2024 World Conference on Lung Cancer

SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

Click to edit Master title style

Author

Best of WCLC 2024

ALK, ROS1 and BRAF + Lung Cancer

Mohana Roy, MD
Clinical Assistant Professor
Stanford University School of Medicine
mohanar@stanford.edu

ALK

2007
Discovery of EML4-ALK translocation

2012
Crizotinib (PROFILE-1014)

2017
Alectinib (ALEX)

2020
Brigatinib (ALTA-1L)

2021
Lorlatinib (CROWN)

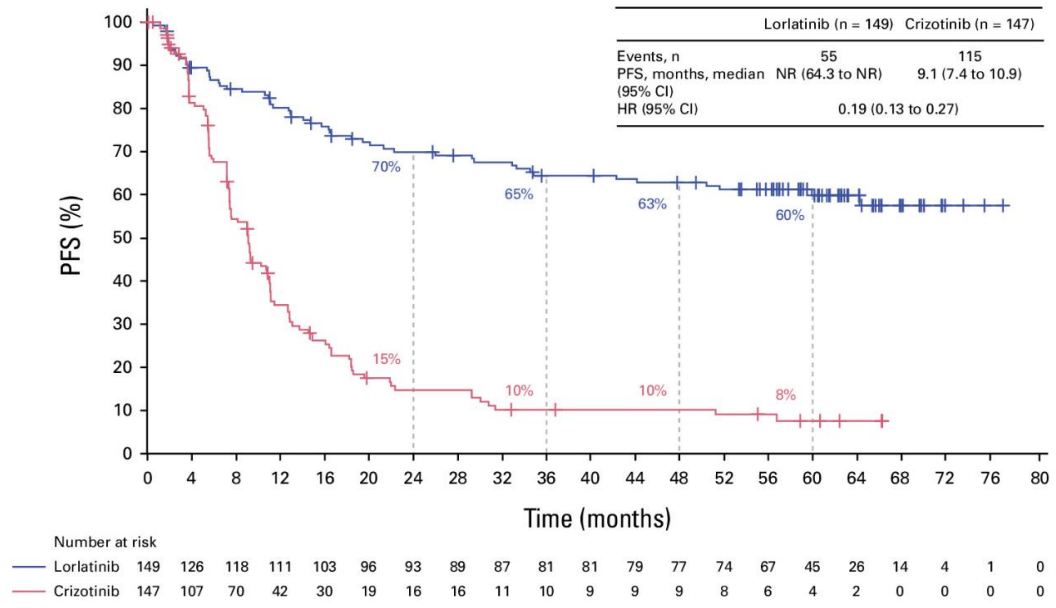
What is Next? What Sequencing Should We Use?

-Further analysis and safety for Lorlatinib

First-line lorlatinib showed prolonged benefit after 5 years of follow-up in the global phase 3 CROWN study

- After 5 years of follow-up, median PFS[a] was **NR** (95% CI, 64.3 months-NR) with lorlatinib and 9.1 months (95% CI, 7.4-10.9 months) with crizotinib (HR, 0.19; 95% CI, 0.13-0.27)[1]

- Median time to IC progression[a] was NR (95% CI, NR-NR) with lorlatinib and 16.4 months (95% CI, 12.7-21.9 months) with crizotinib (HR, 0.06; 95% CI, 0.03-0.12)[1]



ALK, anaplastic lymphoma kinase; **BICR**, blinded independent central review; **HR**, hazard ratio; **IC**, intracranial; **NR**, not reached; **NSCLC**, non-small cell lung cancer; **OS**, overall survival; **PFS**, progression-free survival; **PFS2**, time from randomization to the date of disease progression with first subsequent systemic anticancer therapy or death; **TTP**, time to progression.

[a]By investigator assessment. 1. Solomon BJ, et al. *J Clin Oncol.* 2024 May 31:JCO2400581.

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

Patterns of progression with lorlatinib and insights into subsequent anticancer therapy efficacy in advanced *ALK*+ NSCLC

Tony S.K. Mok,[1] Benjamin J. Solomon,[2] Maria Rosario Garcia Campelo,[3] Yi-Long Wu,[4] Guillermo Streich,[5] Milada Zemanova,[6] Gérard Zalcman,[7] Alessandra Bearz,[8] Gee-Chen Chang,[9] Matteo Setti,[10] Anna Polli,[10] Yasushi Goto[11]

Kinetics and Management of Adverse Events Associated With Lorlatinib After 5 Years of Follow-Up in the CROWN Study

Todd M. Bauer,[1] Benjamin J. Solomon,[2] Julien Mazieres,[3] Dong-Wan Kim,[4] Diego Cortinovis,[5] Takako Inoue,[6] Richu Sharma,[7] Holger Thurm,[8] Anna Polli,[9] Geoffrey Liu[10]

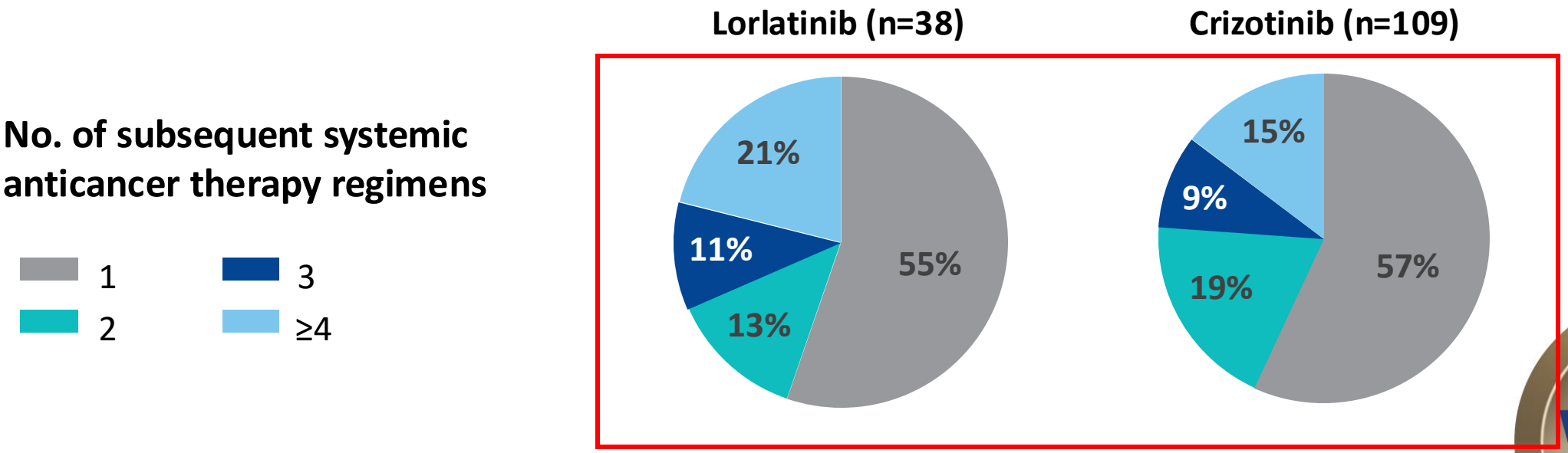
Clinical and molecular characteristics of early progressors (≤12 months) on lorlatinib vs those who remained progression free after 5 years

