19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
MADRID 20 - 21 NOVIEMBRE 2024

Impacto de la Terapia Dirigida en el Cáncer de Pulmón ALK

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Disclosure

Personal financial interests

Consulation Honoraria: AbbVie, Amgen, AstraZeneca, Bayer, BMS, Beigene, Boehringer Ingelheim, F. Hoffmann-La Roche, Johnson & Johnson, Lilly, Merck, MSD, Pfizer, Pharmamar, Sanofi, Takeda

Speaker Honoraria: Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, F. Hoffmann-La Roche, Johnson & Johnson, Lilly, MSD, Pfizer, Pharmamar, Takeda

Institutional financial interests

Clinical Trials: AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, F. Hoffmann-La Roche, GSK, Johnson & Johnson, Lilly, Merck, Mirati, MSD, Novartis, Pfizer, Pharmamar, Sanofi

Research Grant: AstraZeneca, BMS, F. Hoffmann-La Roche, GSK

Other

Executive Board Member of the Commission for the Approval of New Drugs, Regional Health Care Department, Spain

Great Advances in Lung Cancer

Selected Patients

Agenda

1

Advanced Disease

2

Locally Advanced Disease

3

Early Stage

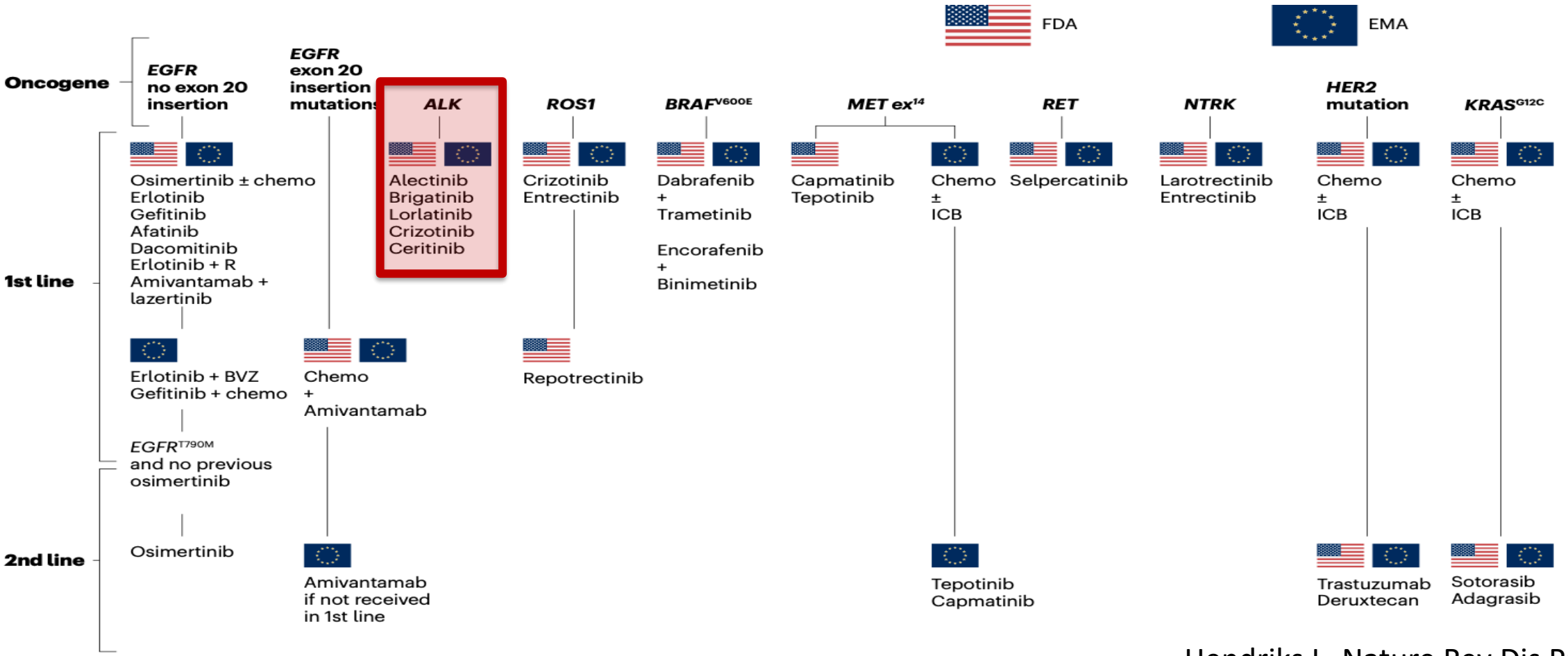
4

Toxicity

1

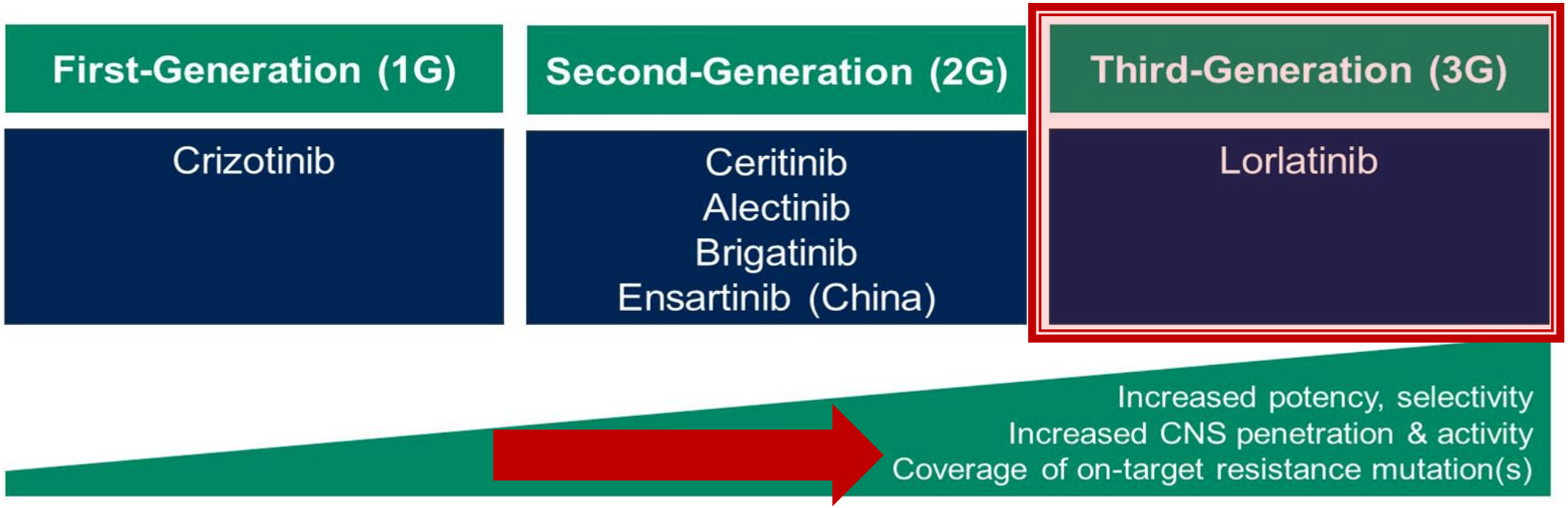
Advanced Disease

Treatment recommendations for Oncogene-driven mNSCLC



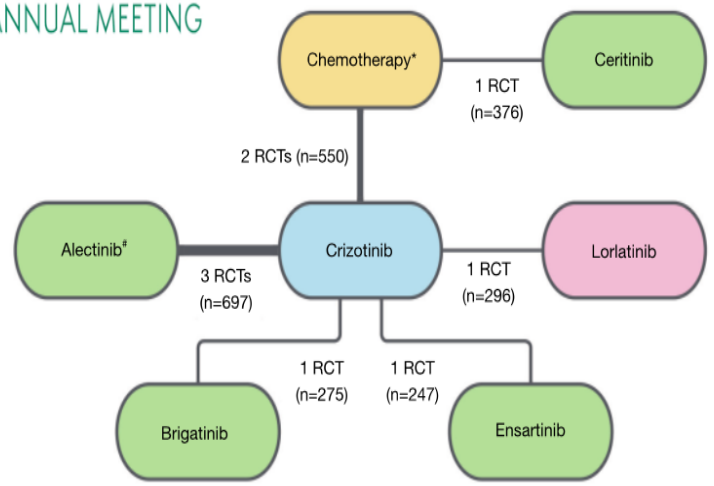
Hendriks L, Nature Rev Dis Prim 2024

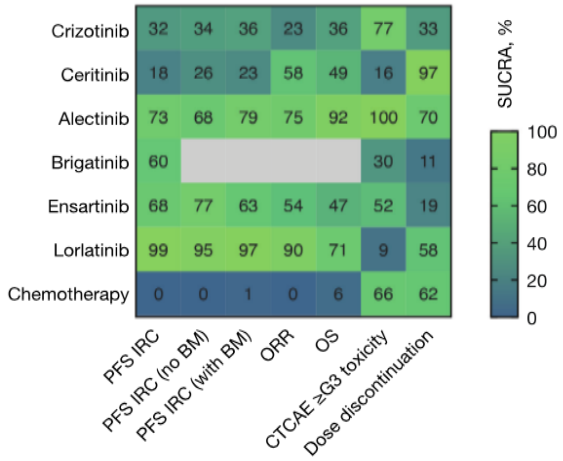
Evolution of First- and Next-Generation ALK Inhibitors for ALK+ NSCLC



	ALEX *Alectinib vs Crizotinib*	ALTA1L *Brigatinib vs Crizotinib*	CROWN *Lorlatinib vs Crizotinib*
Trial Design ✓ N ✓ Primary Objective ✓ Cross-over	303 PFS (INV) No	275 PFS (BIRC) Yes	296 PFS (BIRC) No
ORR (%)	82	74	77
icORR (%) icRC (%)	81 38	78 28	83 72
PFS (m) 3y PFS (%)	34.8 (HR=0.43) 46.4	24 (HR=0.48) 43	NR (HR=0.27) 63.5
OS (%)	62,5 (5y)	66 (4y)	NR
Toxicity			
Treatment after PD	Lorlatinib	Lorlatinib	CT +/- IO

2024 ASCO ANNUAL MEETING





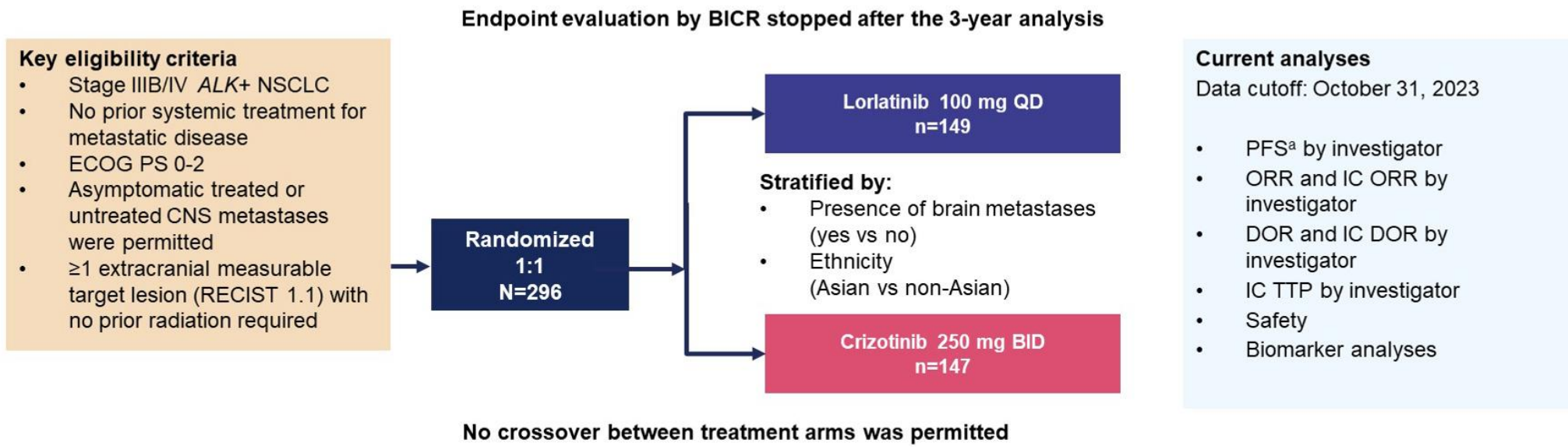
Lin J, et al. IASLC 2023; Hendriks L, et al. Ann Oncol 2023; Solomon B, et al. Lancet Resp Med 2023; Tan D, et al. Precis Cancer Med 2023

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]

Current Post Hoc Analyses at 5 Years

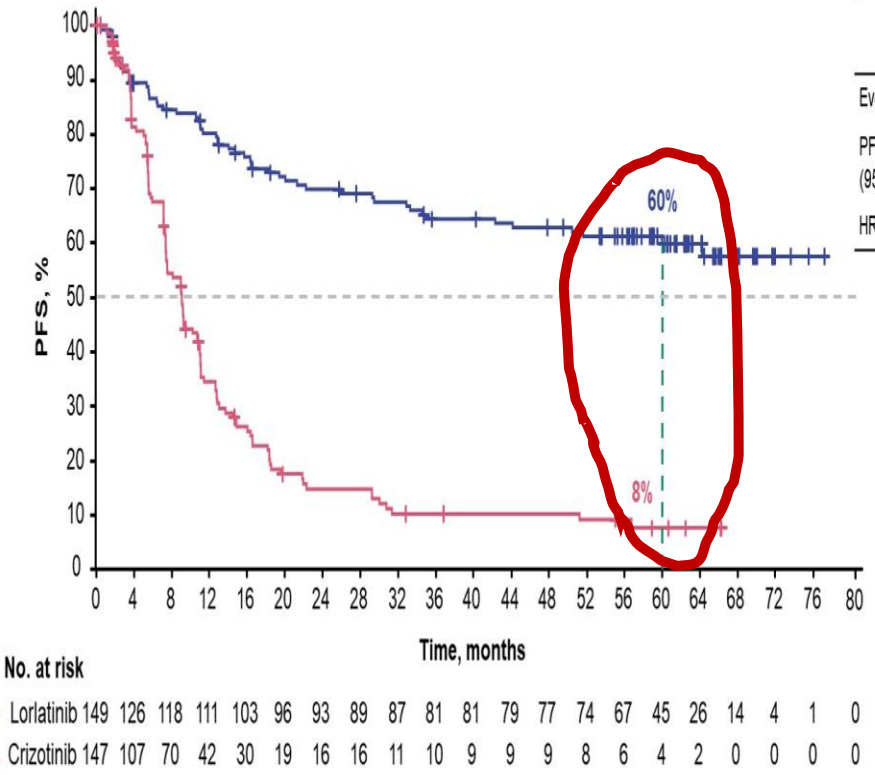


Current analyses

Data cutoff: October 31, 2023

- PFS[a] by investigator
- ORR and IC ORR by investigator
- DOR and IC DOR by investigator
- IC TTP by investigator
- Safety
- Biomarker analyses

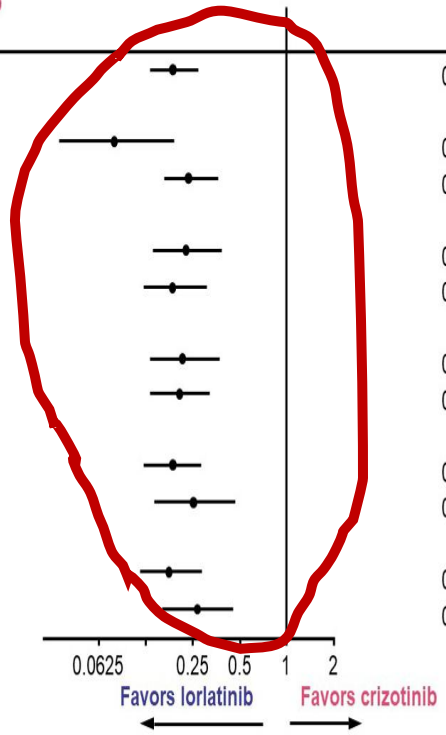
At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



