.7 months	19.3 months	NR (30.4-NR)	21.0 months	35.7
CNS activity	N/A	19/24 (79%) patients with measurable intracranial disease	2/5 (40%) patients with measurable or nonmeasurable intracranial disease	88%	7/11 (64%) patients with measurable or nonmeasurable intracranial disease	8/9 (89%) patients with measurable intracranial disease
Reference	Shaw et al. Ann Oncol 2019	Dziadziuszko et al. JCO 2021	Lim et al. JCO 2017	Li et al., ASCO 2024	Shaw et al. Lancet Oncol 2019	Drilon et al. NEJM 2024

Key Takeaways

- Exceptional clinical activity of 1L Lorlatinib.
- After 5 years of follow-up in the CROWN study, with lorlatinib treatment: Median PFS has still not been reached and PFS was 60%.
- Superb intracranial activity. The probability of being free of intracranial progression was 92%.
- Activity in ALK subsets considered a poorer prognosis.
- Next-gen ALK TKIs and ROS1 TKIs with activity

- **1L, first-line**

2024 ASCO ANNUAL MEETING

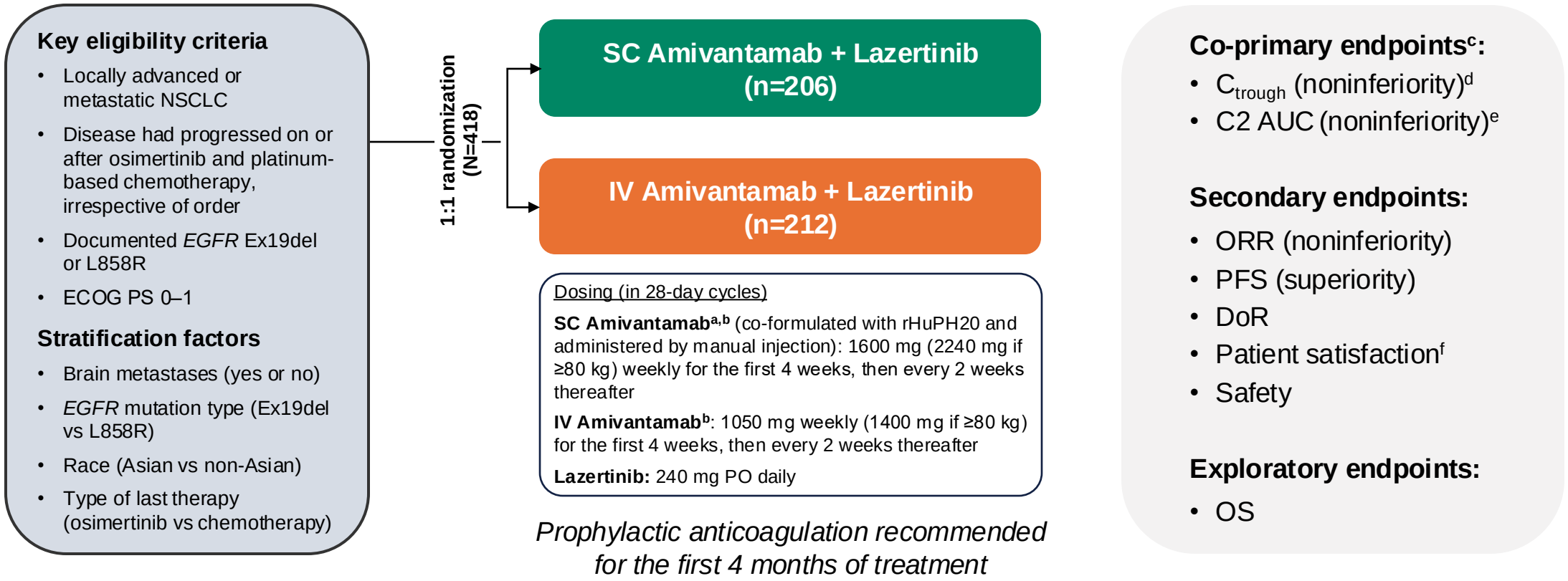
Subcutaneous amivantamab vs intravenous amivantamab, both in combination with lazertinib, in refractory *EGFR*-mutated, advanced non-small cell lung cancer