Clinical Characteristics	Early progressors (n=28)[a]	Nonprogressors (n=45)[a]	Total (n=73)
Age, mean (SD), years	60.5 (12.9)	56.1 (14.0)	57.8 (13.7)
Sex, n (%)			
Male	16 (57)	24 (53)	40 (55)
Female	12 (43)	21 (47)	33 (45)
Race, n (%)[b]			
Asian	15 (54)	28 (62)	43 (59)
White	12 (43)	16 (36)	28 (38)
ECOG performance status, n (%)			
0	11 (39)	23 (51)	34 (47)
1	15 (54)	22 (49)	37 (51)
2	2 (7)	0	2 (3)
Brain metastases at baseline, n (%)			
Yes	6 (21)	10 (22)	16 (22)
No	22 (79)	35 (78)	57 (78)
Tumor burden at baseline, mm			NA
Mean (SD)	84.9 (45.7)	54.7 (34.4)	NA

Molecular profiling, n (%)[c]	Early progressors (n=28)[a]	Nonprogressors (n=45)[a]
Confirmed *ALK* positive	14 (50)	35 (78)
EML4-ALK variant 1	6 (21)	10 (22)
EML4-ALK variant 2	0	5 (11)
EML4-ALK variant 3	5 (18)	11 (24)
EML4-ALK other variant	3 (11)	7 (16)
Other *ALK* fusion	0	2 (4)
Unconfirmed *ALK* positive[d]	14 (50)	10 (22)
***TP53* mutation detected**	16 (57)	10 (22)

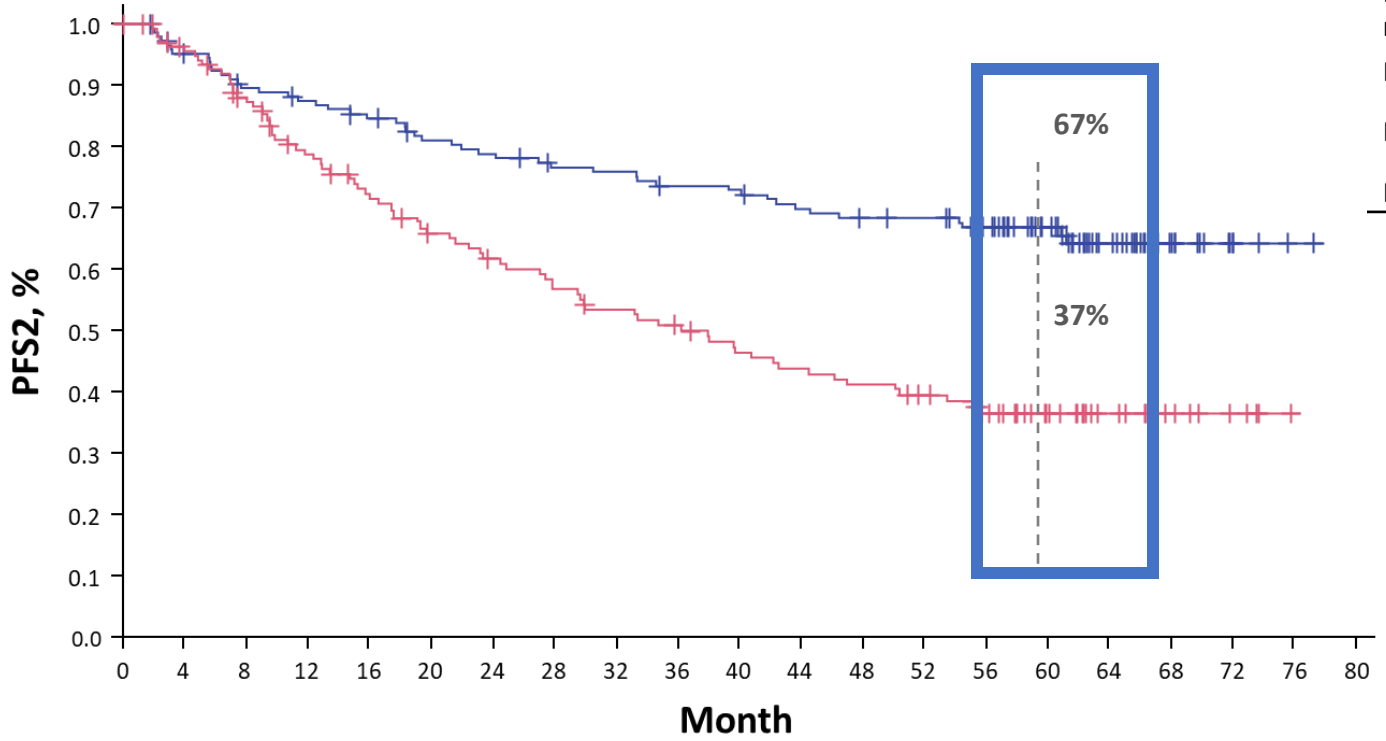
Subsequent systemic anticancer therapy

- After 5 years of follow-up, 75 of 149 (50%) patients had discontinued lorlatinib and 135 of 142 (95%) had discontinued crizotinib[a]
- 38 of 149 (26%) patients in the lorlatinib arm and 109 of 147 (74%) in the crizotinib arm had ≥1 subsequent systemic anticancer therapy



[a]After 5 years of follow-up. Among patients who discontinued lorlatinib, only 8 had intracranial progression.

PFS2 was longer in patients who received lorlatinib vs crizotinib as the study treatment