	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)**	

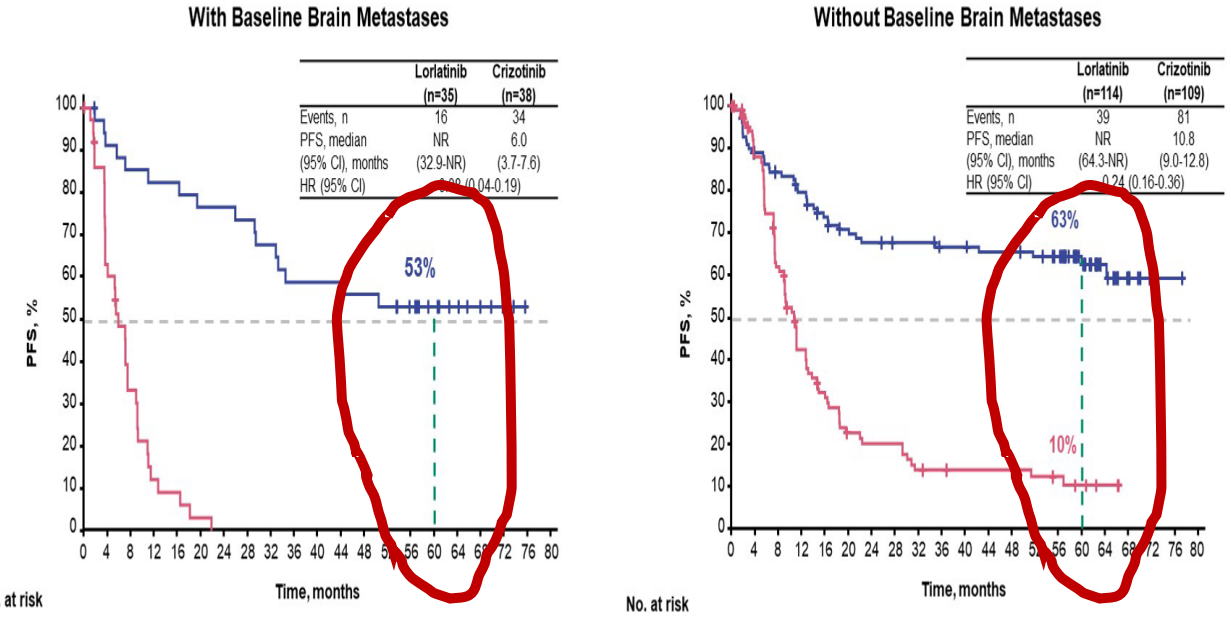
PFS Benefit With Lorlatinib Was Observed Across Patient Subgroups

Subgroup	Patients, n (%)		Events, n		HR (95% CI)
	Lorlatinib	Crizotinib	Lorlatinib	Crizotinib	
All patients (stratified)	149 (100)	147 (100)	55	115	0.19 (0.13-0.27)
Presence of brain metastases					
Yes	35 (23)	38 (26)	16	34	0.08 (0.04-0.19)
No	114 (77)	109 (74)	39	81	0.24 (0.16-0.36)
Ethnic origin					
Asian	66 (44)	65 (44)	25	50	0.23 (0.14-0.38)
Non-Asian	83 (56)	82 (56)	30	65	0.19 (0.12-0.31)
Sex					
Male	65 (44)	56 (38)	24	48	0.22 (0.13-0.37)
Female	84 (56)	91 (62)	31	67	0.21 (0.13-0.32)
Age					
<65 years	96 (64)	110 (75)	33	88	0.19 (0.12-0.28)
≥65 years	53 (36)	37 (25)	22	27	0.26 (0.14-0.47)
Smoking status					
Never	81 (54)	94 (64)	30	75	0.18 (0.12-0.29)
Current/former	68 (46)	52 (35)	25	39	0.27 (0.16-0.45)

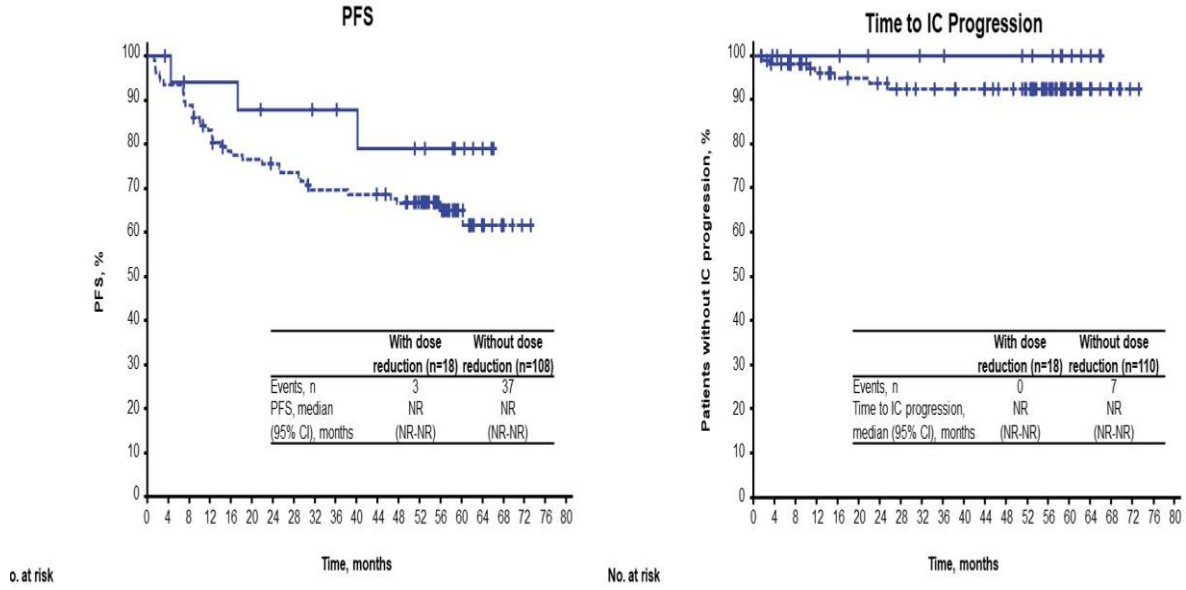


PFS, progression-free survival.

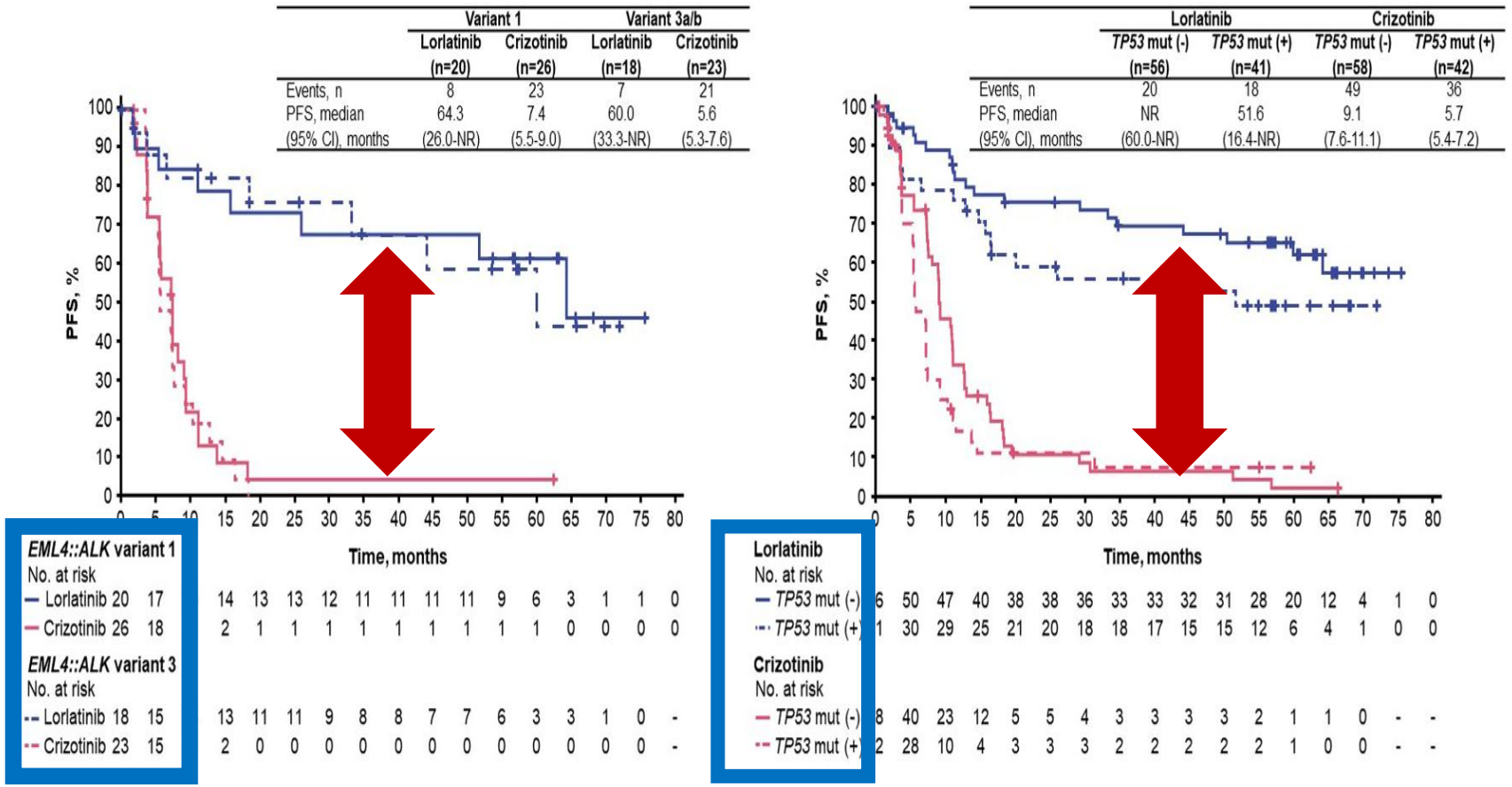
Lorlatinib Showed Superior PFS Benefit Irrespective of Presence or Absence of Baseline Brain Metastases



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



Lorlatinib Treatment Benefited Patients With Poor Prognostic Biomarkers



2024 World Conference on Lung Cancer SEPTEMBER 7-10, 2024 SAN DIEGO, CA USA
#WCLC24
wclc2024.iaslc.org

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]

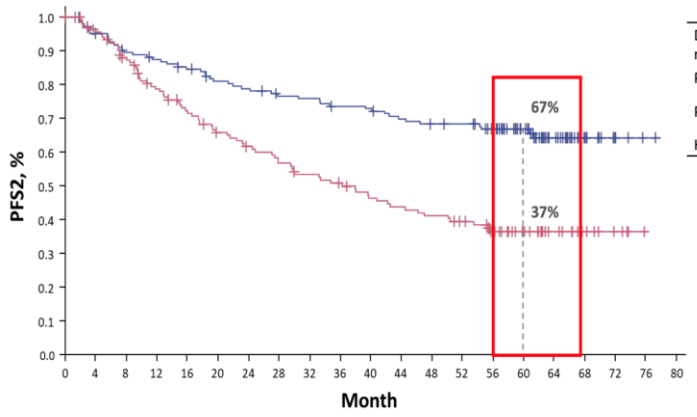
Details of first subsequent systemic anticancer therapy

	Lorlatinib (n=38)	Crizotinib (n=109)
First subsequent systemic anticancer therapy, n (%)		
ALK TKI	23 (61)	101 (93)
Alectinib	12 (52)	68 (67)
Crizotinib	4 (17)	5 (5)
Ceritinib	3 (13)	3 (3)
Lorlatinib	3 (13)	4 (4)
Brigatinib	1 (4)	21 (21)
Chemotherapy ± anti-angiogenic	13 (34)	4 (4)
Chemotherapy/immunotherapy	1 (3)	0
Chemotherapy/immunotherapy/anti-angiogenic	1 (3)	0
Other[a]	0	4 (4)
DOT on first subsequent systemic anticancer therapy, median (IQR), months	9.3 (2.6-22.6)	14.9 (5.3-38.4)
ALK TKIs as first subsequent therapy[b]	12.5 (2.0-31.7)	15.8 (7.0-39.9)
Non–ALK TKIs as first subsequent therapy[c]	6.7 (2.6-19.7)	1.2 (0.8-2.7)

ALK, anaplastic lymphoma kinase; **DOT**, duration of treatment; **TKI**, tyrosine kinase inhibitor.
[a]Includes investigational drug, cabozantinib, and osimertinib. [b]N numbers are 23 for lorlatinib and 101 for crizotinib. [c]N numbers are 15 for lorlatinib and 8 for crizotinib.

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)

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

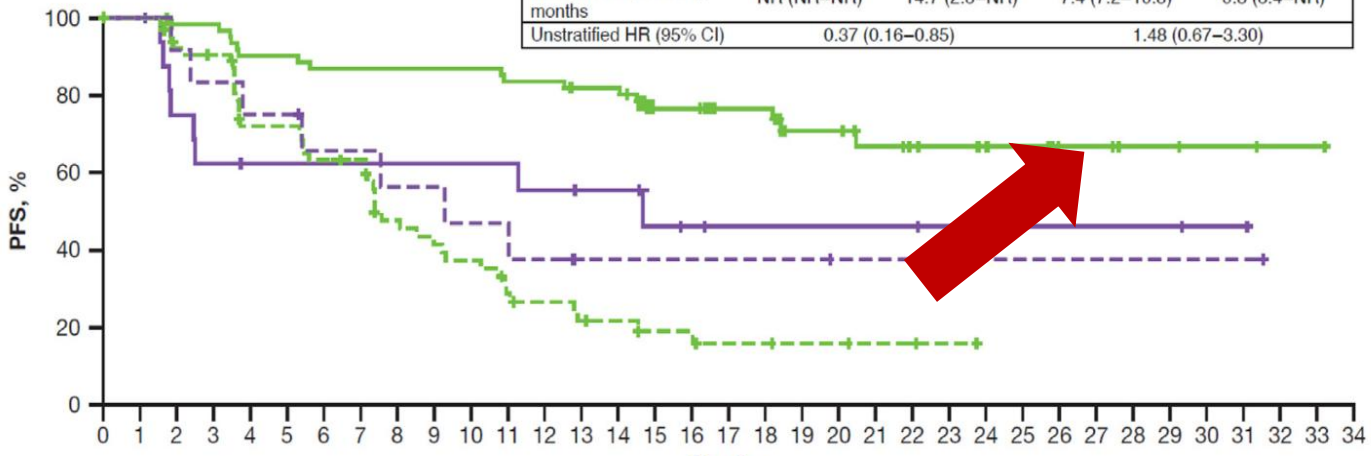


	Lorlatinib (N=149)	Crizotinib (N=147)
Duration of follow-up for PFS2, median (95% CI), months	61.4 (59.2-62.5)	58.4 (56.8-61.9)
PFS2 events, n (%)	48 (32)	78 (53)
PFS2, median (95% CI), months	NR (NR-NR)	37.9 (27.4-50.1)
HR (95% CI)	0.43 (0.30-0.62)	

Early Circulating Tumor DNA Dynamics and Efficacy of Lorlatinib in Patients With Treatment-Naive, Advanced, *ALK*-Positive NSCLC

Ross A. Soo, MBBS, PhD,[a,*] Jean-François Martini, PhD,[b]

	Lorlatinib		Crizotinib	
	MR overall (n = 63)	MNR (n = 17)	MR overall (n = 65)	MNR (n = 12)
Events, n	17	8	44	7
Median PFS (95% CI), months	NR (NR–NR)	14.7 (2.5–NR)	7.4 (7.2–10.3)	9.3 (5.4–NR)
Unstratified HR (95% CI)	0.37 (0.16–0.85)		1.48 (0.67–3.30)	



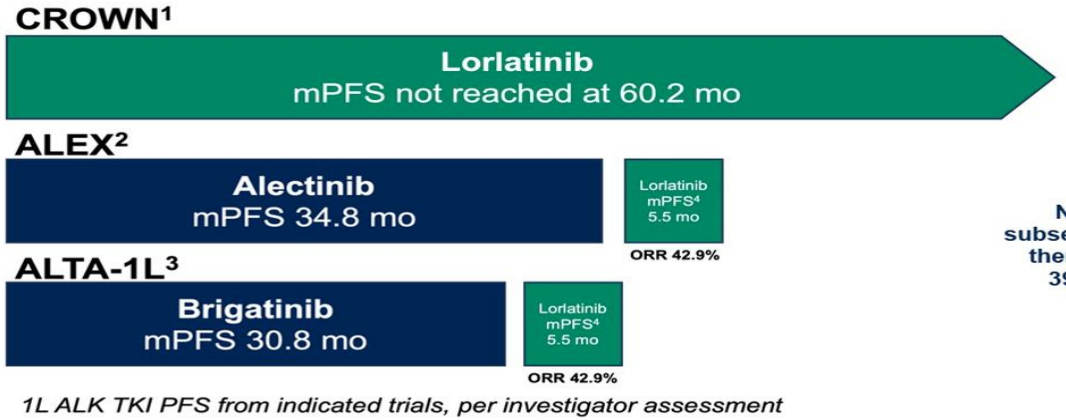
No. at risk																																
Lorlatinib MR overall	63	63	60	60	55	55	53	53	53	53	53	51	51	48	48	35	35	28	28	20	20	17	15	12	10	8	5	5	3	3	2	2	1	1	0
Lorlatinib MNR	17	17	12	10	9	9	9	9	9	9	9	8	7	7	5	4	3	3	3	3	3	3	2	2	2	2	2	2	2	1	1	0	0	0
Crizotinib MR overall	65	64	57	55	41	41	36	35	23	21	18	13	11	9	8	6	6	4	4	3	3	2	2	1	0	0	0	0	0	0	0	0	0	-	-
Crizotinib MNR	12	12	11	10	9	9	7	7	6	6	5	5	4	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	0	-	-

- **Early ctDNA dynamics** predicted better outcome with **Lorlatinib** but not with Crizotinib