Primary results, including overall survival, from the global, phase 3, randomized controlled PALOMA-3 trial

Natasha B Leighl,[1] Hiroaki Akamatsu,[2] Sun Min Lim,[3] Ying Cheng,[4] Anna R Minchom,[5] Melina E Marmarelis,[6] Rachel E Sanborn,[7] James Chih-Hsin Yang,[8] Baogang Liu,[9] Thomas John,[10] Bartomeu Massutí,[11] Alexander I Spira,[12] John Xie,[13] Debopriya Ghosh,[13] Ali Alhadab,[14] Remy B Verheijen,[15] Mohamed Gamil,[16] Joshua M Bauml,[16] Mahadi Baig,[13] Antonio Passaro[17]

[1]Princess Margaret Cancer Centre, Toronto, ON, Canada; [2]Internal Medicine III, Wakayama Medical University, Wakayama, Japan; [3]Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; [4]Jilin Cancer Hospital, Changchun, China; [5]Drug Development Unit, The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, UK; [6]Division of Hematology and Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [7]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [8]Department of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan; [9]Harbin Medical University Cancer Hospital, Harbin, China; [10]Peter

PALOMA-3: Phase 3 Study Design



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

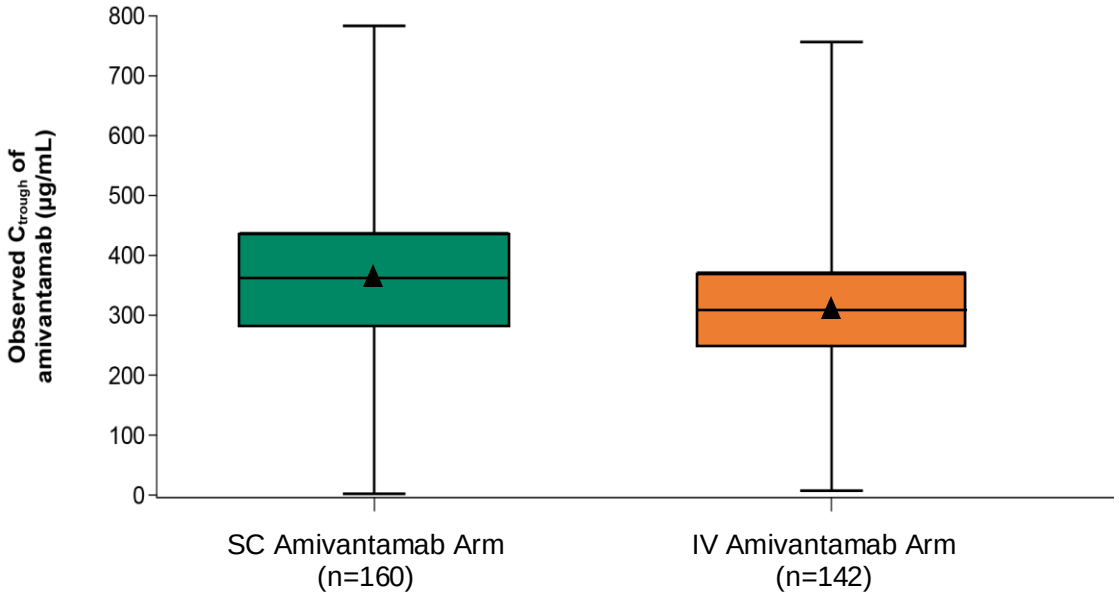
[a]SC amivantamab was co-formulated with rHuPH20 at a concentration of 160 mg/mL. [b]C1 for IV: Days 1 to 2 (Day 2 applies to IV split dose only [350 mg on Day 1 and the remainder on Day 2]), 8, 15, and 22; C1 for SC: Days 1, 8 , 15, and 22; after C1 for all: Days 1 and 15 (28-day cycles). [c]For calculating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