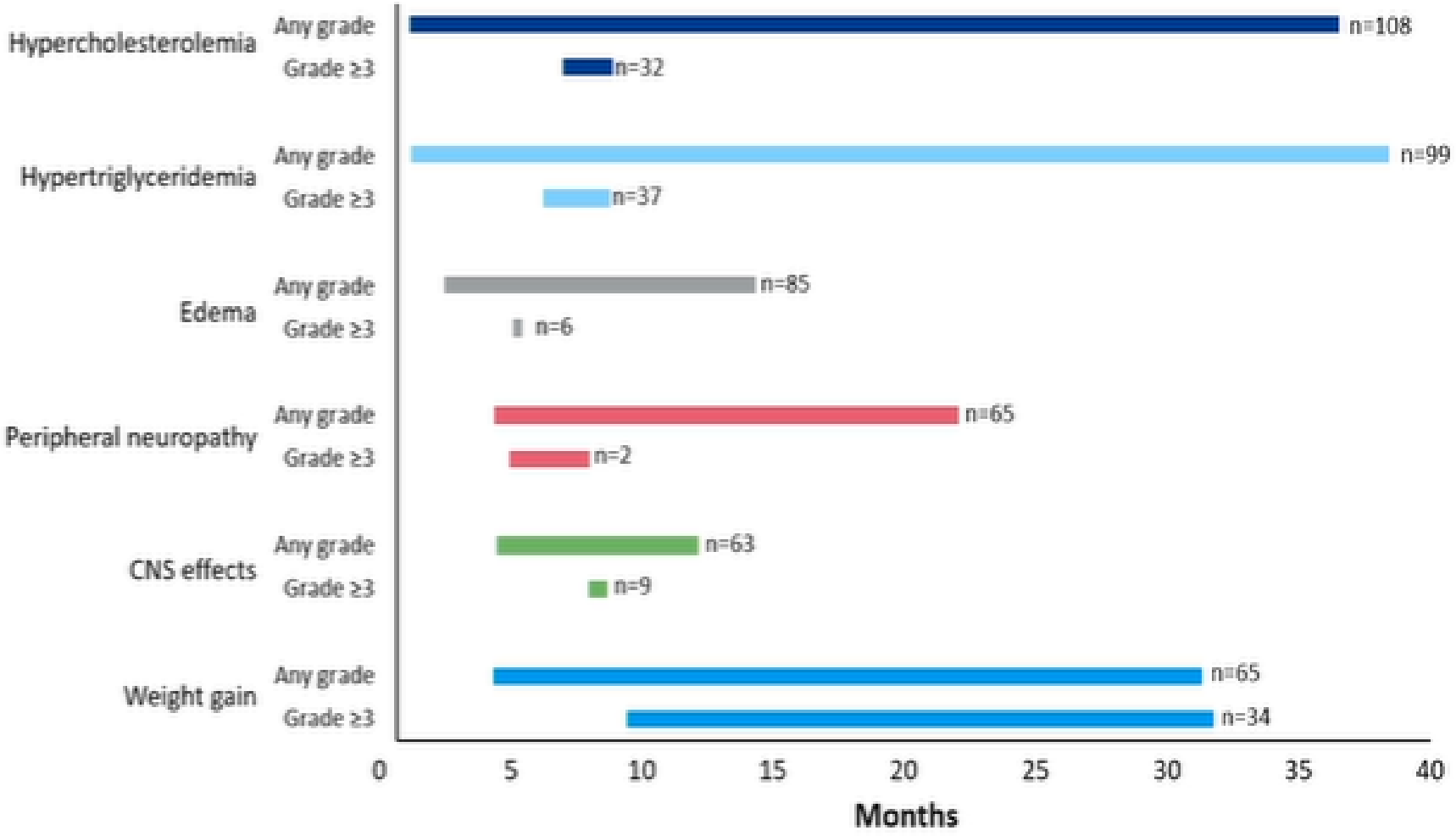
No. at risk

Lorlatinib	149	137	128	124	119	112	109	104	103	99	98	93	90	89	81	57	31	14	4	1	0
Crizotinib	147	130	115	100	90	80	74	68	63	59	53	50	47	43	34	23	14	8	4	0	0

	Lorlatinib (N=149)	Crizotinib (N=147)
Duration of follow-up for PFS2, median (95% CI), months	61.4 (59.2-62.5)	58.4 (56.8-61.9)
PFS2 events, n (%)	48 (32)	78 (53)
PFS2, median (95% CI), months	NR (NR-NR)	37.9 (27.4-50.1)
HR (95% CI)	0.43 (0.30-0.62)	

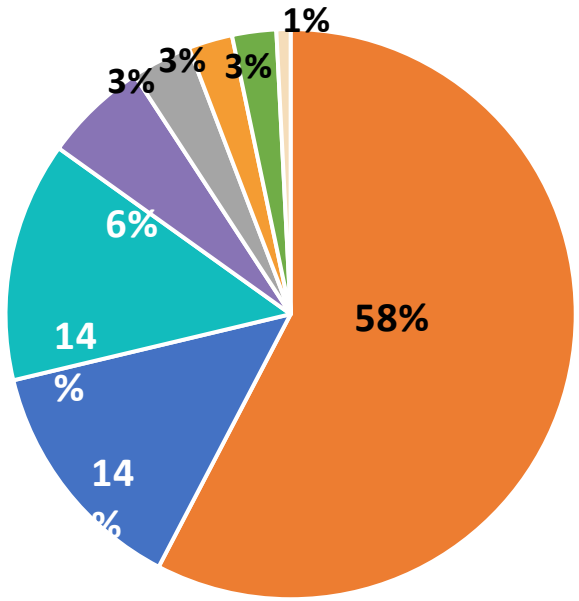
HR, hazard ratio; **NR**, not reached; **PFS2**, time from randomization to the date of disease progression with first subsequent systemic anticancer therapy or death.

Symptom Timeline



2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

CNS Events

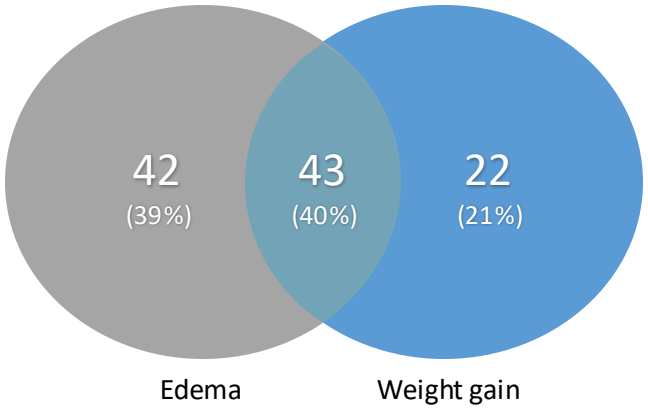


- No medical intervention
- Dose interruption only
- Con med only
- Dose interruption + con med
- Dose reduction + dose interruption
- Dose reduction only
- Permanent treatment discontinuation
- Dose reduction + dose interruption + con med

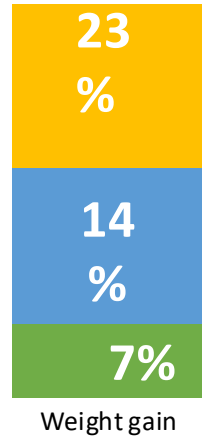
Total CNS evens (n=118)

Weight Gain

Patients with edema and/or weight gain (n=107)



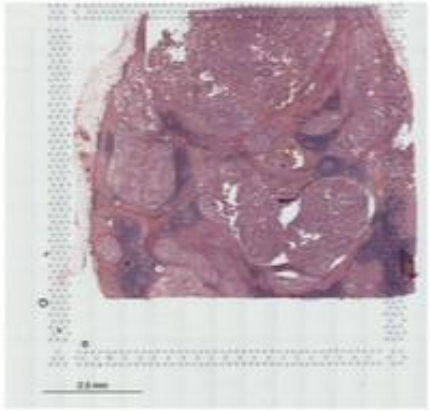
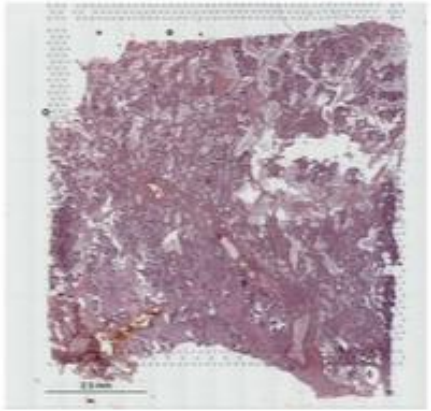
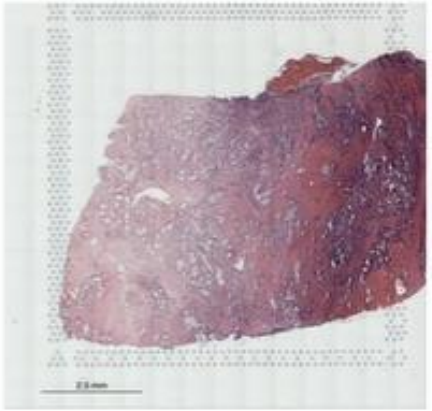
Lorlatinib (N=149)