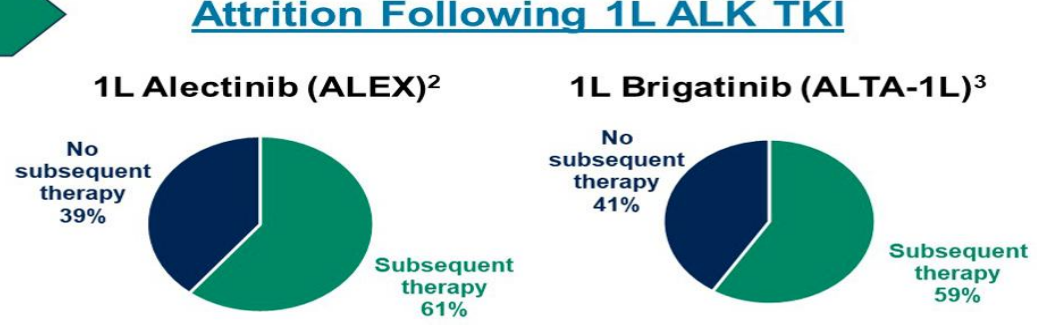
JTO 2023

CROWN: My Conclusions and Implications for Practice

The 5-year updated analyses of CROWN (re)affirm lorlatinib as standard-of-care first-line treatment for patients with metastatic ALK+ NSCLC



1L ALK TKI PFS from indicated trials, per investigator assessment

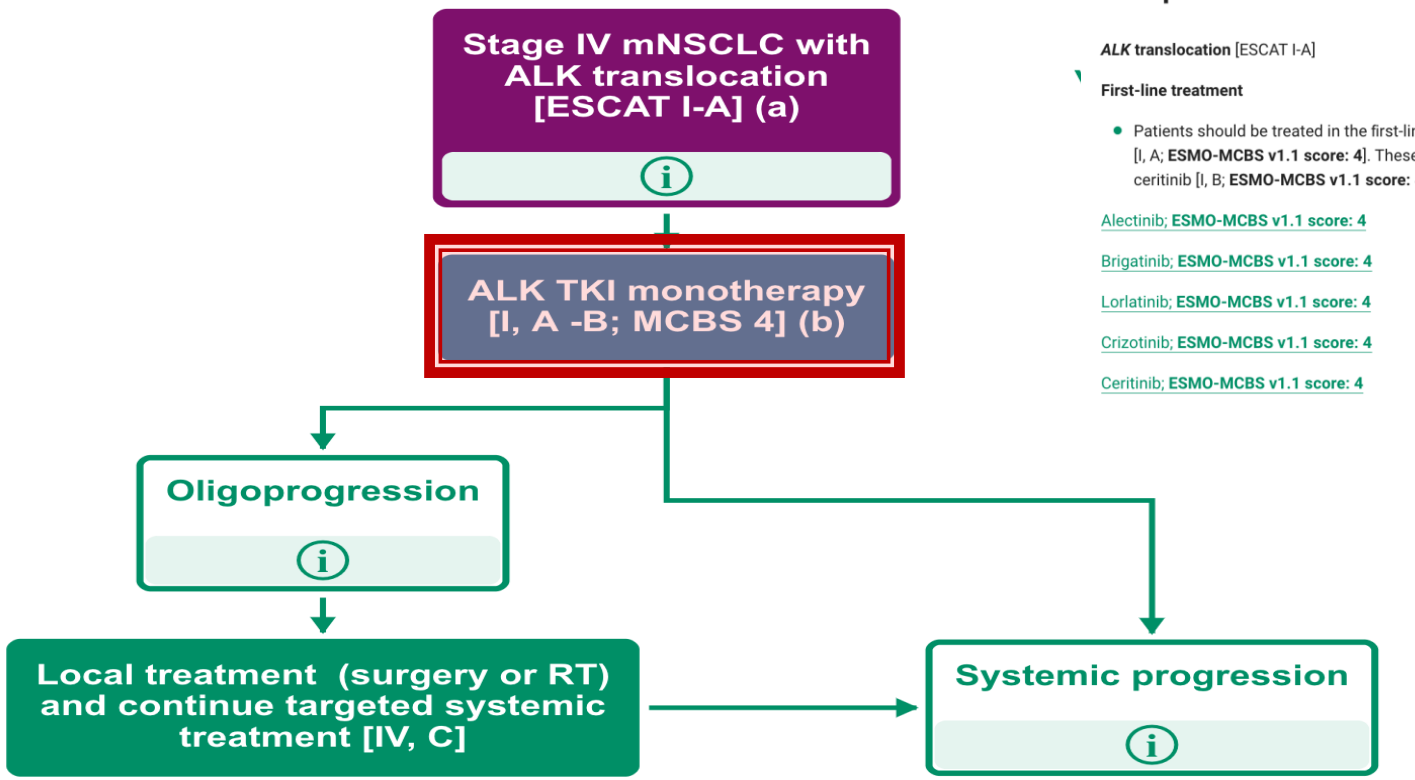


1. Solomon BJ et al., Lancet Respir Med 2023;11(4):354-66; 2. Mok T et al., Ann Oncol 2020;31(8):1056-64
3. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108; 4. Felip E et al., Ann Oncol 2021;32(5):620-30

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

What will I do next week with a patient with newly diagnosed metastatic ALK+ NSCLC presenting to clinic?

Recognizing that treatment decisions will always need to be individualized to meet each patient's goals and needs, *lorlatinib will be my preferred initial therapy* for most patients



ALK-positive NSCLC: First-line Treatment

***ALK* translocation** [ESCAT I-A]

First-line treatment

- Patients should be treated in the first-line setting with alectinib, brigatinib or lorlatinib [I, A; **ESMO-MCBS v1.1 score: 4**]. These options are preferred over crizotinib or ceritinib [I, B; **ESMO-MCBS v1.1 score: 4**].

Alectinib; **ESMO-MCBS v1.1 score: 4**

Brigatinib; **ESMO-MCBS v1.1 score: 4**

Lorlatinib; **ESMO-MCBS v1.1 score: 4**

Crizotinib; **ESMO-MCBS v1.1 score: 4**

Ceritinib; **ESMO-MCBS v1.1 score: 4**

4

Agent Score

Indication details

Control Arm	Crizotinib
Therapeutic Indication	Treatment of adult patients with anaplastic lymphoma kinase (ALK) positive (NSCLC) previously not treated with an ALK inhibitor
Tumour Type	Thoracic Malignancies
Tumour Sub-type	Non-small-cell Lung Cancer
Tumour Stage	Advanced
Tumour Sub-Group	ALK+
Trial Name	CROWN
NCT Number	NCT03052608
Trial Phase	Phase III

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Contents lists available at ScienceDirect

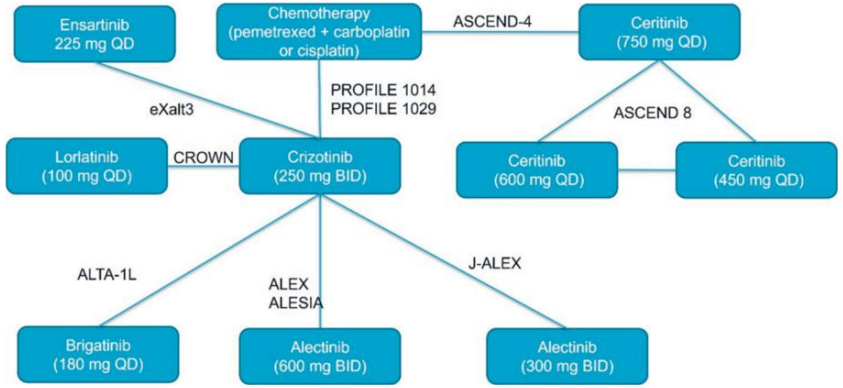
Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

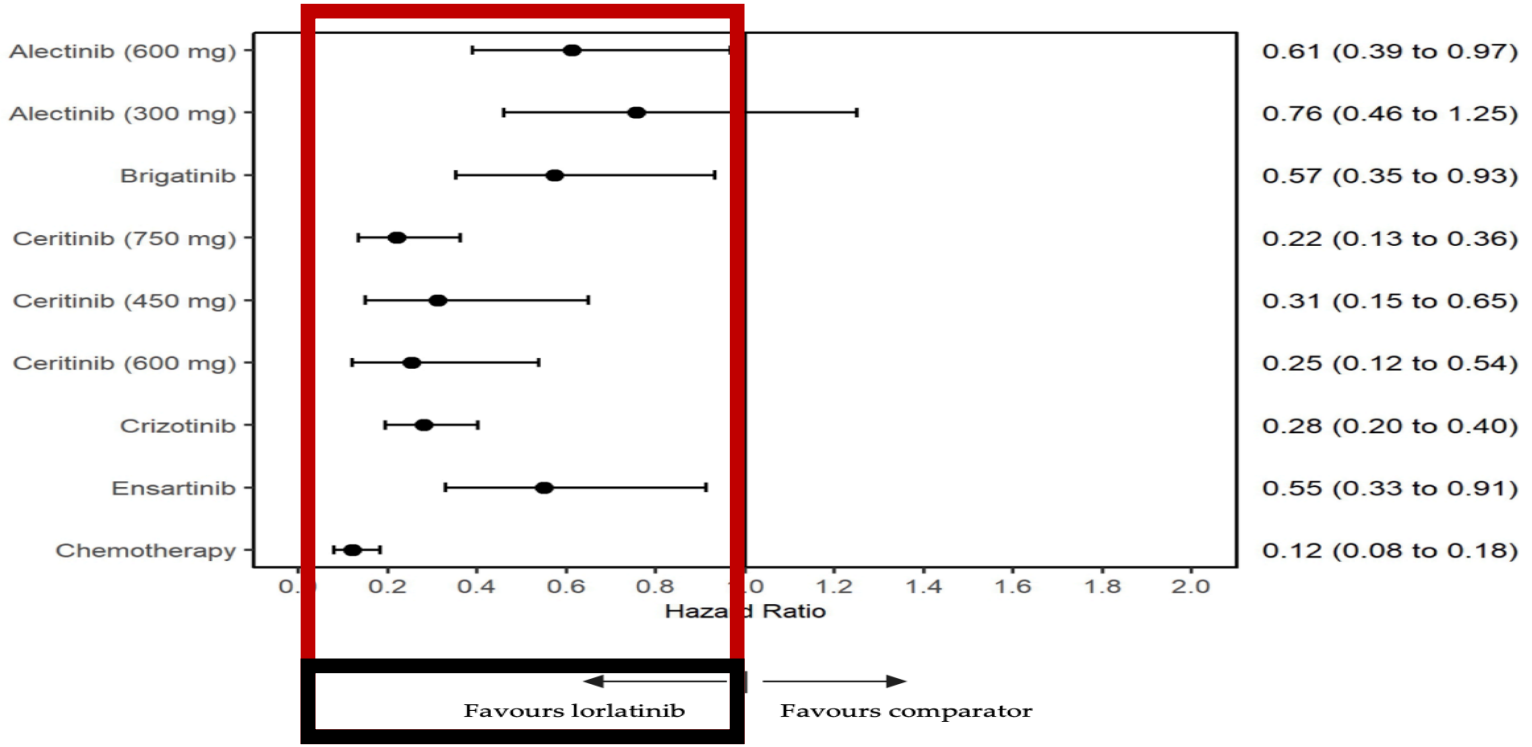
Research Paper

Systematic review and network meta-analysis of lorlatinib with comparison to other anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) as first-line treatment for ALK-positive advanced non-smallcell lung cancer (NSCLC)

Sai-Hong Ou [a], Hannah Kilvert [b], Jane Candlish [b], Ben Lee [b], Anna Polli [c], Despina Thomaidou [c],



PFS

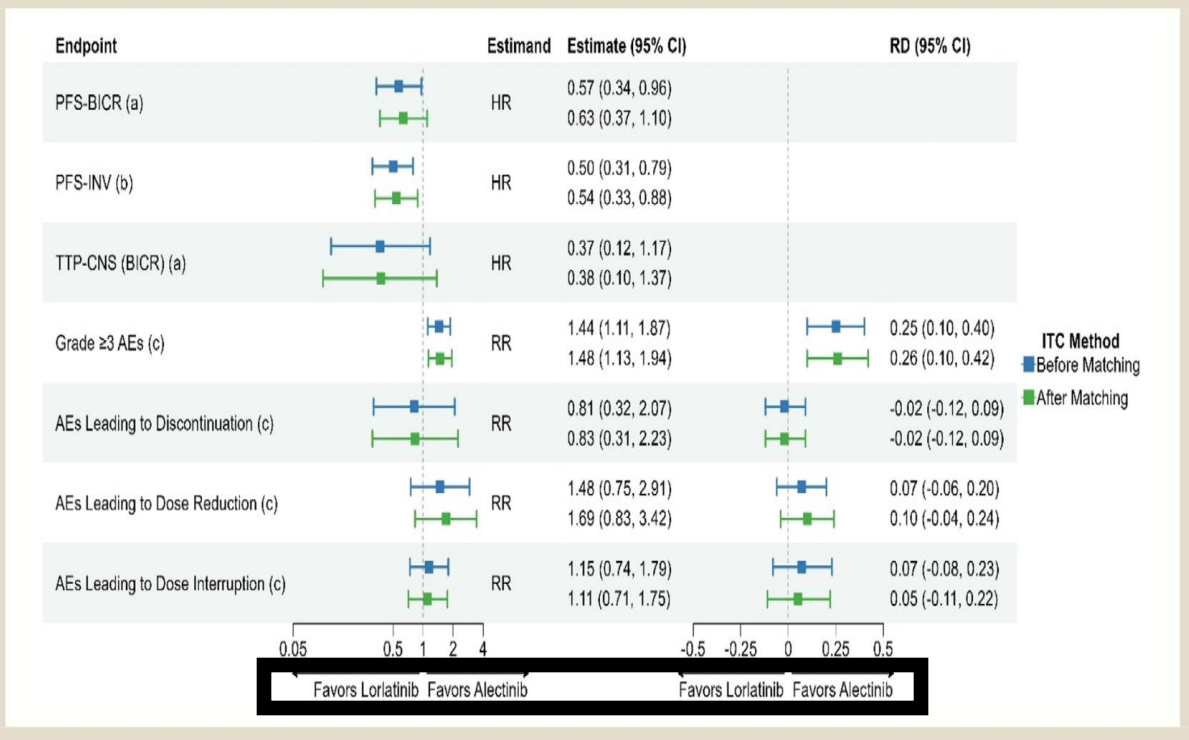


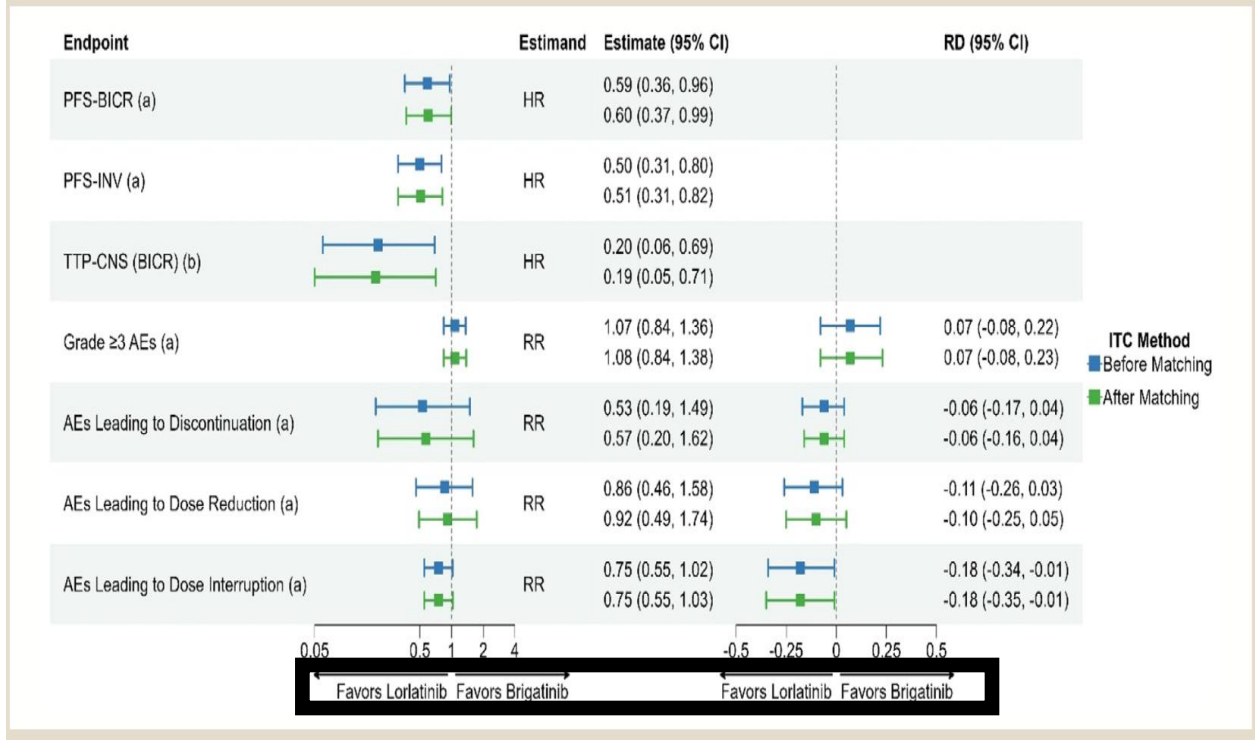
Comparative Efficacy and Safety of Lorlatinib Versus Alectinib and Lorlatinib Versus Brigatinib for ALK-Positive Advanced/Metastatic NSCLC: Matching-Adjusted Indirect Comparisons