Co-primary PK Endpoints Met Noninferiority Criteria

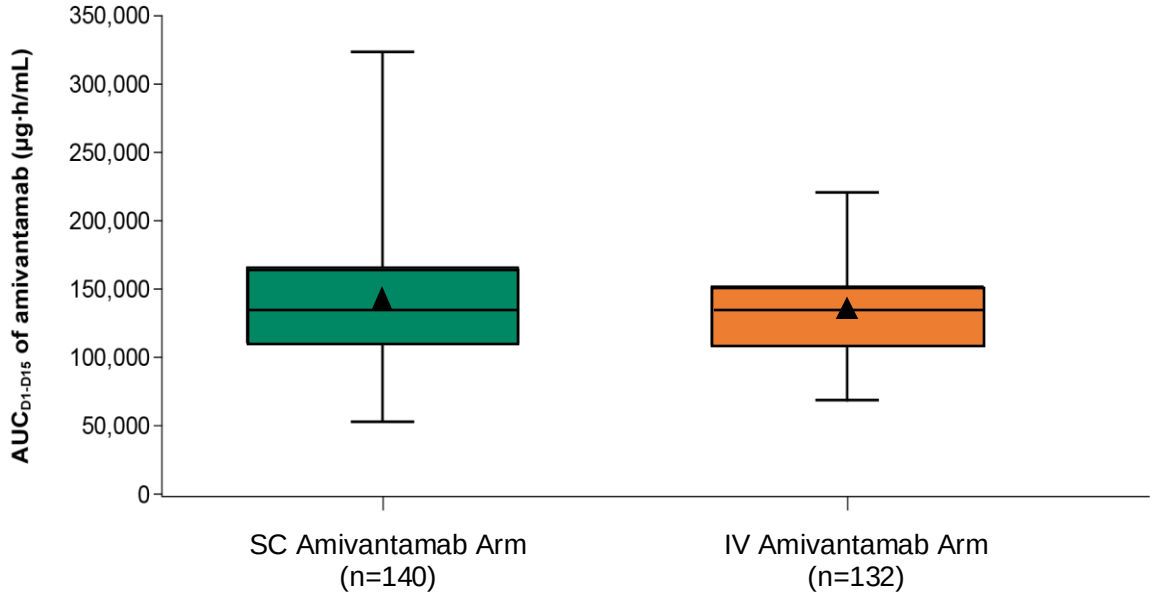
C_{trough} at C2D1

Geometric mean ratio=**1.15**
(90% CI, 1.04–1.26)



C2 $AUC_{D1\text{-}D15}$

Geometric mean ratio=**1.03**
(90% CI, 0.98–1.09)



- Geometric mean ratio for C_{trough} at steady state (C4D1) was 1.43 (90% CI, 1.27–1.61)

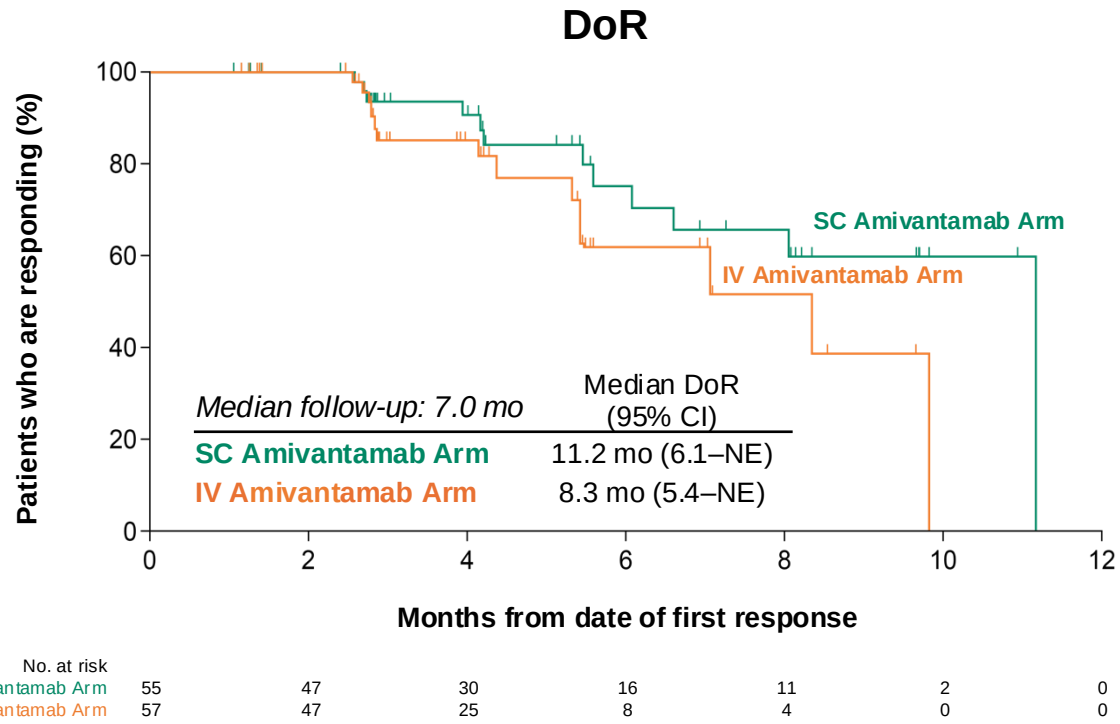
Note: The pharmacokinetic analysis for primary endpoints included all patients who received all doses without dose modification and provided the required PK samples through the final required PK sample relevant to the endpoint. The upper and lower ends of the boxes indicate the 25th and 75th quartiles, the triangles indicate the means, the horizontal lines within the boxes indicate the medians, and the error bars indicate 95% CIs.