Grade 1 Grade 2 Grade 3

Ensartinib

Patients on ensartinib experienced PFS greater than 65 months despite ALK related resistance mechanisms

	Patient 1	Patient 2	Patient 3
Outcome on ensartinib	Stable disease	Partial response	Complete response
Cycles of ensartinib*	73	70	82
Sample notes	Lymph node metastasis	Lung	Lung

*Biopsies were taken prior to ensartinib therapy

My Conclusions

- After 5 years of follow-up, median PFS[a] was **NR vs 9.1 months** for lorlatinib vs crizotinib
  - Most AEs occur within 4 months, significant ones usually within 9 months
  - Hyperlipidemia occurs quickly after start of treatment
  - Weight gain is common (44%), 58% of CNS AEs did not need intervention
- PFS2 was longer in those who received lorlatinib compared to crizotinib
  - Does not answer where alectinib, brigatinib, and ensartinib fit in

ROS1

2007	2016	2017	2019	2019	2020
Discovery of ROS1 rearrangement	Crizotinib (PROFILE-1001)	Ceritinib (ASCEND-5)	Entrectinib (STARTRK-2)	Lorlatinib	Repotrectinib (TRIDENT-1)

What is Next? What Sequencing Should We Use?

-Taletrectinib
-Unectrinib
-Lorlatinib (re-studied)

Taletrectinib

TRUST-II (NCT04919811)
Phase 2 Trial of Taletrectinib in ROS1+ NSCLC[a]

Key Eligibility Criteria

Inclusion Criteria:
- Locally advanced or metastatic NSCLC
- Age ≥18 years[b]
- ECOG PS 0–1
- Evidence of ROS1 fusion
  Stable Brain mets allowed

Cohort 1: ROS1 TKI naive
Taletrectinib 600 mg QD

Cohort 2: 1 Prior ROS1 TKI
Taletrectinib 600 mg QD

Endpoints

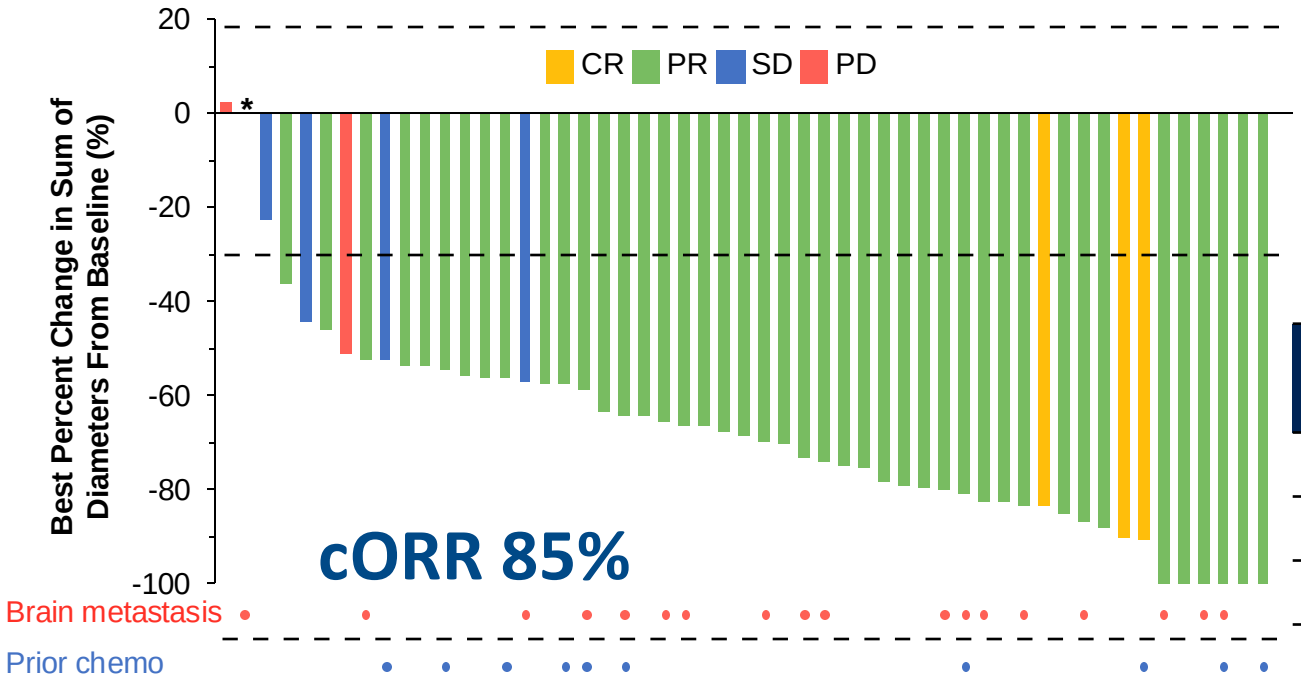
Primary:
- IRC-assessed cORR per RECIST v1.1

Secondary:
- DOR
- BOR
- TTR
- Safety[c]
- IC-ORR
- DCR
- PFS

- TKI Naïve (n=55)
  - 20% with prior chemotherapy, 34% brain metastasis
- TKI Pretreated (n=50)
  - 38% prior chemotherapy, 56% brain metastasis

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

Taletrectinib Responses in TKI-Naive ROS1+ NSCLC[a,b]



Response Rate	TKI Naive (n=54)
cORR, % (95% CI)	**85.2 (72.88, 93.38)**
Asia ORR (n=33)	87.9 (71.80, 96.60)
Non-Asia ORR (n=21)	81.0 (58.09, 94.55)

Measurable baseline brain metastases	TKI Naive (n=9)
IC-ORR, % (95% CI)	**66.7 (29.93, 92.51)**
CR, n (%)	2 (22.2)
PR, n (%)	4 (44.4)