Christine Garcia,[1] Devin Abrahami,[2] Anna Polli,[3] Haitao Chu,[4] Conor Chandler,[5]

Conclusion

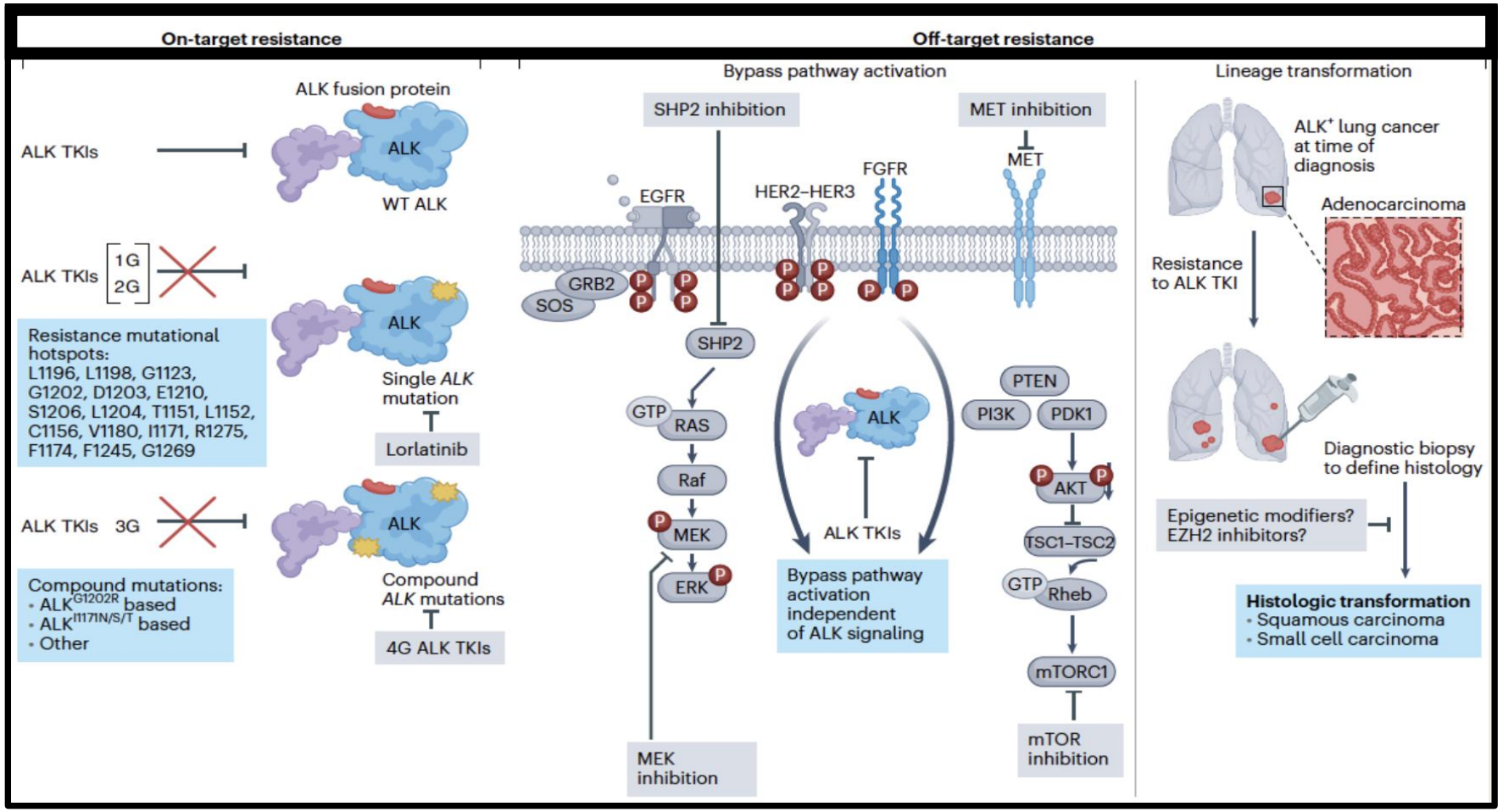
Lorlatinib was associated with superior PFS-INV compared to alectinib and brigatinib in these MAICs. While the estimated rate of Grade ≥3 AEs with lorlatinib was higher than that with alectinib, there were no differences in the other studied safety endpoints or compared to brigatinib. Overall, this study bolsters the totality of evidence concerning the comparative efficacy and safety of lorlatinib and supports its use as a first-line treatment for patients with ALK+ advanced/metastatic NSCLC.





Clin Lung Cancer 2024

Mechanisms of Resistance to ALK Inhibitors



Schneider JL, Nat Cancer 2023

Lorlatinib Versus Crizotinib in Patients With Advanced *ALK*-Positive Non–Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study

Benjamin J. Solomon, MBBS, PhD[1]; Geoffrey Liu, MD[2]; Enriqueta Felip, MD[3]; Tony S.K. Mok, MD[4]; Ross A. Soo, MBBS, PhD[5];

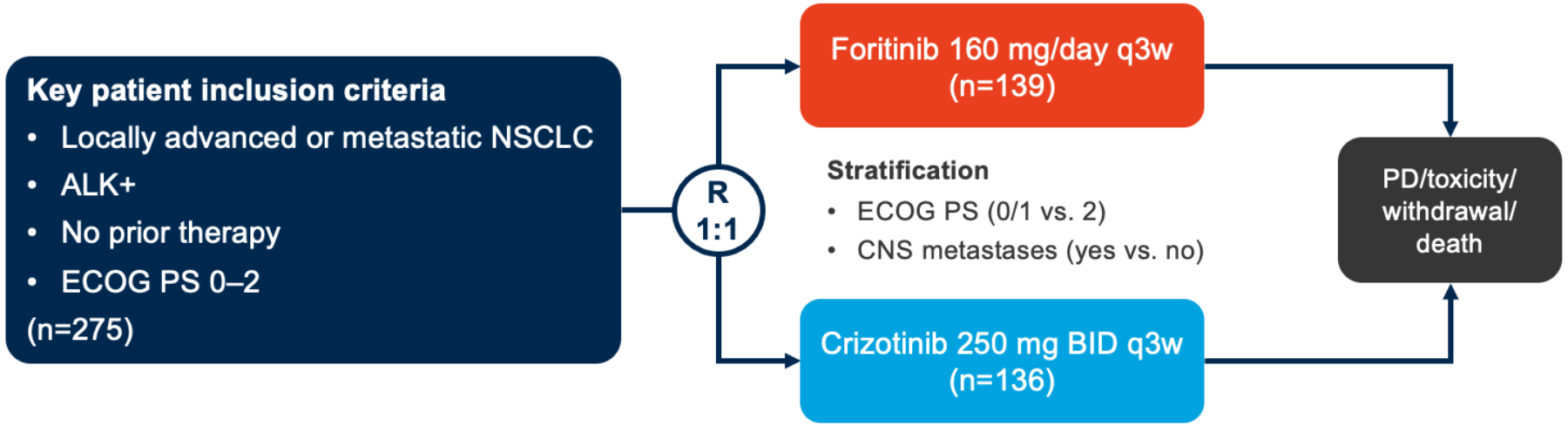
TABLE A8. Summary of Resistance Mechanisms in End-of-Treatment ctDNA Samples

Resistance Mechanisms	Lorlatinib (n = 31)	Crizotinib (n = 89)
Resistance mechanisms, No. (%)		
New single *ALK* mutation	0	8 (9)
ALK compound mutation	0	2 (2)
Bypass mechanism, No. (%)	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, No. (%)	11 (35)	19 (21)
Unknown, No. (%)	13 (42)	56 (63)

Solomon B, JCO 2024

Randomized, Open-label, Phase III Study of SAF-189s Versus Crizotinib in First-Line *ALK*-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) REMARK Study

Anwen, Xiong
East Hospital Affiliated to Tongji University
China



Primary endpoint

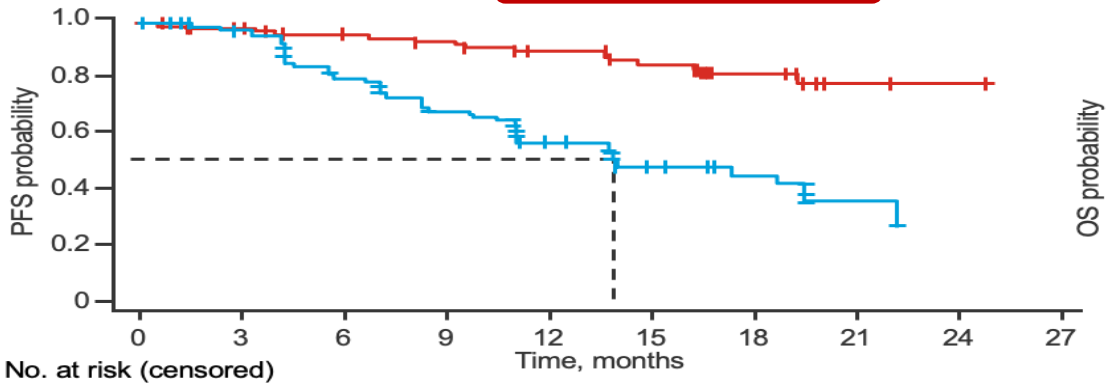
- PFS (IRC assessed)

Secondary endpoints

- PFS (investigator assessed), ORR, TTR, DoR, OS, safety

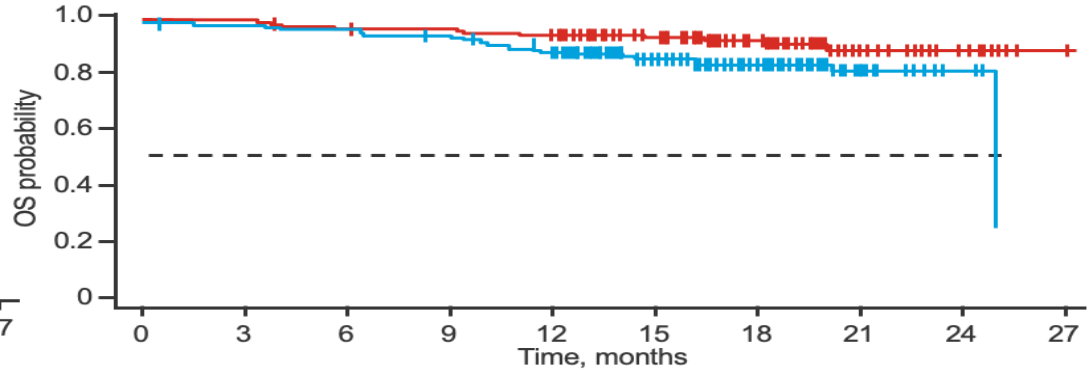
Progression-free survival

	Foritinib (n=139)	Crizotinib (n=136)
mPFS, mo (95%CI)	NR (NR, NR)	13.93 (11.07, 19.35)
HR (95%CI); p-value	0.23 (0.14, 0.38); <0.0001	



Overall survival

	Foritinib (n=139)	Crizotinib (n=136)
mOS, mo (95%CI)	NR (NR, NR)	24.94 (NR, NR)
HR (95%CI); p-value	0.60 (0.30, 1.20); 0.0723	



Outcomes	Foritinib (n=139)	Crizotinib (n=136)
ORR, n (%) [95%CI]	29 (92.8) [87.2, 96.5]	110 (80.9) [73.5, 87.1]
OR (95%CI)	3.04 (1.41, 6.57)	
BOR, n (%)		
PR	129 (92.8)	110 (80.9)
SD	6 (4.3)	22 (16.2)
PD	2 (1.4)	1 (0.7)
NE	2 (1.4)	3 (2.2)
mDoR, mo (95%CI)	NR	15.9 (11.2, NR)

Intracranial response*	Foritinib (n=10)	Crizotinib (n=18)
ORR, n (%) [95%CI]	10 (100) [69.2, 100]	9 (50.0) [26.0, 74.0]
OR (95%CI)	NC	
BOR, n (%)		
CR	2 (20.0)	2 (11.1)
PR	8 (80.0)	7 (38.9)
SD	0	8 (44.4)
PD	0	1 (5.6)
mDoR, mo (95%CI)	NR	11.0 (2.9, NR)

TRAEs, n (%)	Foritinib (n=138)	Crizotinib (n=135)
Any	135 (97.8)	133 (98.5)
Grade ≥3	52 (37.7)	75 (55.6)
Serious	22 (15.9)	16 (11.9)
Led to dose interruption	37 (26.8)	48 (35.6)
Led to dose reduction	33 (23.9)	51 (37.8)
Led to discontinuation	5 (3.6)	3 (2.2)

- **Conclusions**
  - In Chinese patients with ALK+ advanced NSCLC, 1L foritinib demonstrated a significant improvement in PFS over crizotinib along with a trend in improvement in OS and no new safety findings

BARCELONA 2024 ESMO congress

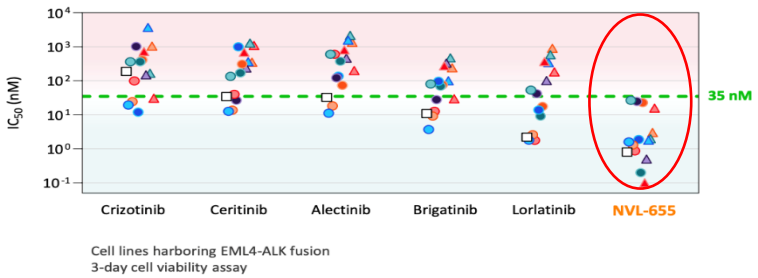
Phase 1/2 ALKOVE-1 study of NVL-655 in ALK-positive (ALK+) solid tumors

A. Drilon[1], J. J. Lin[2], M. L. Johnson[3], C. S. Baik[4], L. Paz-Ares[5], B. Besse[6],

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

ALK Fusion and ALK Single/Compound Mutation Activity

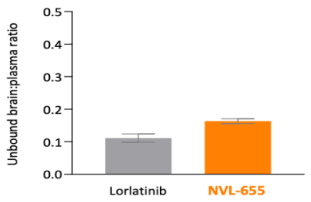
Potent activity (IC_{50} = 0.1 – 30 nM) against ALK-driven cell lines, including ALK single and compound mutants



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

Brain Penetrance

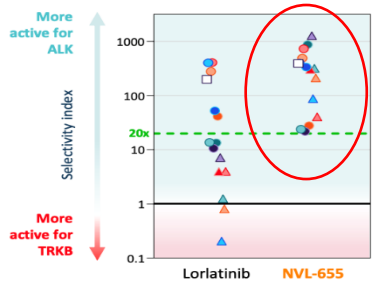
Preclinical pharmacokinetic data similar to lorlatinib



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



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

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)

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

PHASE 1 DOSE-ESCALATION COMPLETED, FOLLOW-UP CONTINUES

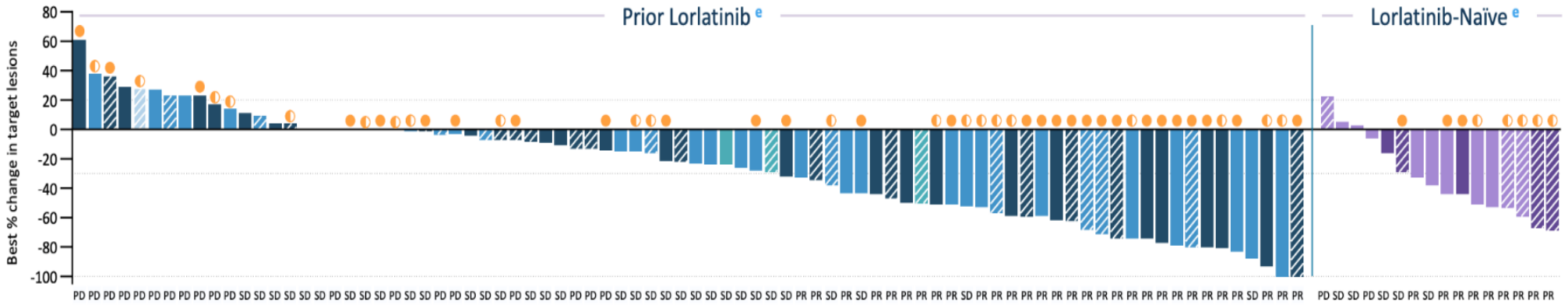
Enrollment June 2022 to February 2024 (Data cut-off: 15 June 2024)

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

Drilon A, ESMO 2024

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

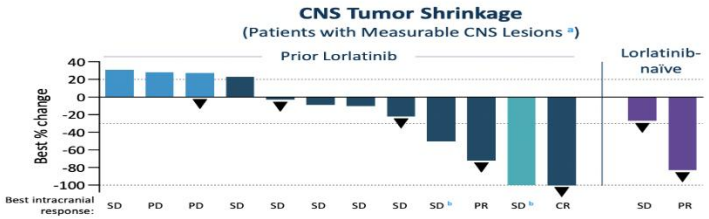
RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [b]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	**38%** (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)