AUC, area under the concentration-time curve; C, Cycle; CI, confidence interval; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous.

ORR and DoR

- ORR was noninferior between the SC and IV amivantamab arms
- DoR was 11.2 months in the SC arm vs 8.3 months in the IV arm, with twice as many patients, 29% in the SC arm vs 14% in the IV arm, having a response ≥6 months

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI)[a]		
All responders	**30 (24–37)**	**33 (26–39)**
	Relative risk, 0.92 (95% CI, 0.70–1.23); *P*=0.001	
Confirmed responders	**27 (21–33)**	**27 (21–33)**
	Relative risk, 0.99 (95% CI, 0.72–1.36); *P*<0.001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI)[b]	**75 (69–81)**	**71 (64–77)**
Median time to response (range), mo	**1.5 (1.2–6.9)**	**1.5 (1.2–9.9)**

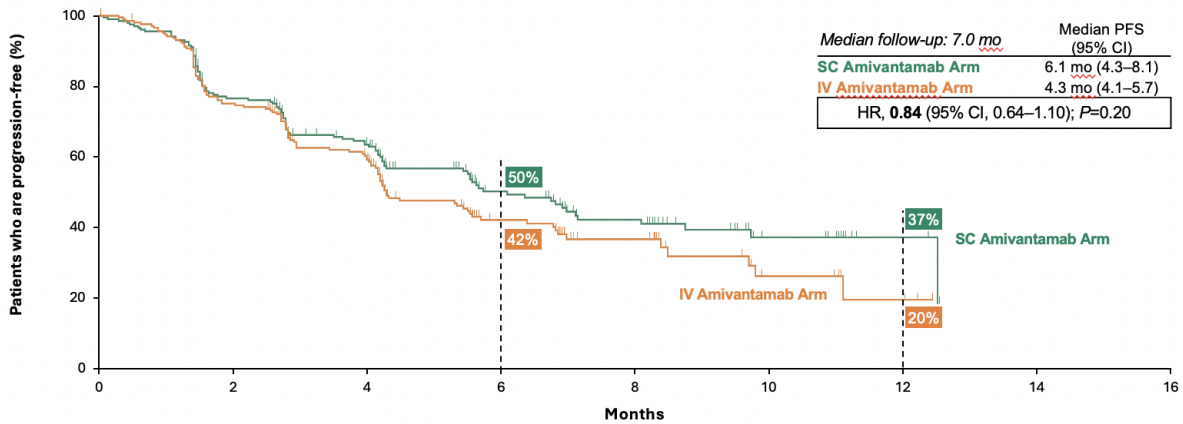


[a]The objective response (CR or PR) was assessed using RECIST v1.1 and analyzed using logistic regression. The lower bound of the 95% CI indicated ≥70% retention of ORR exceeding the predefined 60% retention assumed for determining noninferiority. [b]Not protocol specified.

CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD); DoR, duration of response; IV, intravenous; mo, months; NE, not estimable; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous; SD, stable disease.