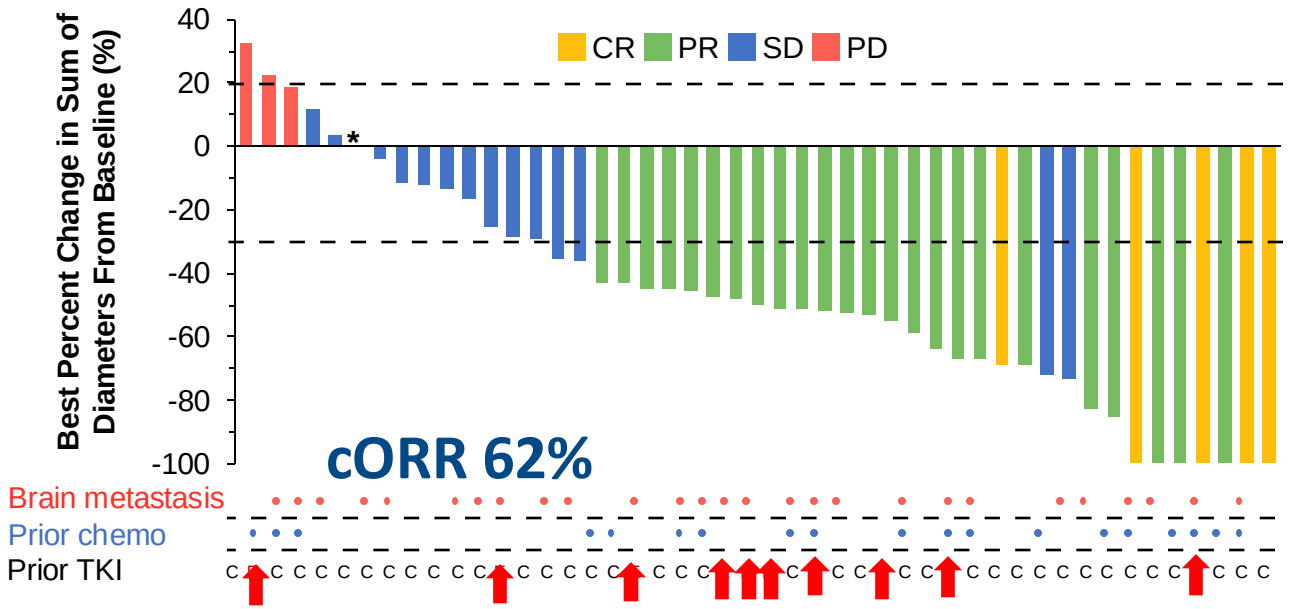
Median follow-up: 15.8 mo (range: 3.6–29.8)

Data cutoff: June 7, 2024. [a]Response evaluable population (patients with ≥1 measurable lesion at baseline who received ≥1 dose of taletrectinib). [b]Patients with confirmed BOR as not evaluable are not displayed in the waterfall plots. *One patient had a best percent change of 0%. BOR, best overall response; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; IC, intracranial; DOR, duration of response; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

Taletrectinib Responses in TKI-Pretreated ROS1+ NSCLC[a,b]

Response Rate	TKI Pretreated (n=47)
cORR, % (95% CI)	**61.7 (46.38, 75.49)**
Asia ORR (n=21)	57.1 (34.02, 78.18)
Non-Asia ORR (n=26)	65.4 (44.33, 82.79)



Measurable baseline brain metastases	TKI Pretreated (n=16)
IC-ORR, % (95% CI)	**56.3 (29.88, 80.25)**
CR, n (%)	1 (6.3)
PR, n (%)	8 (50.0)

Median follow-up: 15.7 mo (range: 3.9–29.8)

Data cutoff: June 7, 2024. [a]Response evaluable population (patients with ≥1 measurable lesion at baseline who received ≥1 dose of taletrectinib). [b]Patients with confirmed BOR as not evaluable are not displayed in the waterfall plots. *One patient had a best percent change of 0%. C, crizotinib; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; E, entrectinib; IC, intracranial; DOR, duration of response; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Taletrectinib Safety: TEAEs in ≥15% of Patients (N=159)

	Any grade, n (%)	Grade ≥3, n (%)
Increased ALT	108 (67.9)	24 (15.1)
Increased AST	107 (67.3)	11 (6.9)
Diarrhea	90 (56.6)	1 (0.6)
Nausea	82 (51.6)	3 (1.9)
Vomiting	53 (33.3)	2 (1.3)
Constipation	40 (25.2)	0 (0)
Anemia	32 (20.1)	7 (4.4)
Dysgeusia	31 (19.5)	0 (0)
Increased blood CPK	29 (18.2)	6 (3.8)
Dizziness	27 (17.0)	0 (0)
Prolonged QT	24 (15.1)	5 (3.1)

GI toxicities: Majority were Grade 1

7.5% of patients had a TEAE leading to treatment discontinuation; **1.3% were treatment-related**

Rates of neurologic TEAEs were low (dysgeusia: 19.5%; dizziness: 17.0%); none were grade ≥3

Data cutoff: June 7, 2024. AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; TEAE, treatment-emergent adverse event.

Unectritinib

Key Eligible Criteria

- ≥ 18 years old
- ECOG PS 0-1
- Locally advanced or metastatic NSCLC
- Received no more than two chemotherapy regimens
- ROS1-TKI naive

→

Unecritinib (TQ-B3101)
300 mg p.o. BID
N=111

Until disease progression or intolerable toxicity

→

Primary Endpoint

- IRC assessed ORR by RECIST 1.1

Secondary Endpoints

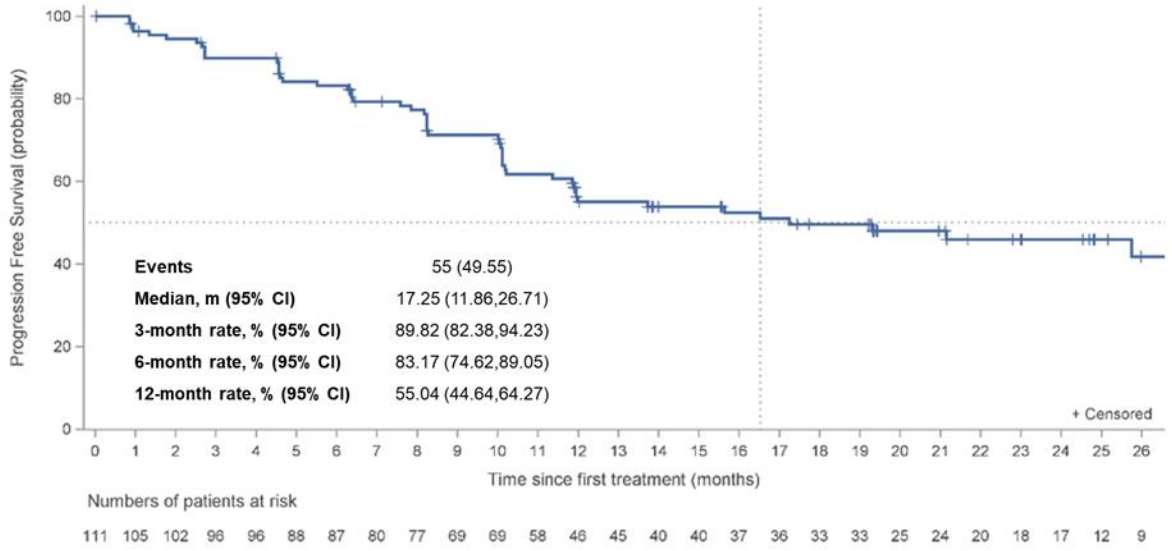
- DCR, DoR, PFS, OS
- Safety

- The ORR assessed by investigator (RECIST 1.1) is for sensitivity analysis.
- A sample size of 111 patients achieving >85% power to detect a difference of 0.15 (P0=0.50, P1=0.65) using an 2 sided binomial test with a significance level of 0.05.
- A total 111 Chinese patients entered the study from 29 sites in China between Nov, 2019 to Jan, 2021.