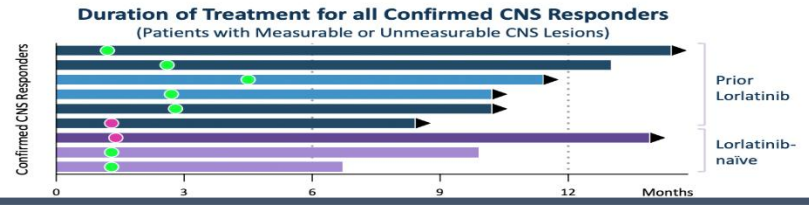


Drilon A, ESMO 2024

CNS Activity: Durable Intracranial Responses in Lorlatinib-naïve and Lorlatinib Pre-treated Patients with ALK+ NSCLC

- **IC-ORR** (patients with measurable CNS lesions):
  - **Lorlatinib-naïve**: 50% (1/2)
  - **Prior lorlatinib:** 15% (2/13)
    - 31% (4/13) including 2 CNS uPRs not confirmed due to discontinuation of treatment in absence of CNS progression
- **No CNS progression among confirmed CNS responders, including in patients who previously received the brain-penetrant TKI lorlatinib** (measurable or unmeasurable CNS lesions)
  - Treatment duration: 6.7 - 14.4+ months





- Discontinuation due to TRAE: 2% (3/133) [a]
- Dose reduction due to TRAE: 15% (20/133) [b]
- Preliminary overall safety profile consistent with avoiding TRK-related neurotoxicities

Treatment-Related Adverse Events (TRAEs) in ≥ 10% of Patients
All Treated (N = 133)

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)
ALT increased	21 (16%)	6 (5%)	17 (13%)	1 (1%)	45 (34%)
AST increased	21 (16%)	7 (5%)	12 (9%)	-	40 (30%)
Constipation	15 (11%)	6 (5%)	-	-	21 (16%)
Dysgeusia	15 (11%)	2 (2%)	-	-	17 (13%)
Nausea	15 (11%)	1 (1%)	-	-	16 (12%)

Well tolerated

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MADRID 2023 ESMO congress

TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer with actionable genomic alterations

Luis Paz-Ares,[1] Myung-Ju Ahn,[2] Aaron Lisberg,[3] Satoru Kitazono,[4] Byoung Chul Cho,[5]

Screening

Key inclusion criteria

- Stage IIIB, IIIC, or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS of 0 or 1
- ≥1 line of targeted therapy
- 1 or 2 prior cytotoxic agent–containing therapies including platinum-based therapy in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

Dato-DXd
6 mg/kg
Q3W

Endpoints[a]

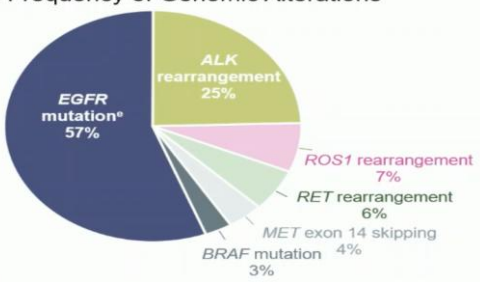
Primary: ORR by BICR

Secondary:

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)

Relative Frequency of Genomic Alterations[b-d]



2

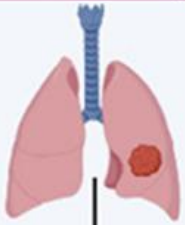
Locally Advanced Disease

Consolidation *ALK* Tyrosine Kinase Inhibitors versus Durvalumab or Observation After Chemoradiation in Unresectable Stage III *ALK*+ Non-Small Cell Lung Cancer

Journal of Thoracic Oncology

COHORT

Unresectable Stage III NSCLC after concurrent CRT (n=67)

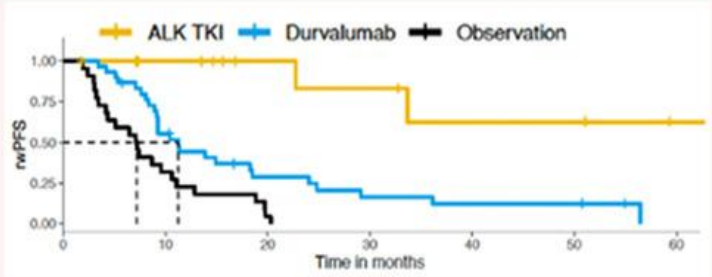


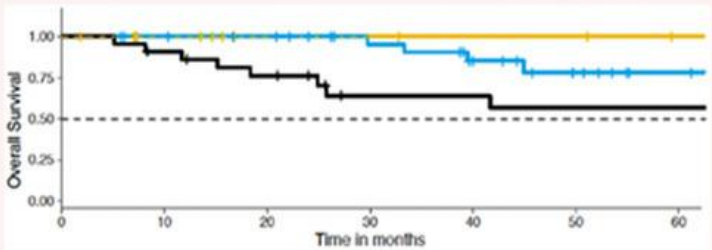
- ALK TKI (n=15)
- Durvalumab (n=30)
- Observation (n=22)

ALK TKI:
Alectinib (n=10),
Crizotinib (n=3),
Lorlatinib (n=1),
Brigatinib (n=1)

Global Retrospective Study (17 institutions)

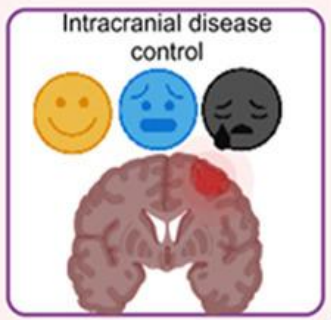
SURVIVAL



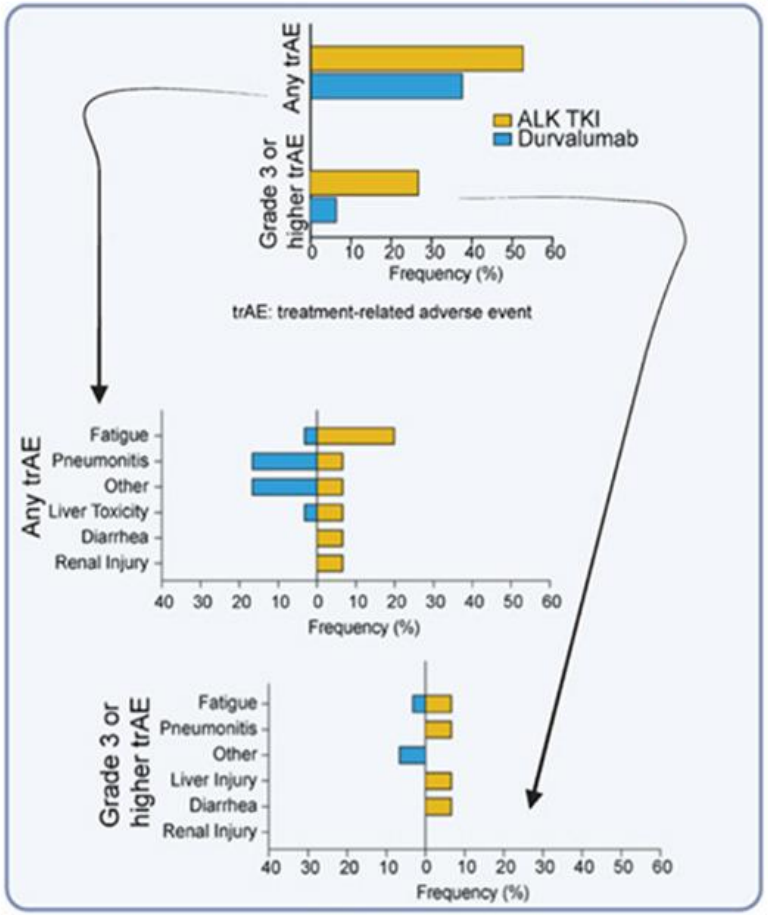


	Median	95% CI
rwPFS	NR	22.7-NR
OS	NR	NR-NR
rwPFS	11.3 mo	8.9-18.5
OS	NR	NR-NR
rwPFS	7.2 mo	3.4-10.6
OS	70.6 mo	24.9-NR

OS: Overall survival; rwPFS: real-world PFS; NR: not reached mo: months



TOXICITY



***CONCLUSION**: Consolidation ALK TKI treatment is associated with significantly improved real-world progression-free survival compared to Durvalumab or observation in patients with ALK+ NSCLC*

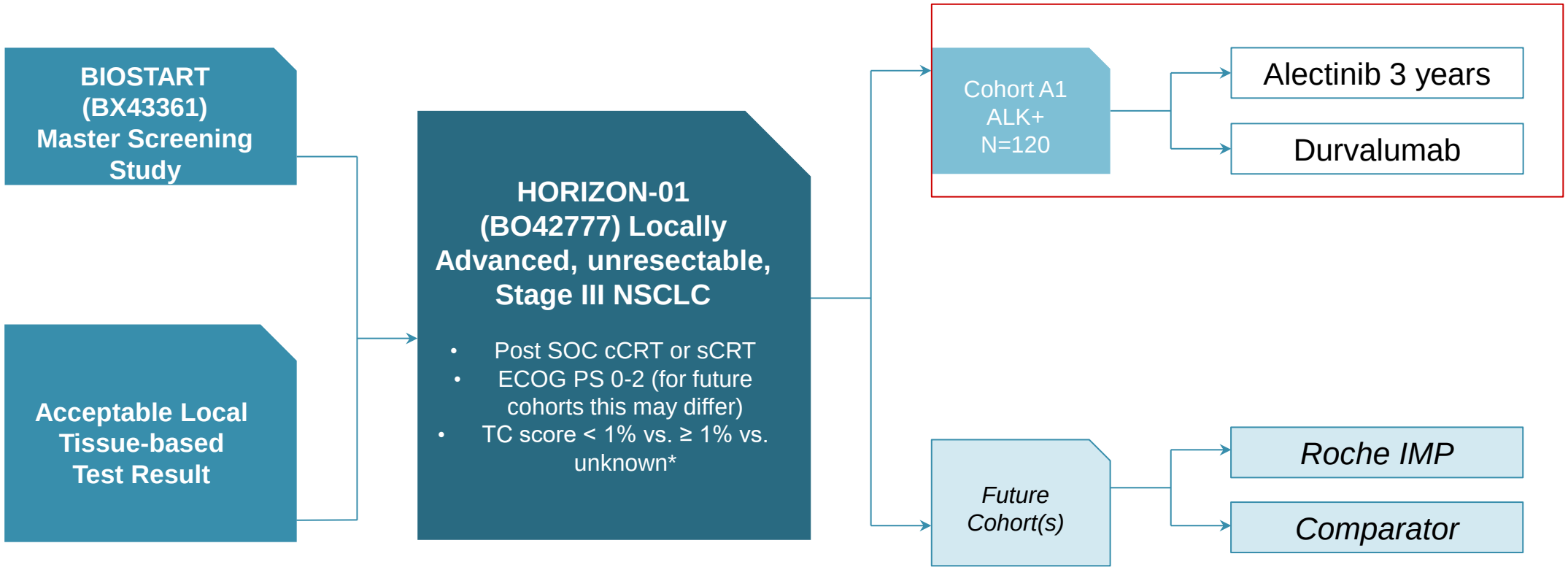
IASLC

Nassar et al., *J Thorac Onc* (2024)

HORIZON-01

International
NCT05170204

A Study Evaluating the Efficacy and Safety of Multiple Therapies in Cohorts of Participants With Locally Advanced, Unresectable, Stage III NSCLC

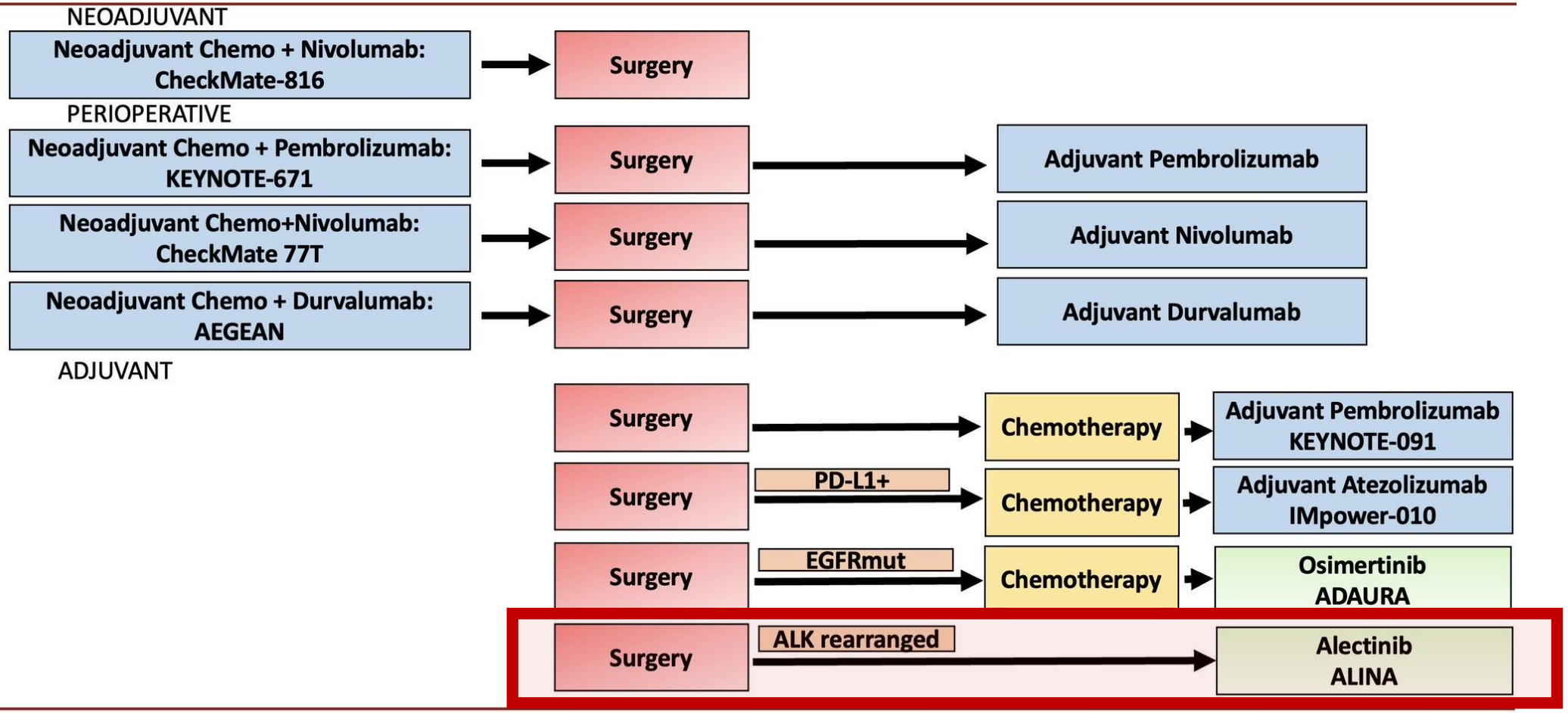


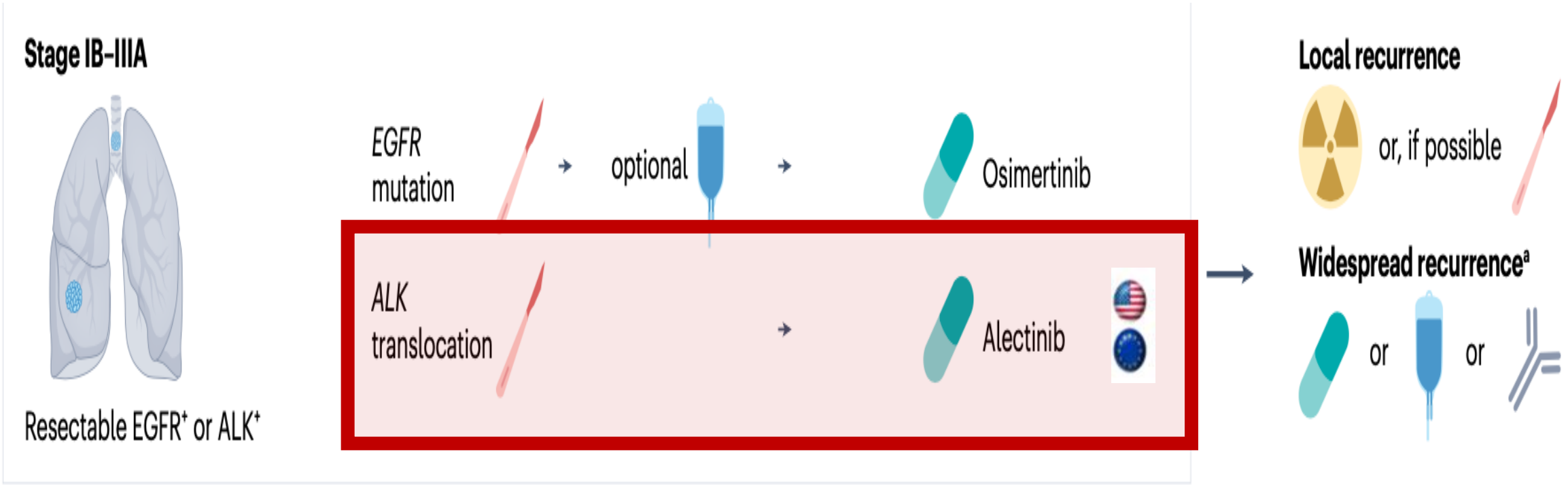
ClinicalTrials ID NCT05170204

3

Early Stage

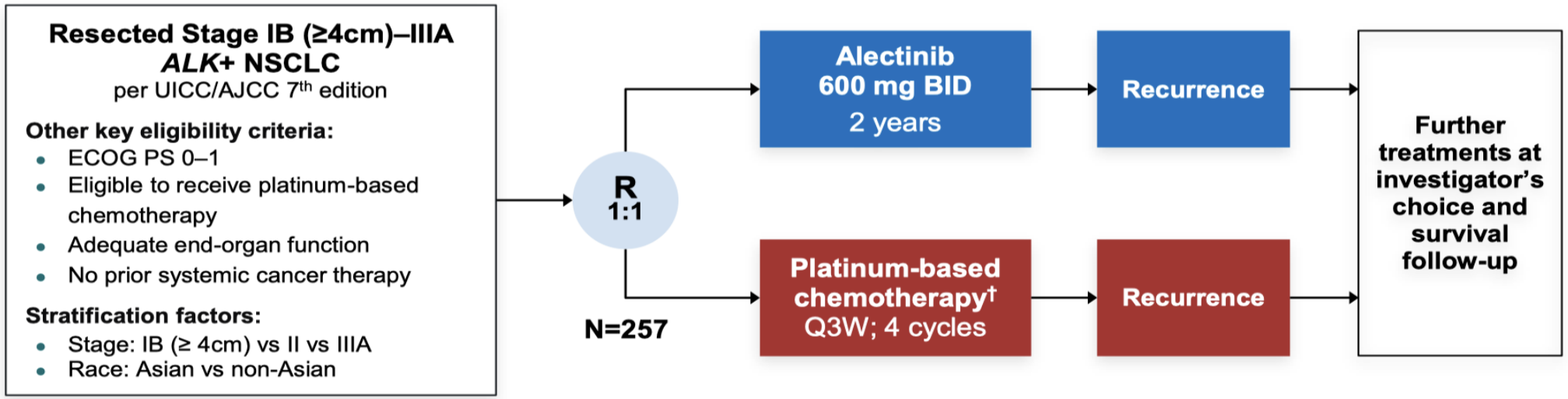
2024 Paradigm for Resectable Early-stage NSCLC