Progression-free Survival

PFS was numerically longer with SC vs IV amivantamab, with an HR of 0.84



No. at risk									
SC Amivantamab Arm	206	153	116	57	37	14	3	0	0
IV Amivantamab Arm	212	154	109	43	23	7	3	0	0

Note: The efficacy population included all the patients who had undergone randomization. PFS was tested for superiority as part of the hierarchical testing strategy; *P* value was calculated from a log-rank test stratified by history of brain metastases, Asian race, *EGFR* mutation type (Ex19del or L858R), and last line of therapy (osimertinib or platinum-based therapy).

CI, confidence interval; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; IV, intravenous; mo, months; PFS, progression-free survival; SC, subcutaneous.

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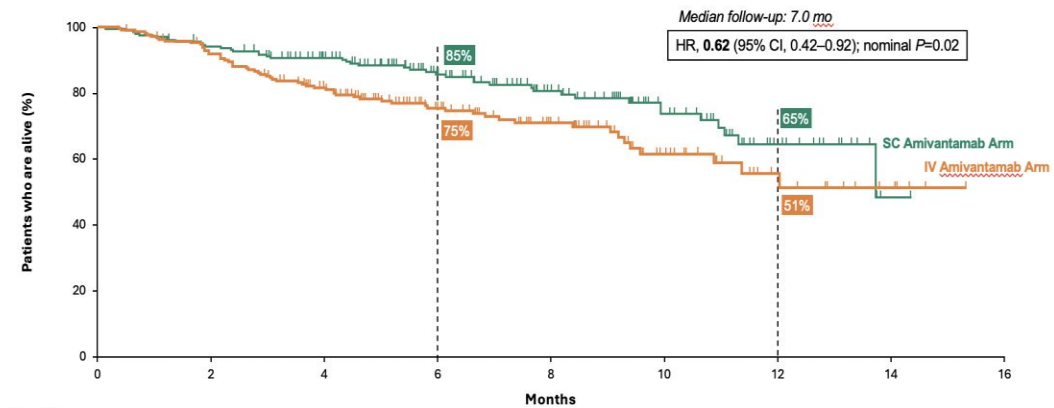
Overall Survival

There was an OS benefit associated with SC amivantamab, with an HR of 0.62 compared to the IV amivantamab arm[a].



No. at risk									
SC Amivantamab Arm	206	192	163	109	71	36	10	0	0
IV Amivantamab Arm	212	191	144	92	51	24	10	1	0

Note: The efficacy population included all the patients who had undergone randomization. [a]There were 43 deaths in the SC amivantamab arm and 62 deaths in the IV amivantamab arm. Nominal *P* value was calculated from a log-rank test stratified by history of brain metastases, Asian race, *EGFR* mutation type (Ex19del or L858R), and last line of therapy (osimertinib or platinum-based therapy); the prespecified endpoint was exploratory and not part of hierarchical hypothesis testing.

CI, confidence interval; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; IV, intravenous; mo, months; OS, overall survival; SC, subcutaneous.