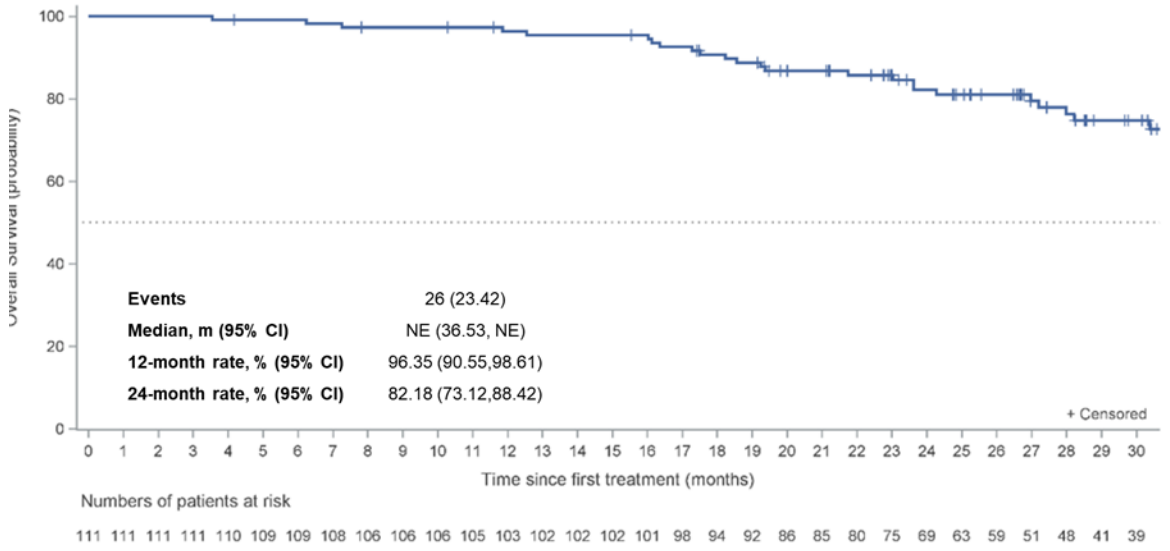
Efficacy

	Overall populations (N=111)	Baseline brain metastases (N=33)	Prior chemotherapy (N=48)
ORR, % (95% CI)	**81.08 (72.55,87.89)**	**72.73 (54.48,86.70)**	**79.17 (65.01,89.53)**
Median DoR, m (95% CI)	20.30 (12.88,26.12)	9.23 (7.36,11.04)	20.30 (11.04,NE)
Median PFS, m (95% CI)	17.25 (11.86,26.71)	10.09 (5.52,11.89)	19.32 (10.12,NE)
Median OS, m (95% CI)	NE (36.53, NE)	**28.22 (19.25,36.53)**	NE (30.39,NE)

Progression-Free Survival by IRC



Overall Survival



Data cut-off: June 20, 2022

DoR, duration of response; IRC, independent review committee; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression free survival.

What about Lorlatinib?

A Phase II Study of Lorlatinib in Advanced ROS1+ NSCLC Pre-treated with Crizotinib and Platinum-Based Chemotherapy

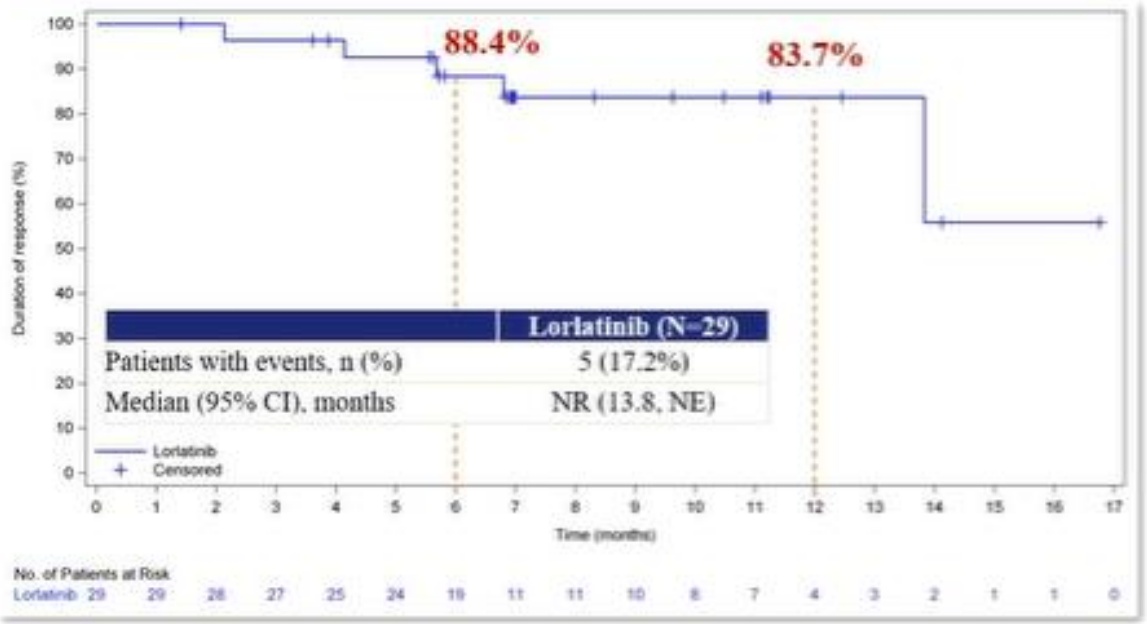
Presenter: Yi-Long Wu

Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

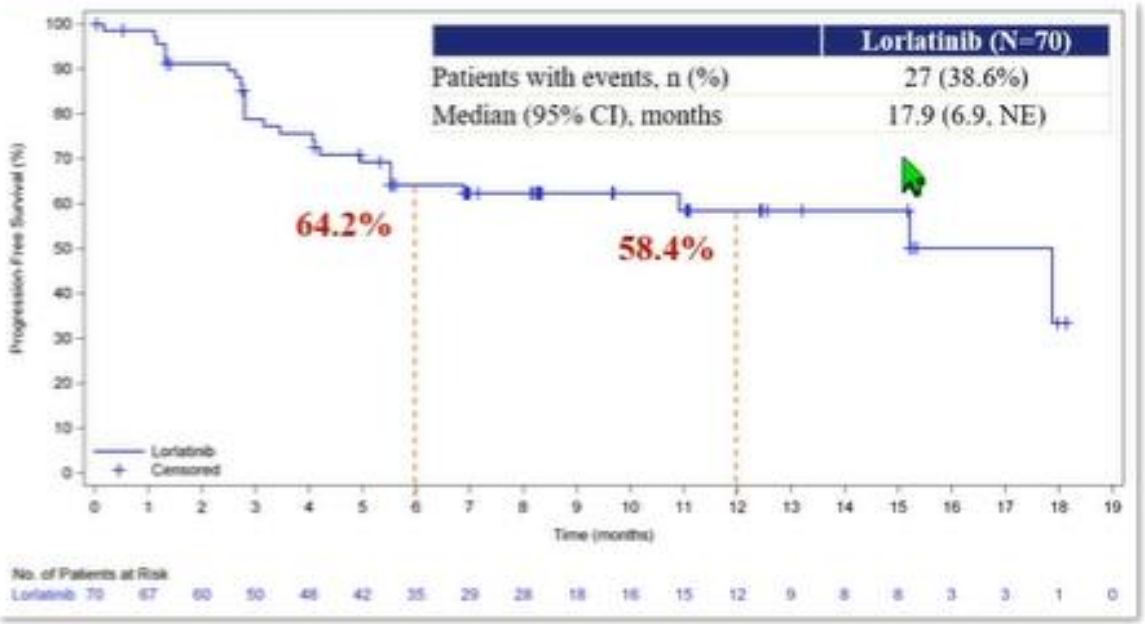
Huajun Chen[1]; Zhiyu Huang[2]; Longhua Sun[3]; Xingya Li[4]; Likun Chen[5]; Juan Li[6]; Zhengfei Zhu[7]; Wu Zhuang[8]; Kaihua Lu[9]; Yongchang Zhang[10]; Ke Wang[11]; Yanfan Chen[12]; Dingzhi Huang[13]; Jun Zhao[14]; Yong He[15]; Peng Zhang[16]; Xiangjiao Meng[17]; Yingying Du[18]; Yubiao Guo[19]; Xiaorong Dong[20]; Anwen Liu[21]; Junling Li[22]; Shundong Cang[23]; Qiang Wang[24]; Hangjun Dai[24]; Teng Fang[24]; Sheng Yao[24]; Qingmei Shi[24]; Jason Yang[24]; Yi-Long Wu[1]