Hendriks L, Nature Rev Dis Prim 2024

ALINA Study



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

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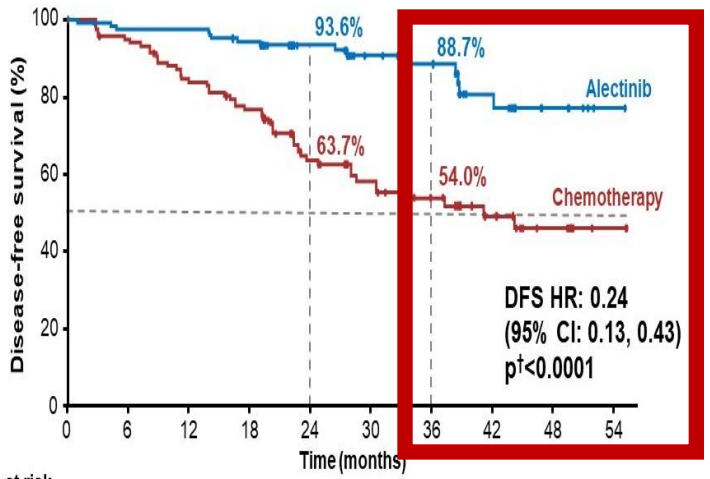
Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time 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

Wu YL, NEJM 2024

DFS in stage IB–IIIA (ITT)*

Primary endpoint

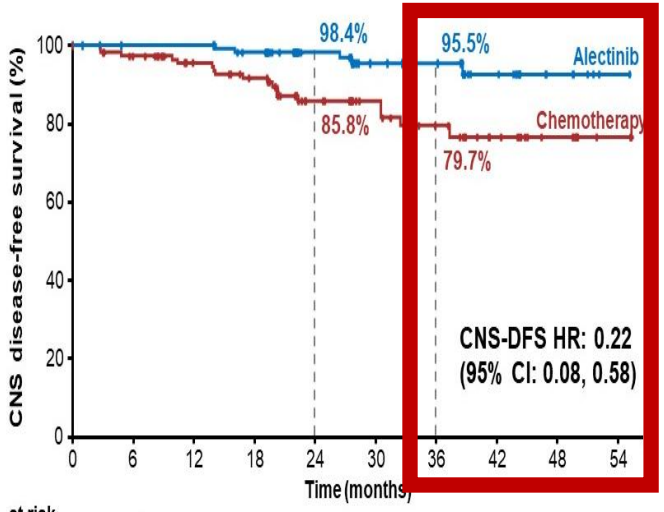


No. at risk

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

CNS-DFS in stage IB–IIIA (ITT)*

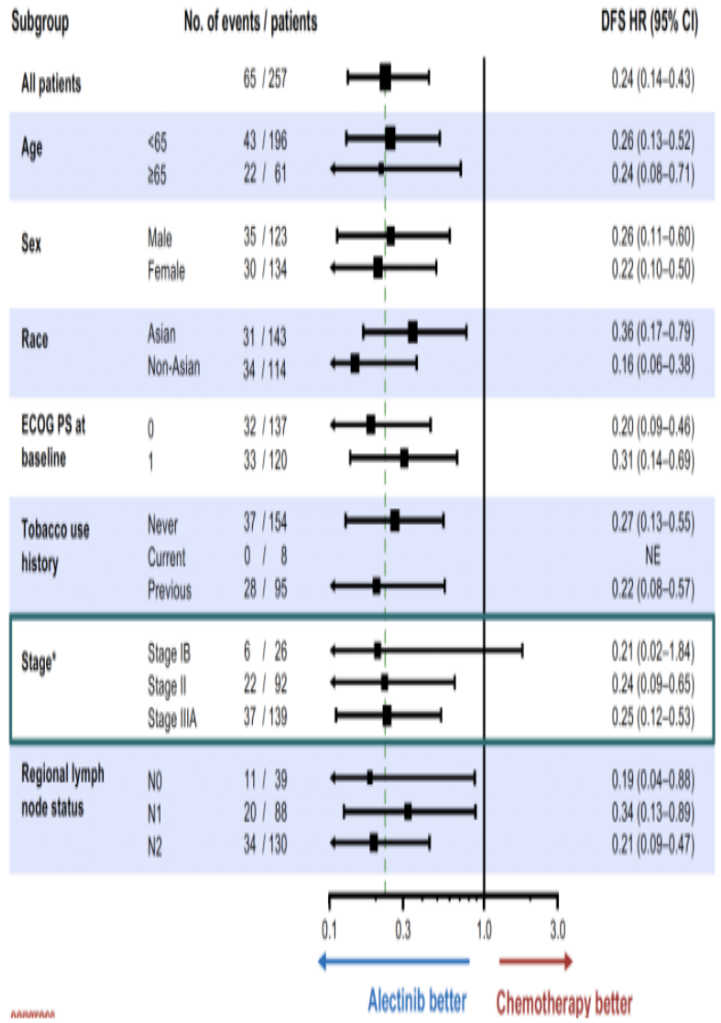
Exploratory endpoint



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

Treatment with adjuvant alectinib resulted in a significant DFS benefit and clinically meaningful CNS-DFS benefit compared with chemotherapy in patients with resected stage IB–IIIA *ALK*+ NSCLC*

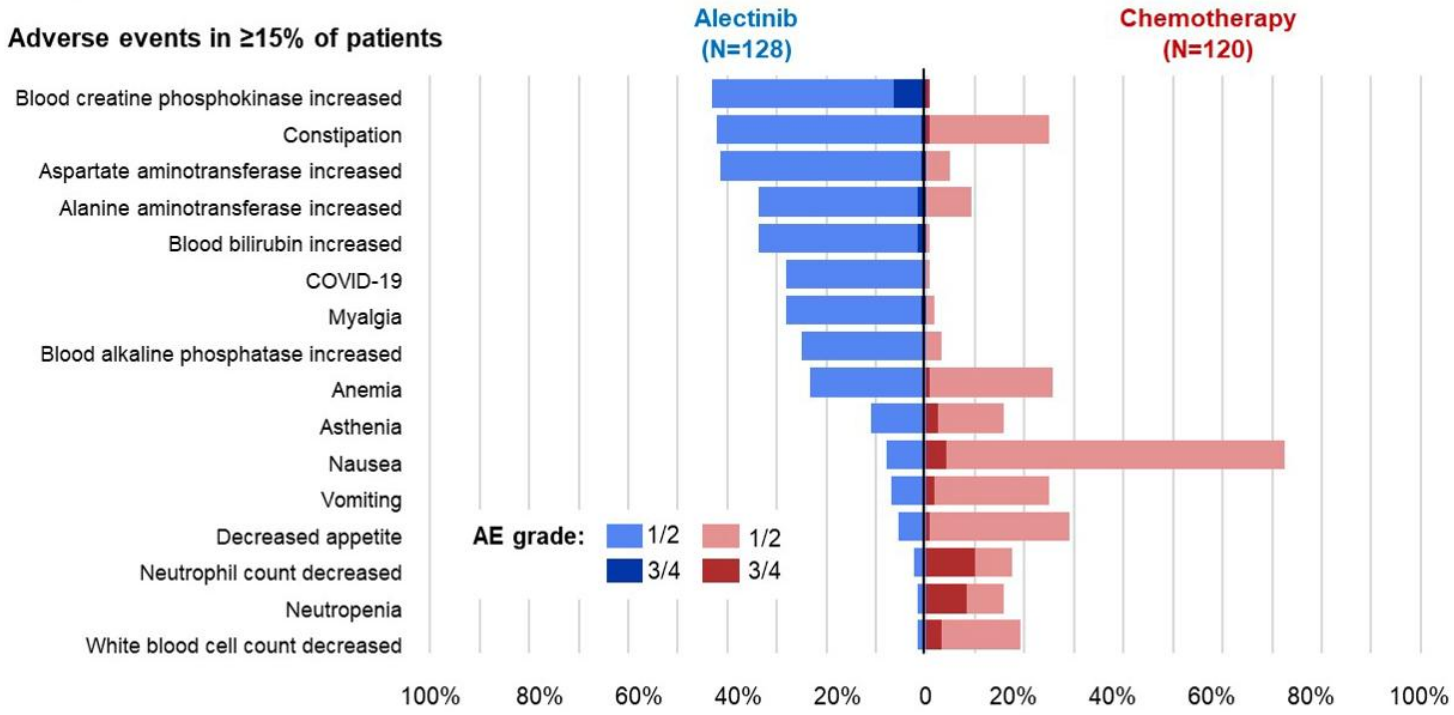


Data cut-off: June 26, 2023; Median follow up, 27.8 months; Time from last patient in to data cut-off was ~18 months; DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat population; *Stage IB (≥4cm)–IIIA per UICC/AJCC 7th edition; †Stratified log rank; DFS defined as the time from randomization 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-DFS defined as time from randomization to the first documented recurrence of disease in the CNS, or death from any cause; Solomon et al. ESMO 2023 (LBA2); Wu et al. N Engl J Med 2024

PRESENTED BY: Prof. Makoto Nishio

AEs occurring in ≥15% of patients

Adjuvant alectinib was tolerable, with a manageable safety profile which was in line with the known profile of alectinib[1,2]



AEs leading to:

- Dose reduction
  Alectinib: **26%** / Chemo: **10%**
- Dose interruption
  Alectinib: **27%** / Chemo: **18%**
- Treatment withdrawal
  Alectinib: **5%** / Chemo: **13%**

Median treatment duration

Alectinib: **23.9 months**
Chemo: **2.1 months**

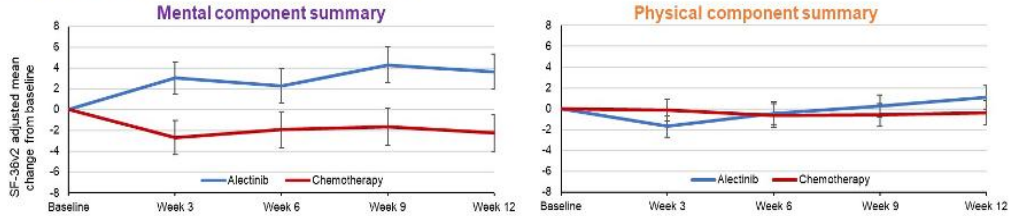
AE, adverse event;
1. Solomon et al. ESMO 2023 (LBA2); 2. Wu et al. N Engl J Med 2024

2024 ASCO ANNUAL MEETING

Health-related quality of life (HRQoL) results for adjuvant alectinib vs chemotherapy in patients with resected *ALK*+ NSCLC: data from ALINA

Makoto Nishio,[1] Yi-Long Wu,[2] Fabrice Barlesi,[3] Jin Seok Ahn,[4] Dae Ho Lee,[5] Jong-Seok Lee,[6] Wenzhao Zhong,[2] Hidehito Horinouchi,[7]

Adjusted mean change from baseline in MCS and PCS to Week 12



	Minimal important difference[1,2]	MMRM adjusted mean change from baseline at Week 12 (95% CI)		
		Alectinib	Chemotherapy	Difference (alectinib − chemo)*
MCS	± 3	+ 3.65 (1.96, 5.35)	− 2.24 (−4.05, −0.43)	+ 5.89 (3.41, 8.37)
PCS	± 2	+ 1.10 (−0.02, 2.21)	− 0.40 (−1.59, 0.78)	+ 1.50 (−0.13, 3.13)

Improvement in HRQoL ≥ positive MID
Decline in HRQoL ≥ negative MID
Clinically meaningful difference between arms*

- Within arms, change from baseline for MCS and PCS were compared with the respective MID:
  - For MCS, a clinically meaningful improvement from baseline was seen with alectinib but not chemotherapy
  - PCS scores remained stable
- Clinically meaningful improvements from baseline in MCS were seen for alectinib versus chemotherapy*

CI, confidence interval; HRQoL, health-related quality of life; MCS, mental component summary; MID, minimal important difference; MMRM, mixed-effects model of repeated measures; PCS, physical component summary; *Post hoc MMRM analysis, highlighted as clinically meaningful where the 95% CI did not cross 0, not statistically tested; 1. Ware et al. SF-36v2 Administration Guide 2008; 2. Maruish et al. SF-36v2 User Manual 2011

Adjusted mean change from baseline in health domain scores to Week 12

SF-36v2 health domain	Minimal important difference[1,2]	MMRM adjusted mean change from baseline at Week 12 (95% CI)		
		Alectinib	Chemotherapy	Difference (alectinib − chemo)*
Bodily pain	± 3	+ 4.33 (2.79, 5.87)	+ 1.27 (−0.36, 2.89)	+ 3.06 (0.83, 5.30)
General health	± 2	+ 0.28 (−1.05, 1.62)	− 2.94 (−4.38, −1.50)	+ 3.23 (1.26, 5.19)
Physical functioning	± 3	− 0.86 (−2.15, 0.43)	− 0.75 (−2.12, 0.62)	− 0.11 (−1.99, 1.77)
Role physical	± 3	+ 3.46 (1.89, 5.03)	− 1.18 (−2.84, 0.47)	+ 4.64 (2.36, 6.92)
Role emotional	± 4	+ 2.75 (0.80, 4.69)	− 2.94 (−5.00, −0.89)	+ 5.69 (2.86, 8.51)
Mental health	± 3	+ 3.65 (2.06, 5.24)	− 0.31 (−1.99, 1.38)	+ 3.96 (1.64, 6.27)
Social functioning	± 3	+ 3.88 (2.26, 5.50)	− 2.17 (−3.91, −0.44)	+ 6.05 (3.68, 8.43)
Vitality	± 2	+ 2.39 (0.75, 4.03)	− 2.03 (−3.76, −0.29)	+ 4.41 (2.02, 6.80)

Improvement in HRQoL ≥ positive MID
Decline in HRQoL ≥ negative MID
Clinically meaningful difference between arms*

- Within arms, change from baseline for each health domain were compared with the respective MID:
  - With alectinib, clinically meaningful improvements from baseline were seen for most health domains
  - With chemotherapy, there were no improvements in any domains, and declines in General health and Vitality
- Clinically meaningful improvements from baseline were seen for alectinib versus chemotherapy across all health domains except Physical functioning*

CI, confidence interval; HRQoL, health-related quality of life; MID, minimal important difference; MMRM, mixed-effects model of repeated measures; *Post hoc MMRM analysis, highlighted as clinically meaningful where the 95% CI did not cross 0, not statistically tested; 1. Ware et al. SF-36v2 Administration Guide 2008; 2. Maruish et al. SF-36v2 User Manual 2011

Early improvement from baseline with alectinib, clinically meaningful improvement vs CT up to week 12

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ALINA: exploratory biomarker analyses in patients with resected *ALK*+ non-small cell lung cancer (NSCLC) treated with adjuvant alectinib vs chemotherapy