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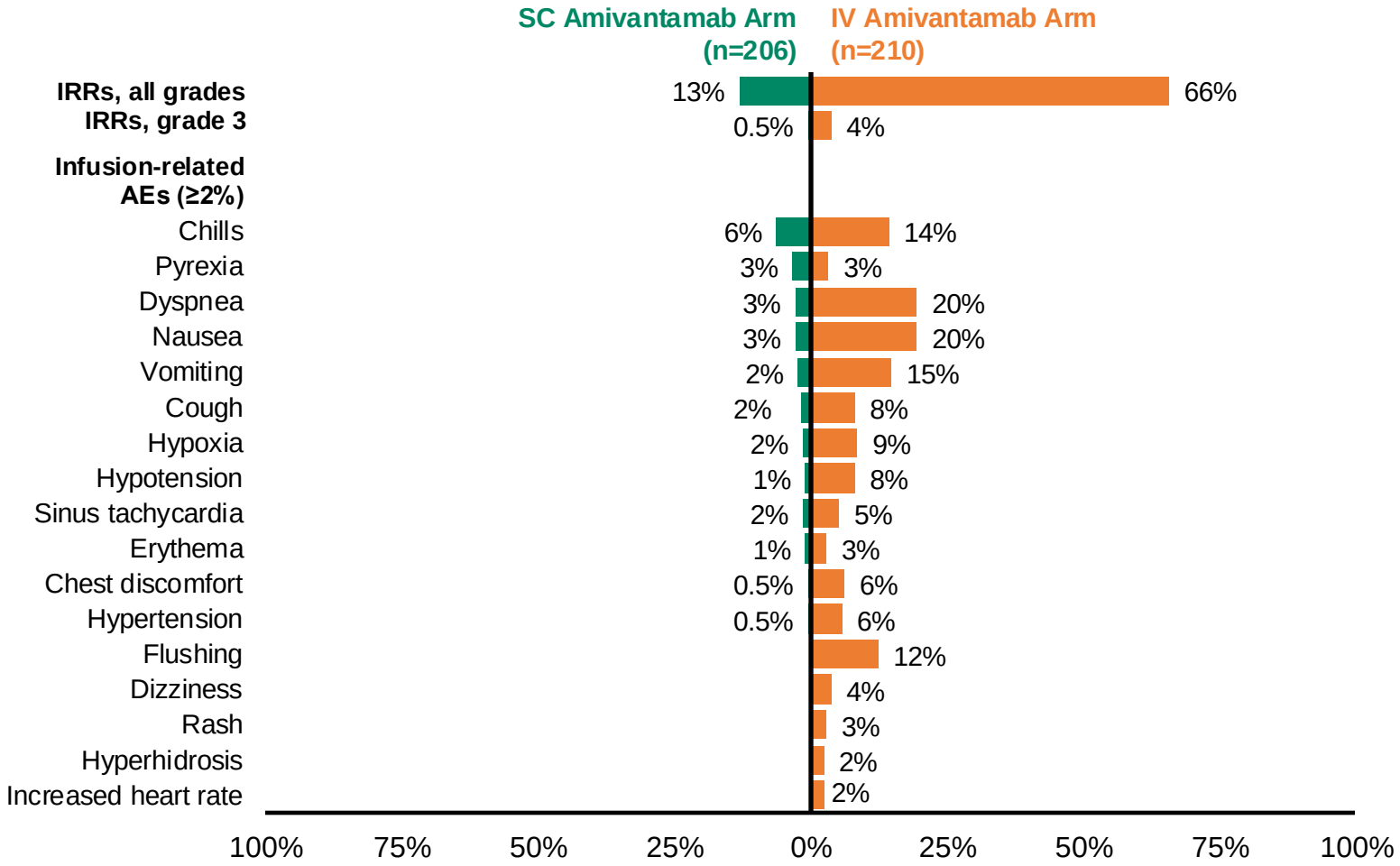
Incidence of IRR-related Symptoms



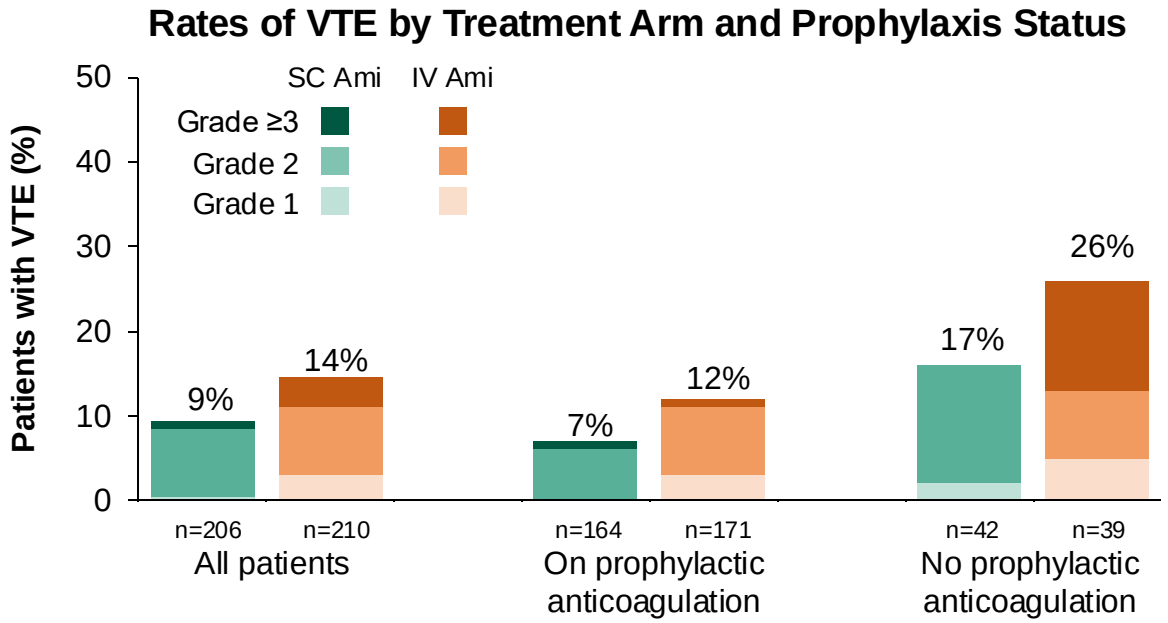
- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
  - There were no grade 4 or 5 IRRs
  - Most IRRs occurred during Cycle 1
- IRRs leading to hospitalization were not observed in the SC arm vs 2 events in the IV arm
- No IRR-related discontinuations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