Efficacy: DoR and PFS by ICR

DoR by ICR



PFS by ICR



- Of the 29 participants with confirmed response, the median time to tumor response assessed by ICR was 1.4 months (range 1.2-8.4).
- Median OS was not reached at a median follow-up of 9.4 months. 12-month OS rate was 73.2% (95% CI: 60.1%, 82.6%).

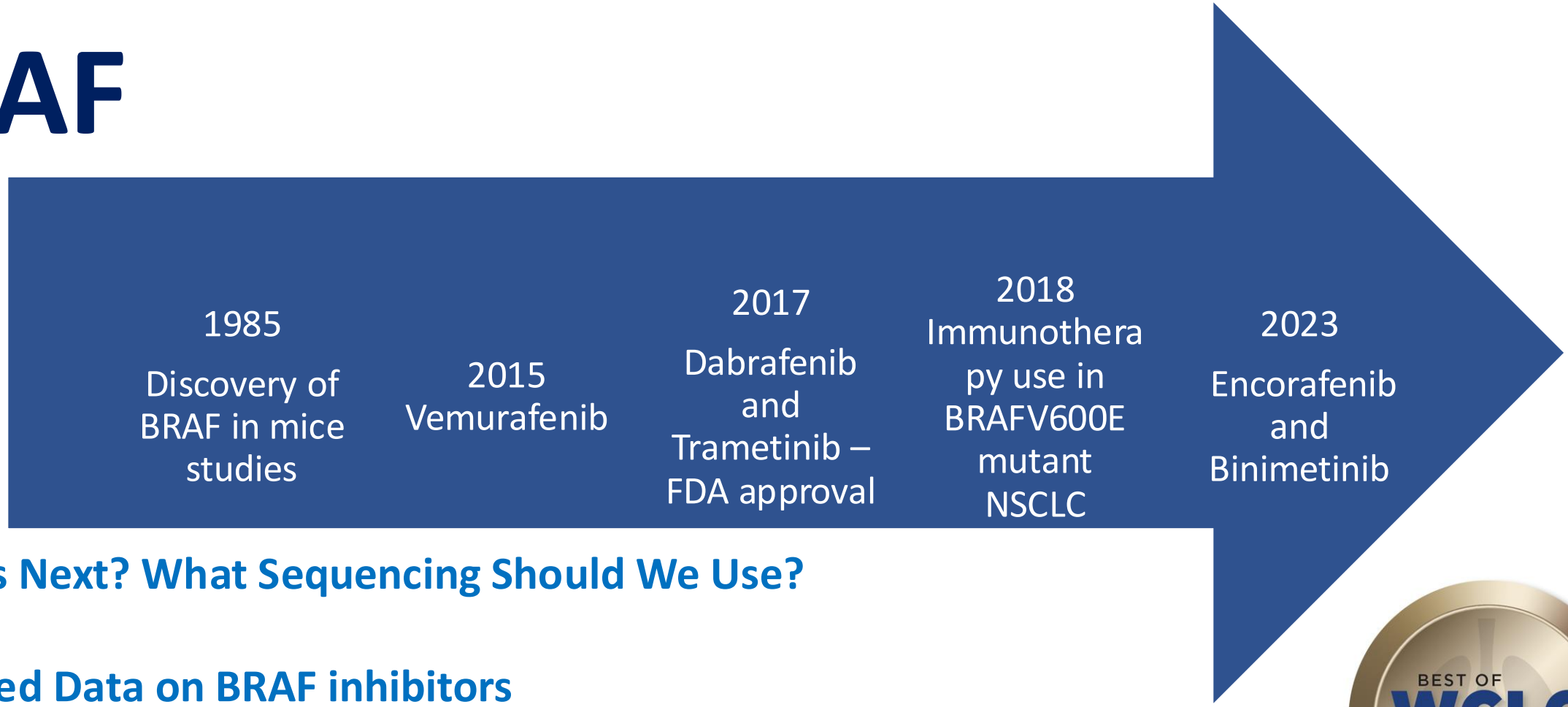
	Comparator Arm	PFS	OS	Intracranial Response	Major Side Effects
Ceritinib	CHEMO	19.3 months	NR		
Crizotinib	NA	19.2 months	NR	20%	
Entrectinib	NA	19 months	NR	55%	
Lorlatinib	NA	21 months	NR	60%	
Repotrectinib	NA	35.7 months ORR 79%	NR	89%	
Taletrectinib	NA	? **ORR 85%**	?	67%	Grade 3 LFTs (15%) GI side effects grade 1
Unectritinib	NA	17.25 months **ORR 81%**	?	72% (small n of 33 patients)	Grade 3 AEs 51%

My Conclusions

- Two effective ROS1 inhibitors were presented
  - Taletrectinib had compelling overall response rates in TKI naïve and pre-treated populations
- Lorlatinib in patients with pretreatment with crizotinib and chemotherapy, still can have significant activity, with a median PFS of 17 months
- With current data, standard of care still likely repotrectinib

ALK, anaplastic lymphoma kinase; **BICR**, blinded independent central review; **HR**, hazard ratio; **IC**, intracranial; **NR**, not reached; **NSCLC**, non-small cell lung cancer; **OS**, overall survival; **PFS**, progression-free survival; **PFS2**, time from randomization to the date of disease progression with first subsequent systemic anticancer therapy or death; **TTP**, time to progression.
[a]By investigator assessment. 1. Solomon BJ, et al. *J Clin Oncol.* 2024 May 31:JCO2400581.

BRAF



What is Next? What Sequencing Should We Use?