Benjamin J. Solomon,[1] Yi-Long Wu,[2] Rafal Dziadziuszko,[3] Fabrice Barlesi,[4]

- In these exploratory biomarker analyses in patients with resected *ALK*+ NSCLC from ALINA
  - Alectinib showed DFS benefit vs chemotherapy regardless of *EML4-ALK* fusion variant
  - Comparable DFS was seen regardless of *EML4-ALK* fusion variant in the alectinib arm
    - This is consistent with the findings of the ALEX trial in the metastatic setting, which showed that *EML4-ALK* fusion variants did not affect efficacy in patients with metastatic *ALK*+ NSCLC[1]
  - In the alectinib arm, patients with *TP53* mutations showed a trend towards worse DFS vs patients with WT *TP53*

Neoadjuvant Alectinib in Potentially Resectable Stage III ALK-positive NSCLC:

ALNEO Phase II Trial

ALNEO Study Design

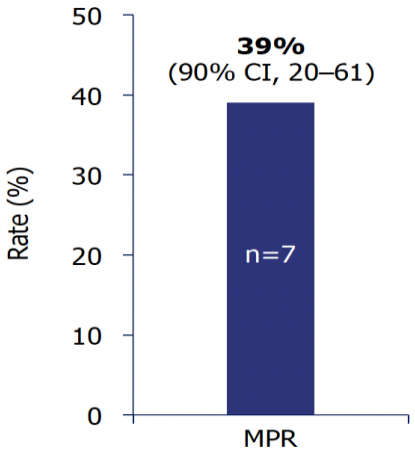
20 Italian Centers

- Resectable locally advanced stage III NSCLC
- Candidate for surgical resection after multidisciplinary discussion
- ALK positive (IHC/FISH/NGS)
- No Previous treatment
- ECOG PS 0-1

Primary Endpoint: MPR by BICR
Secondary Endpoints: pCR by BICR, OR, EFS, DFS, OS, AEs

Results – Primary Endpoint

MPR: 39%
pCR: 17%



Pathologic Response	n=18
MPR, n (%)	7 (39)
pCR, n (%)	3 (17)
No MPR, n (%)	6 (33)
Not Assessed, n (%)	5 (28)[a]

Objective Response[b]	n=25
CR, n (%)	1 (4)
PR, n (%)	19 (76)
SD, n (%)	4 (16)
PD, n (%)	1 (4)
ORR, (%)	20 (80)

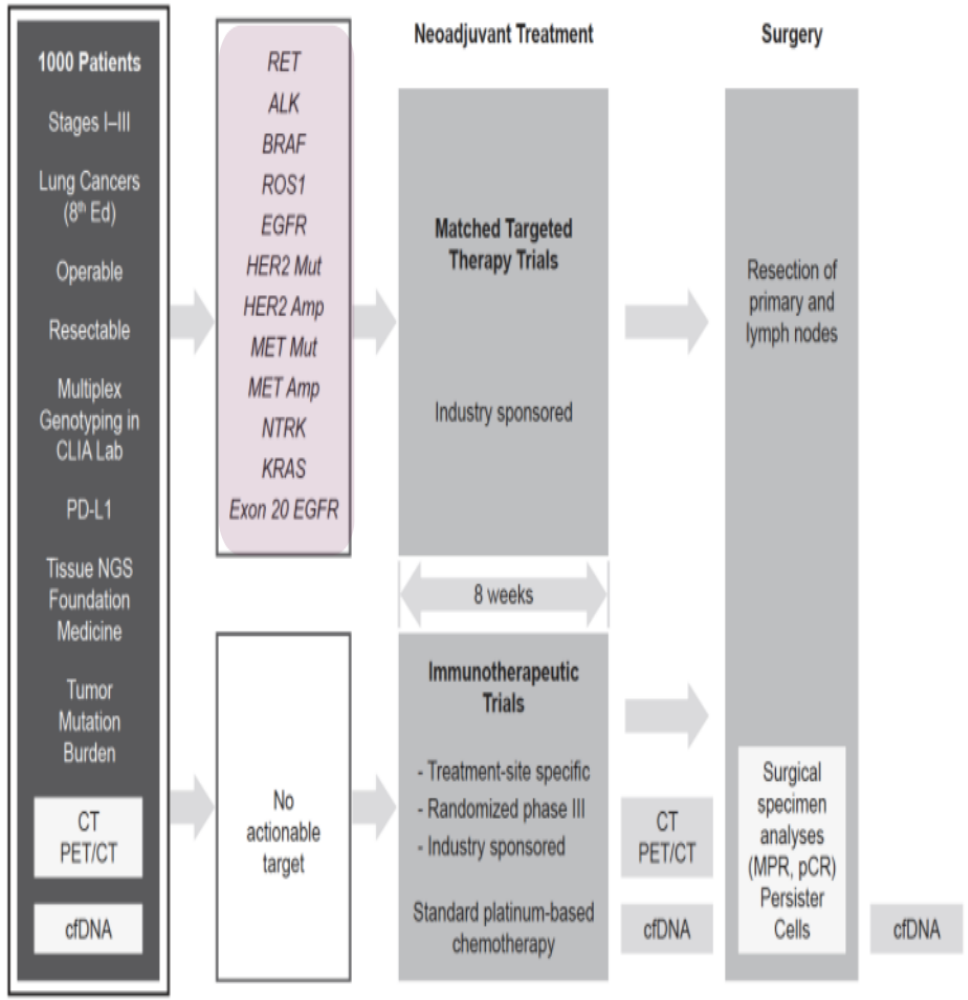
	n=25
Underwent Surgery, n (%)	21 (84)
R0, n (% of surgery)	18 (86)
Type of surgery, n (%)	
Lobectomy	17 (81)
Pneumonectomy	2 (9.5)
Other Surgery	2 (9.5)
Received adjuvant alectinib, n (% of surgery)	20 (95)[c]
Median interval from surgery, weeks (IQR)	4.5 (2.7–6.0)
Median n of cycles, n (IQR)	6 (1–20)

[a]4 patients did not undergo surgery, 1 patient underwent explorative thoracotomy; [b]at pre-surgical evaluation;
[c]2 patients received adjuvant alectinib even though surgery was not radical.

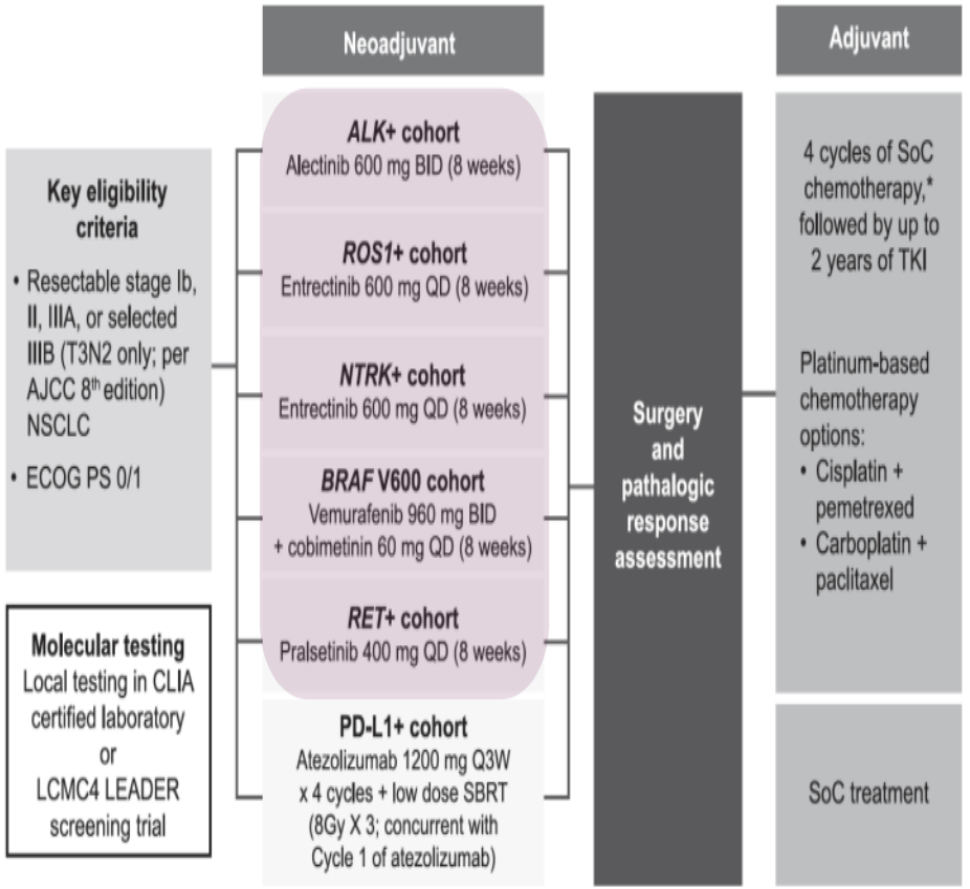
- Neoadjuvant treatment was well tolerated. G1-2 TEAEs were reported in 14 (56%) cases. No Grade ≥3 treatment-related AEs were observed;
- After a median follow-up of 10.8 months (IQR: 4.9–22.5), a total of 159 adjuvant courses were administered and the treatment appeared to be well tolerated.

Leonetti A, WCLC 2024

LCMC Leader study, neoadjuvant



NAUTIKA study, perioperative



Lee JM, JTO 2023

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Toxicity

Toxicity Profiles of ALK TKIs are distinct and manageable

Alectinib[1]	Brigatinib[2]	Lorlatinib[3]
• Constipation • Anemia • Fatigue • Blood bilirubin increased	• Diarrhea • Increased CPK level • Cough • Nausea • Hypertension • Increased AST • Back pain • Dyspnea • Headache • Increased lipase • Increased ALT • Vomiting • Fatigue Pruritus Constipation Arthralgia	• Hypercholesterolemia • Hypertriglyceridemia • Edema • Increased weight • Peripheral neuropathy • Cognitive effects • Diarrhea

**Most common AEs occurring in ≥20% of patients in ALEX, ALTA-1L, and CROWN trials are shown*

[1]Mok T et al., Ann Oncol 2020;31(8):1056-1064. [2]Camidge DR et al., J Thorac Oncol 2021;16(12):2091-2108. [3]Shaw AT et al., N Engl J Med 2020;383(21):2018-2029

Clinical Drug Investigation
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CURRENT OPINION

Expert Consensus on the Management of Adverse Events of Lorlatinib in the Treatment of *ALK*+ Advanced Non-small Cell Lung Cancer

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Accepted: 23 June 2024

- **Lorlatinib**:
  - an effective treatment
  - long-term use: AEs may occur, to ensure its efficacy and the QoL
- **Lorlatinib** has **AEs** that need to be monitored and treated appropriately to maximize drug efficacy and patient safety

Hypercholesterolemia and hypertriglyceridemia

- **Main goal**
  - LDL-cholesterol 100 mg/dl (70 mg/dl for high-risk patients; 55 mg/dl for very-high risk patients).
  - Triglycerides < 200 mg/l.
- **Determinations**
  - Before starting lorlatinib.
  - 2 weeks, 4 weeks, 2 months, and every 3-6 months later according patient's condition and how the dyslipidemia is controlled.
- **Management**
  - Baseline hypercholesterolemia should be managed based on LDL-cholesterol goals.
  - Treatment should be complemented with changes in lifestyle, adequate diet, and physical exercise.
  - For new lorlatinib induced hypercholesterolemia:
    - Mild/moderate increase in cholesterol (grade 1-2): lipid-lowering therapy + continue lorlatinib.
    - Severe increase in cholesterol (grade 3-4): lipid-lowering therapy + discontinue lorlatinib until mild/moderate toxicity is reached, then resume at lower dose.
- **First-line lipid-lowering therapy for hypercholesterolemia**
  - Mild/moderate (grade 1-2): rosuvastatin 10 mg/day orally at dinner.
  - Severe (grade 3-4): rosuvastatin 20 mg/day + ezetimibe 10 mg/day orally at dinner, with a dose increase being considered if there is no improvement.
  - If intolerance: ezetimibe ± bempedoic acid.
  - Combination of statins with other intensive lipid-lowering strategies (e.g. iPCSK9) are recommended in severe cases.
- **First-line lipid-lowering therapy for hypertriglyceridemia**
  - Fenofibrate 250 mg/day during meals if triglycerides > 200 mg/dl under statins.
  - Icosapent ethyl 2 g at breakfast and 2 g at dinner (patients with atherosclerotic cardiovascular disease and LDL-cholesterol ≤ 100 mg/dl and triglycerides > 150 mg/dl).

Arterial hypertension

- **Main goal:** < 140/90 mm Hg (< 130/80 mm Hg for high-risk patients).
- **Management**
  - Monitor blood pressure 2 weeks after initiation and at least once a month throughout treatment.
  - Grade 2 (< 160/100 mm Hg): angiotensin-converting enzyme inhibitor or angiotensin receptor blocker + continue lorlatinib → if not controlled at moderate doses add dihydropyridine calcium channel blockers → if not controlled, patient should be referred to the Cardio-Oncology clinic.
  - Grade 3-4 (≥ 160/100 mm Hg): angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and dihydropyridine calcium channel blockers → if not controlled add spironolactone → if not controlled patient should be referred to the Cardio-Oncology clinic.
  - If severe hypertension is diagnosed (systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 110 mm Hg), lorlatinib should be temporarily withheld until the blood pressure is < 160/100 mm Hg.
  - Avoid β-blockers, verapamil or diltiazem.
  - Treatment should be complemented with a low-salt diet and physical exercise.

	Initial doses	Moderate doses	Max doses
Ramipril	2.5 mg/24 h	5 mg/24 h	10 mg/24 h
Enalapril	2.5 mg/12 h	10 mg/12 h	20 mg/12 h
Candesartan	4-8 mg/24 h	16 mg/24 h	32 mg/24 h
Telmisartan	20 mg/24 h		40 mg/24 h

Hyperglycemia

- **Determinations**
  - HbA1c at baseline and every 6 months.
  - Blood glucose and the usual blood tests at baseline and every month.
- **Management**
  - Lifestyle changes, a diabetic diet, and physical exercise should be considered.
  - Grade 2: oral antidiabetic: iSGLT2s (empagliflozin, canagliflozin, dapagliflozin) and GLP1-RAs (liraglutide, semaglutide) → if not controlled, add metformin.
  - Grade 3-4 (> 250 mg/dl glucose despite treatment): insulin + discontinue lorlatinib until glycemic control is achieved and resume a reduced dose.

Neurological adverse events (Part 1)

Suggestions before initiating lorlatinib

- To know the rate of neurological toxicity related to lorlatinib.
- Check for possible factors that could increase or favor neurological toxicity (brain metastases, brain radiation, brain surgery, psychiatric disease, psychiatric medication, antiepileptics, corticoids, opioids or derivatives).
- Review the patient's drugs and change all those identified as possible potentiators of toxicity (see Table 4 of drug interactions).
- Interview with the patient and family to notify them of the possible occurrence of neurological adverse reactions and how to identify them correctly.
- Baseline study to know the starting situation:
  - MRI (or TC if not available) to establish the existing damage in the nervous system (brain metastases, leptomeningeal infiltration, vascular impairment, etc.).
  - Baseline cognitive study, either by means of anamnesis, questions to the patient/family or by means of objective quick and easy tests (e.g., Controlled Oral Word Association Test, COWAT).
  - Check for symptoms of carpal tunnel syndrome and basal peripheral neuropathy.

How to assess the occurrence of toxicity during treatment with lorlatinib

- Compare cognitive status with baseline to learn whether early dose reduction could affect toxicity in patients with a history of cognitive impairment or prior mental disease or who develop toxicity during treatment with lorlatinib. In the case of patients with brain metastases, it is suggested to repeat cranial MRI every 3 months.
- Repeat the MRI only in case of cognitive symptoms or dysarthria.
- Propose assessment by a psychiatrist or neurologist depending on the toxicity control and the personal situation of each patient.

Neurological adverse events (Part 2)

What to do if toxicity appears

- Teach the patient and family members how to proceed with each of these adverse events.
- *Peripheral neuropathy*:
  - Grade 1-2: maintain lorlatinib without changing the dose or consider a lower dose depending on the patient's profile and as clinically indicated. If grade ≥ 2, before dose reduction or discontinuation, refer the patient for neurological assessment.
  - Grade ≥ 3: discontinue lorlatinib until resolution of symptoms to grade ≤ 2 or baseline values. Then, resume at a reduced dose.
  - Treatments:
    - If associated with pain or disturbing paresthesia → duloxetine.
    - If associated with edema → diuretics.
- *Cognitive effects, mood effects, and effects on speech* (first, review again potential new medications introduced during the treatment, and the psychiatric status):
  - Grade 1: maintain or reduce the dose of lorlatinib is recommended.
  - Grade 2-3: lorlatinib should be discontinued until toxicity is grade ≤1 and lorlatinib can be resumed at a lower dose.
  - Grade 4: lorlatinib should be permanently discontinued.
  - Treatments:
    - For anxiety → benzodiazepines, avoiding alprazolam and midazolam.
    - For depression → duloxetine and agomelatine.
    - For speech effects → management based on the subjective impact experienced by the patient, reminding the pros and cons of increasing or decreasing lorlatinib dose.
    - For psychosis/mania/hallucinosis → olanzapine is recommended; avoid quetiapine and ziprasidone because of interactions with lorlatinib. Risperidone and clozapine should be used with caution.