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.

AE, adverse event; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous.

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



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

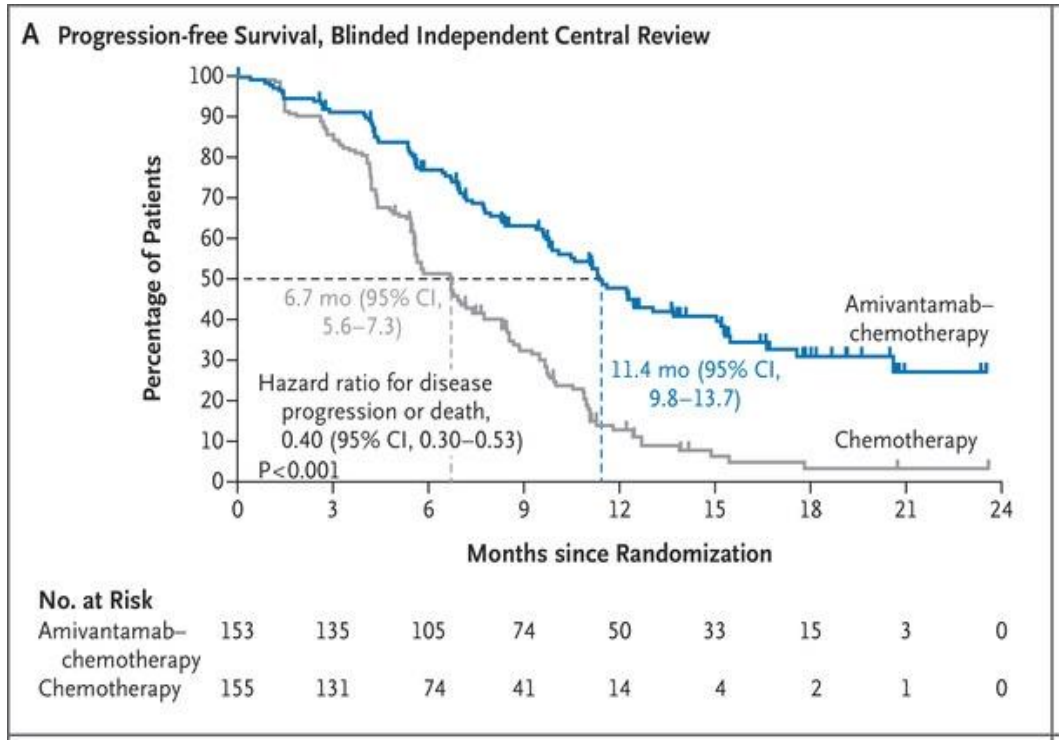
Note: The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment.

[a]Grouping includes pulmonary embolism, deep vein thrombosis, venous embolism, venous thrombosis limb, embolism, thrombosis, subclavian vein thrombosis, superficial vein thrombosis, pulmonary infarction, venous thrombosis. [b]VTE prophylaxis with apixaban, rivaroxaban, dalteparin, or enoxaparin was recommended by protocol (per the National Comprehensive Cancer Network guideline *Cancer-Associated Venous Thromboembolic Disease* v1.2022).