-Updated Data on BRAF inhibitors

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

Updated safety analysis of encorafenib plus binimetinib in patients with BRAF V600E-mutant metastatic NSCLC from PHAROS study

Egbert Smit,[1] Myung-Ju Ahn,[2] Ibiayi Dagogo-Jack,[3] Enriqueta Felip,[4] Francesco Gelsomino,[5] Bruce E. Johnson,[6] Melissa Johnson,[7] Marcelo V. Negrao,[8] Michael Offin,[9] Suresh Ramalingam,[10] Rachel Sanborn,[11] Anne Tsao,[8] Keith Wilner,[12] Ann Alcasid,[13] Tiziana Usari,[14] Xiaosong Zhang,[15] Gregory Riely[9]

[1]Leiden University Medical Center, Leiden, Netherlands; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Massachusetts General Hospital, Boston, MA, USA; [4]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]IRCCS Azienda Ospedaliero-Universitaria diBologna, Bologna, Italy; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN, USA; [8]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [9]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [10]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [11]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [12]Pfizer, La Jolla, CA, USA; [13]Pfizer, Collegeville, PA, USA; [14]Pfizer, Milan, Italy; [15]Pfizer, South San Francisco, CA, USA

PHAROS: a phase 2, open-label study (NCT03915951)

Key eligibility criteria

- BRAF V600E-mutant metastatic NSCLC[a]
- ECOG performance status 0 or 1
- No *EGFR* mutation, *ALK* fusion, or *ROS1* rearrangement
- ≤1 prior line of treatment in the advanced setting
- No prior treatment with BRAF or MEK inhibitor
- No symptomatic brain metastases

Patients enrolled

Treatment naive n=59

Previously treated n=39

Treatment

Binimetinib 45 mg BID

28-day cycles

Until progression or

Additional safety analyses included:

- TRAE profile by treatment line
- TRAE profile by history of prior immunotherapy
- Time to onset of specific TRAE clusters
- Dose modifications

[a] *BRAF* mutation testing was determined by PCR- or NGS-based assay and sent to a central laboratory.
[b] Other reasons for ending treatment were withdrawal of consent, initiation of subsequent anticancer therapy, or death.
ALK, anaplastic lymphoma kinase; BID, twice daily; BRAF, v-Raf murine sarcoma viral oncogene homolog B; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; FDA, US Food and Drug Administration; MEK, mitogen-activated protein kinase kinase; NE, not estimable; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; PCR, polymerase chain reaction; PFS, progression-free survival; QD, once daily; *ROS1*, proto-oncogene receptor tyrosine-protein kinase 1; TRAE, treatment-related adverse event.

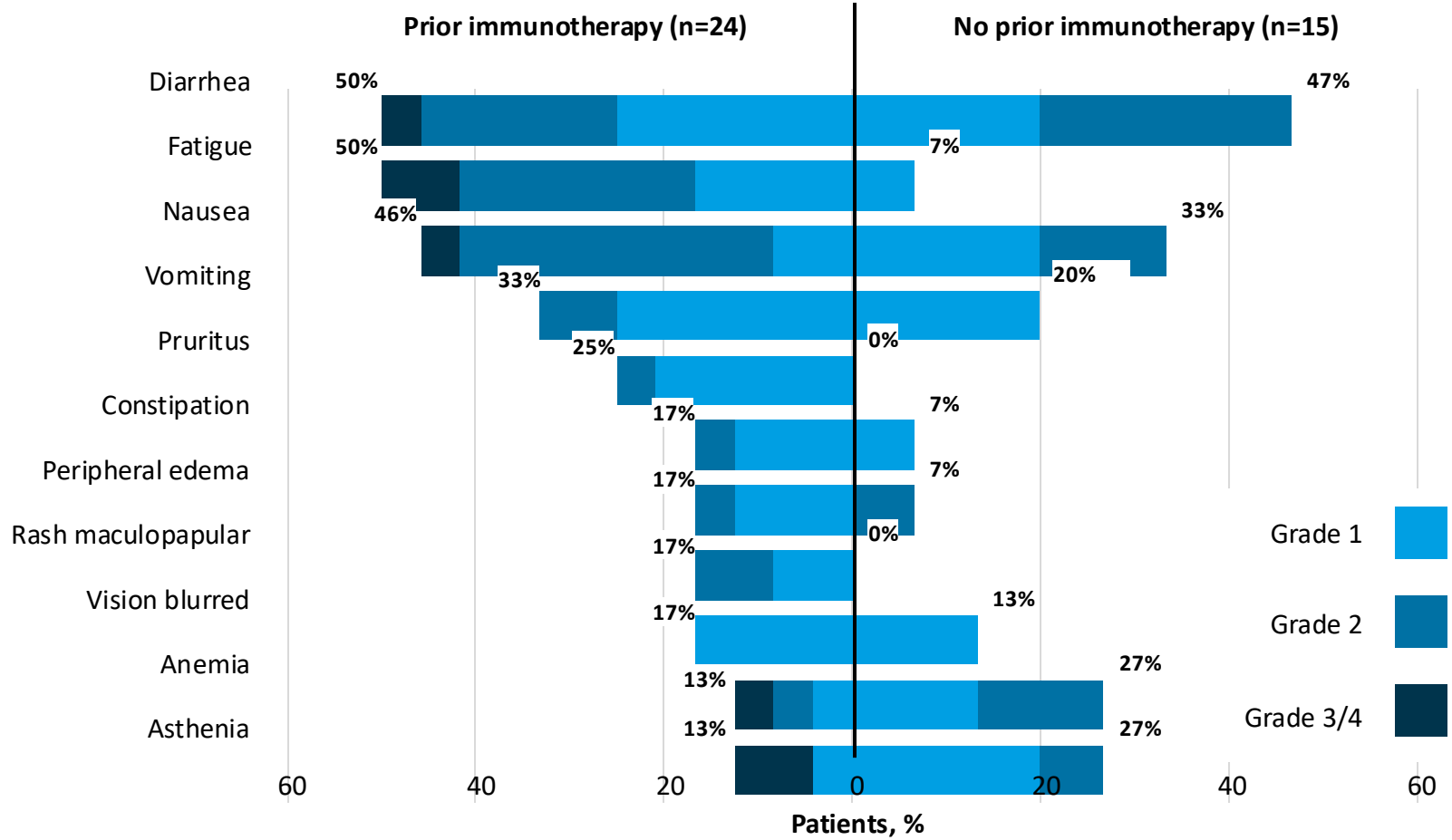
1. Riely GJ, et al. *J Clin Oncol.* 2023;41(21):3700-3711. 2. Braftovi (encorafenib). Prescribing information. Array BioPharma, Inc; 2018. Accessed June 11, 2024. https://labeling.pfizer.com/ShowLabeling.aspx?id=12990. 3. Mektovi (binimetinib). Array BioPharma, Inc; 2018. Accessed June 11, 2024. https://labeling.pfizer.com/ShowLabeling.aspx?id=12988.

Treatment ongoing and median duration of treatment

	Primary analysis cutoff (September 22, 2022)[1]		Current analysis cutoff (July 19, 2023)	
	Treatment naive (n=59)	Previously treated (n=39)	Treatment naive (n=59)	Previously treated (n=39)
Treatment ongoing, n (%)	25 (42)	8 (21)	19 (32)	4 (10)
Encorafenib treatment duration, median (range), months	15.1 (0-35.1)	5.4 (0.1-31.2)	16.3 (0-45.5)	5.5 (0.1-41.0)
Binimetinib treatment duration, median (range), months	14.4 (0-35.1)	5.4 (0.1-31.2)	16.3 (0-45.5)	5.5 (0.1-41.0)
Patients who have received >2 years of treatment, n (%)	14 (24)	3 (8)	24 (41)	4 (10)

1. Riely GJ, et al. *J Clin Oncol.* 2023;41(21):3700-3711.

TRAEs (≥15%) in previously treated patients with or without prior immunotherapy



TRAE, treatment-related adverse event.

Thank you!