Edema

- Monitor edema at each visit.
- **Grade < 3:**
  - Physical measures (leg elevation, moderate exercise or compression stockings).
  - Delay the use of diuretics as late as possible.
  - If diuretic is needed → furosemide 20-40 mg/day (take care if hypokalemia or renal insufficiency).
  - Maintain lorlatinib, although it should be taken into account how it may affect the patient's quality of life.
  - N-terminal pro-brain natriuretic peptide (NT-proBNP) assessment.
- **Grade ≥ 3:**
  - NT-proBNP assessment + echocardiogram to rule out other causes.
  - Discontinue lorlatinib until resolution of symptoms to grade ≤ 2 or baseline values, then resume at lower doses. If there are doubts about the existence of associated heart failure, an electrocardiogram and echocardiogram should be considered. Then resume treatment with reduced dose lorlatinib.

Diarrhea, nausea, vomiting, constipation

- **Grade < 3:**
  - Maintain lorlatinib or reduce dose if clinically indicated.
  - If grade 2 diarrhea is sustained over time (15-30 days), and interferes with daily life, reduce lorlatinib dose.
- **Grade ≥ 3:**
  - Discontinue lorlatinib until resolution of symptoms to grade ≤ 2 or baseline values, then resume at a reduced dose.
- **Treatments:**
  - Diarrhea → loperamide (initially two tablets [4 mg] and then one [2 mg] for each additional bowel movement up to a maximum of 8 tablets [16 mg]).
  - Constipation → lactulose.
  - Nausea and vomiting → recommended treatment for this level of emesis and the next level include metoclopramide, domperidone or chlorpromazine or 5-HT3 inhibitors such as ondasetron, granisetron or dolasetron.

Interstitial lung disease/pneumonitis

- **Diagnosis:**
  - Clinical evaluation (new pulmonary symptoms or worsening of existing ones, such as dyspnea, cough, chest pain, hypoxia).
  - Imaging tests (to consider other etiologies, such as pneumonia, heart failure or metastatic disease).
  - Biopsy only to rule out an infectious process.
  - Check if the patient has history of pulmonary disease, have undergone previous radiotherapy or have received immunotherapy.
- **Treatment:**

Grade 1:
- Observation
- Stop lorlatinib and then resume at the same dose
- CT scan at 6 weeks

Grade 2:
- Stop lorlatinib
- Oral corticosteroid (1 mg/kg/day)
- Imaging tests
- If improvement occurs after 3-4 weeks, resume lorlatinib at the same dose
- If the patient is receiving corticosteroids, a reduced dose of lorlatinib of 75 mg/day would be used

Grade 3:
- Hospitalization
- Lorlatinib should be permanently discontinued
- Intravenous corticosteroids (1-2 mg/kg/day)

Grade 4:
- ICU admission
- Lorlatinib should be permanently discontinued
- Intravenous corticosteroid (2 mg/kg/day) and other treatments as needed
- Not to exceed the maximum dose of corticoids (prednisone) of 80 mg/day

- If there is **intolerance to a corticosteroid**, another corticosteroid with equivalent dose should be considered.
- If the patient is going to be treated with high doses of corticosteroids for a prolonged period, it is suggested to perform a **prophylaxis** against:
  - *Pneumocystis jirovecii*
    - Indication:
      - Prednisone (or equivalent) ≥ 30 mg/day for ≥ 4 weeks.
      - Prednisone ≥ 15 mg/day and < 30 mg/day for ≥ 8 weeks (uninterrupted or intermittent).
      - Prednisone ≥ 10 mg/day for ≥ 4 weeks and ≥ 2 risk factors: age >65, coexisting lung disease (lung cancer, COPD, fibrosis...), use of immunotherapy (rituximab, anti-TNF), ECOG ≥ 3, malnutrition, diabetes.
    - Management:
      - Cotrimoxazole 800/160 mg every 48 hours or 400/80 mg per day.
      - Alternatively, inhaled pentamidine 300 mg/month, atovaquone 1500 mg/day or dapsone 100 mg/day.
    - Duration:
      - At least 4-6 weeks after the tapering period of corticosteroids.
  - Tuberculosis
    - Indication:
      - Prednisone ≥ 10 mg/day for ≥ 4 weeks.
    - Management:
      - Screening for latent tuberculosis is recommended, by IFN-γ test (preferred over tuberculin skin test).
      - If positive, consultation with an infectious disease specialist is recommended.

Conclusions

1. Follow the guidelines of the **product data sheet**, but also **individually** to reduce the dose of lorlatinib to avoid *possible drug interactions* with concomitant treatments or to prevent *worsening of the patient's QoL*
2. Some severe toxicities, that are **laboratory findings** with no symptomatology (e.g., amylase elevation grade ≥3), may not require discontinuation of treatment or may be left to physician's discretion
3. **Current clinical context** of what is known, and **other possible causes** must be ruled out.
4. **Patient / family education** and **direct communication**
5. AEs of lorlatinib can affect different organs and systems, participation of a **MDT**: cardiologists, neurologists, internal medicine specialists, and oncology pharmacists

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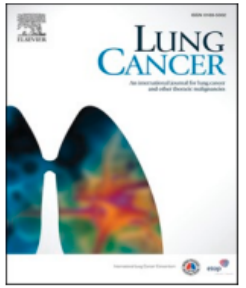

Review article

A pragmatic guide for management of adverse events associated with lorlatinib

Geoffrey Liu [a,*], Julien Mazieres [b], Jan Stratmann [c], Sai-Hong Ignatius Ou [d], Tony Mok [e], Mary Grizzard [f], Yasushi Goto [g], Enriqueta Felip [h], Benjamin J. Solomon [i], Todd M. Bauer [f]

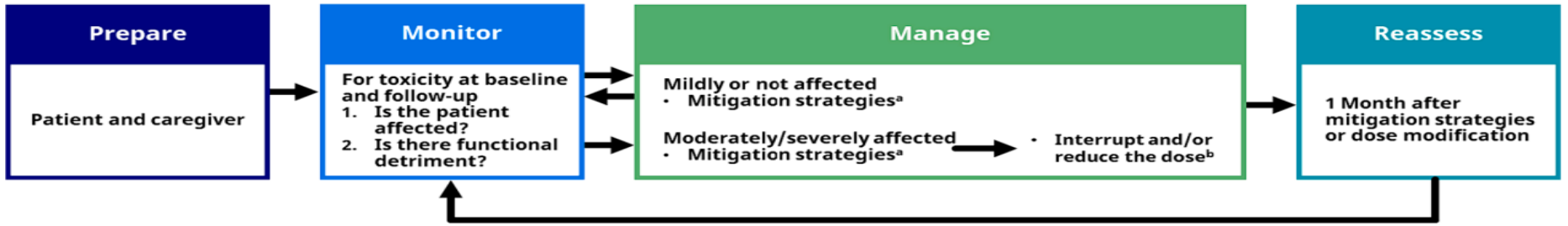

Fig. 1. General management of lorlatinib toxicities: prepare, monitor, manage, reassess. [a]See Fig. 3A and B and Table 2 for details. [b]Interrupt refers to a temporary dose interruption. Reduce refers to dose reduction.

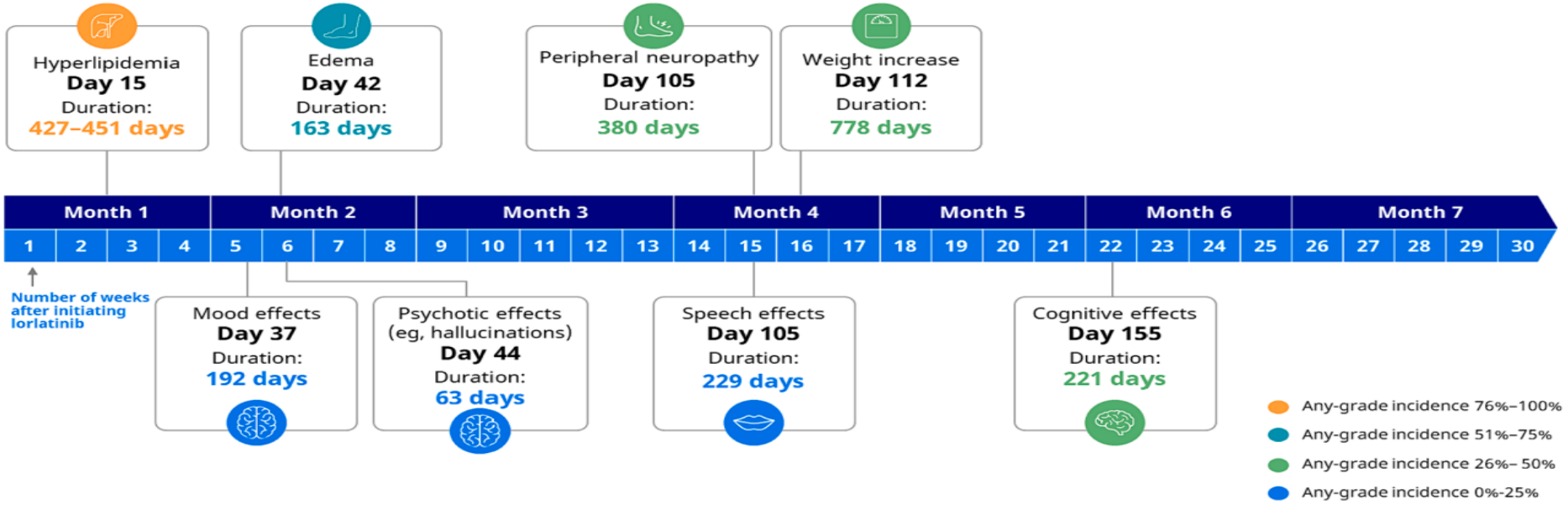

Fig. 2. Typical timeline of lorlatinib select adverse events.[a] [a]The values listed here represent median time to first occurrence for each AE. There is a distribution in which some may occur earlier or later than these median values.[12–14,18,27].

Liu G, Lung Cancer 2024

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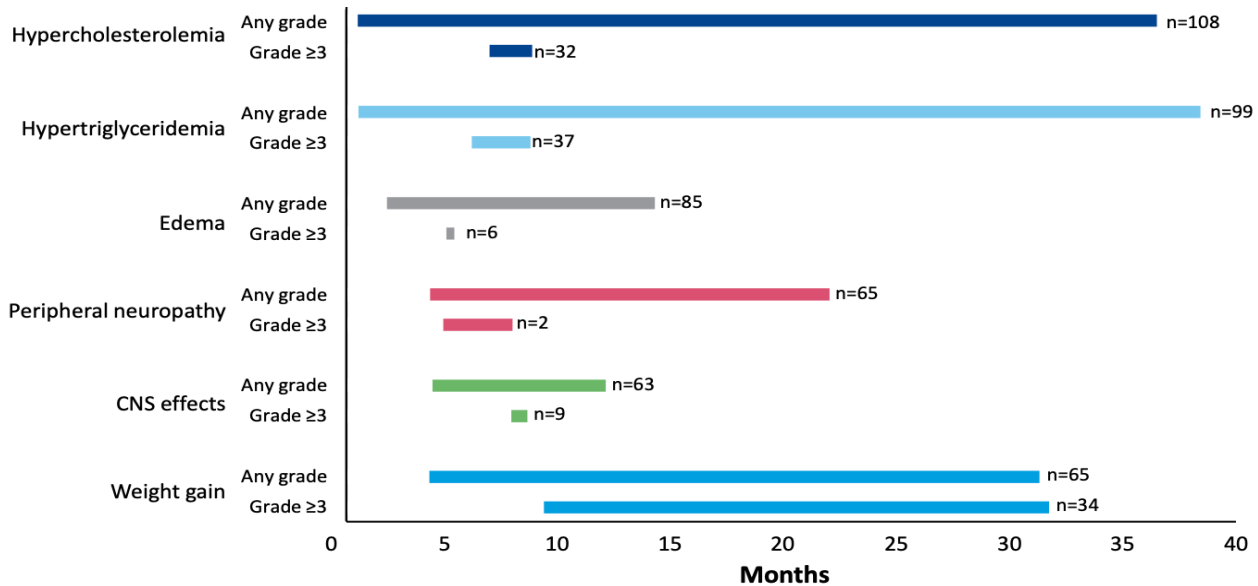
Kinetics and Management of Adverse Events Associated With Lorlatinib After 5 Years of Follow-Up in the CROWN Study

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]

Time to Onset and Duration of AEs

- For hyperlipidemia, median time to onset of any-grade AEs was 15 days, and median duration was ≈37 months; median time to onset of grade ≥3 AEs was ≈6 months
- For any grade edema, peripheral neuropathy, and CNS effects, median time to onset was 2-4 months, and median duration was 8-18 months
- Only weight gain showed grade ≥3 AE that lasted more than 3 months



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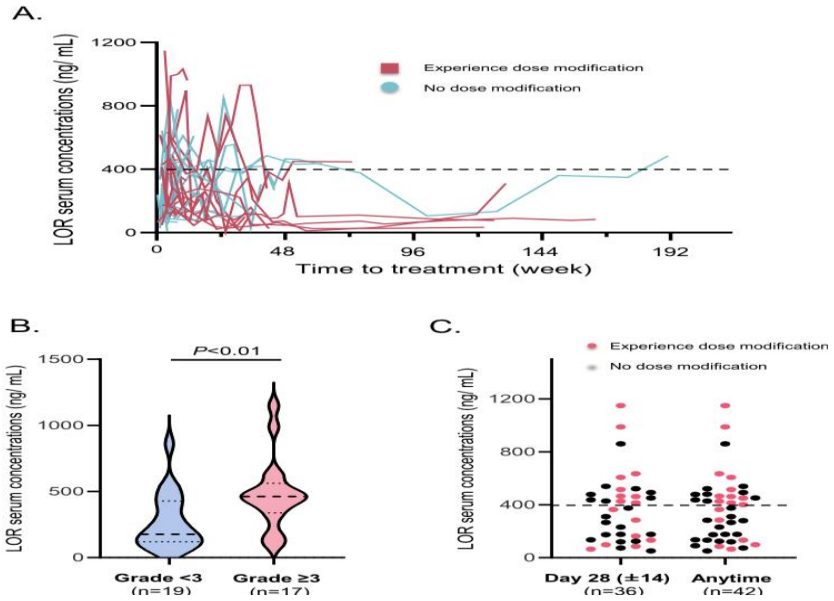
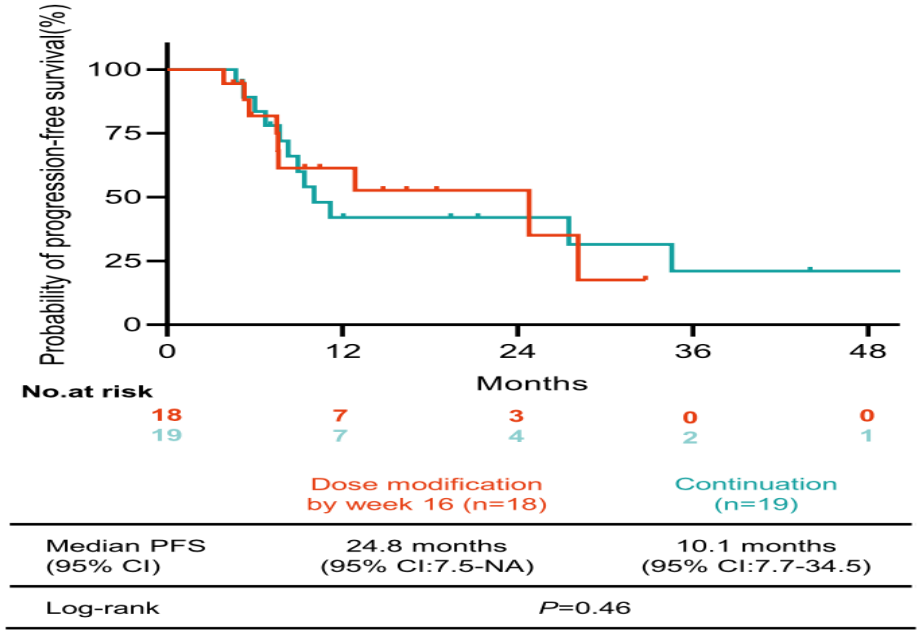
Research Paper

Association between lorlatinib blood concentration and adverse events and clinical impact of dose modification

Yukiko Shimoda Igawa [a], Tatsuya Yoshida [a,b,*], Reiko Makihara [c], Masahiro Torasawa [a],





	Dose modification by week 16 (n=18)	Continuation (n=19)
Median PFS (95% CI)	24.8 months (95% CI:7.5-NA)	10.1 months (95% CI:7.7-34.5)
Log-rank	*P*=0.46	

CONCLUSIONS: We suggest that **lorlatinib** be administered with **dose monitoring** to ensure **safe** and **effective treatment**, especially for **high-grade AEs**

Gracias

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