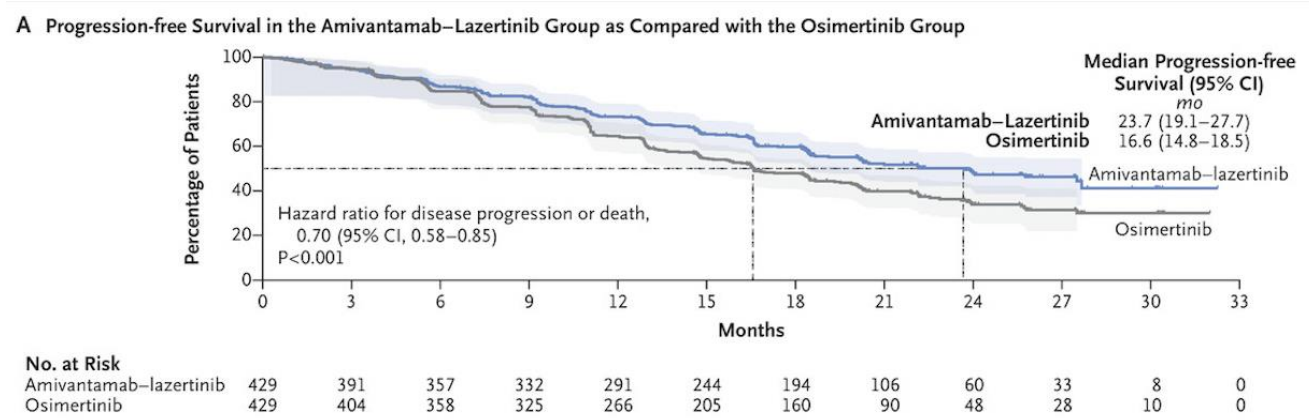
IV, intravenous; SC, subcutaneous; VTE, venous thromboembolism.

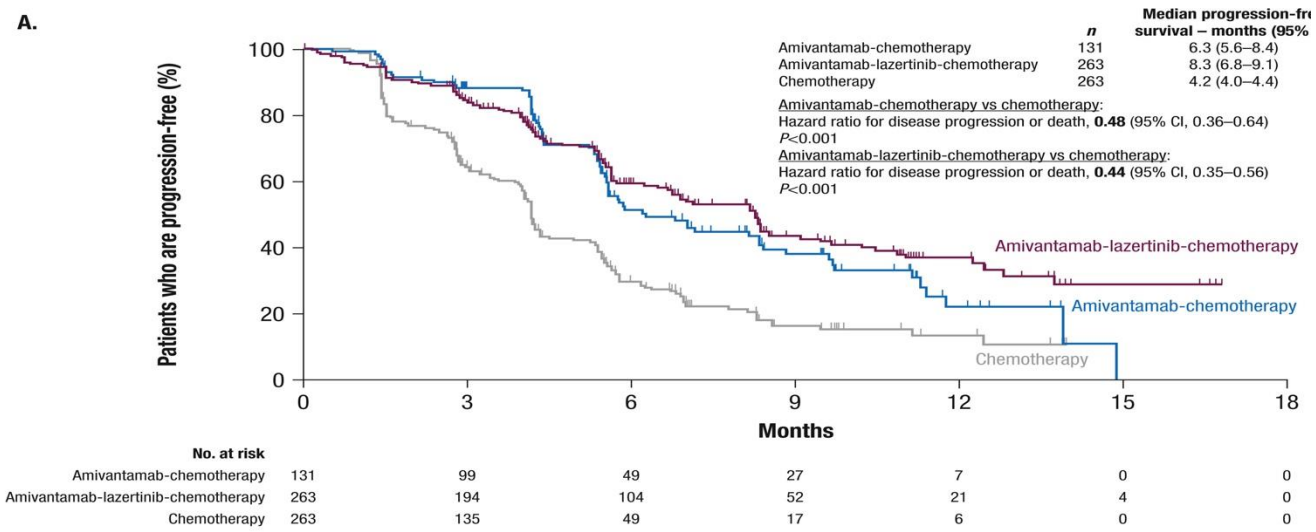
Impact on Practice

Papillon: 1L EGFR Exon 20 ins NSCLC



Mariposa: 1L EGFR-mutant NSCLC





C. Zhou et al. 2023. Cho et al. NEJM 2024. Passaro et al. Ann Oncol. 2023.