Trattamento della malattia ALK-positiva

S.C. Oncologia Medica – Ospedale Santa Maria della Misericordia,

Azienda Ospedaliero-Universitaria di Perugia

Carcinoma del polmone: quali novità nel 2024?

Verona – 28 Ottobre 2024

AGENDA

- Where are we now
- Current clinical data
- The issue of progressing disease
- Novel approach on the horizon

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Are we curing some patients with oncogene disease?

Survival past five years with advanced, *EGFR*-mutated or *ALK*-rearranged non-small cell lung cancer—is there a "tail plateau" in the survival curve of these patients?

Shoko Sonobe Shimamura, Takehito Shukuya*, Tetsuhiko Asao, Daisuke Hayakawa, Kana Kurokawa, Shiting Xu, Keita Miura, Yoichiro Mitsuishi, Ken Tajima, Rina Shibayama, Naoko Shimada, Fumiyuki Takahashi and Kazuhisa Takahashi

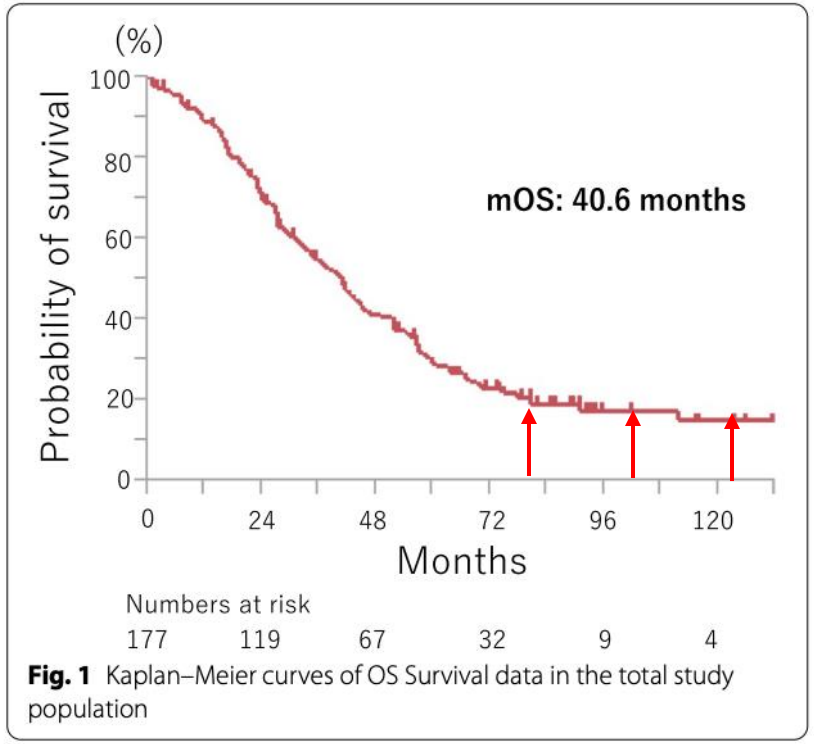
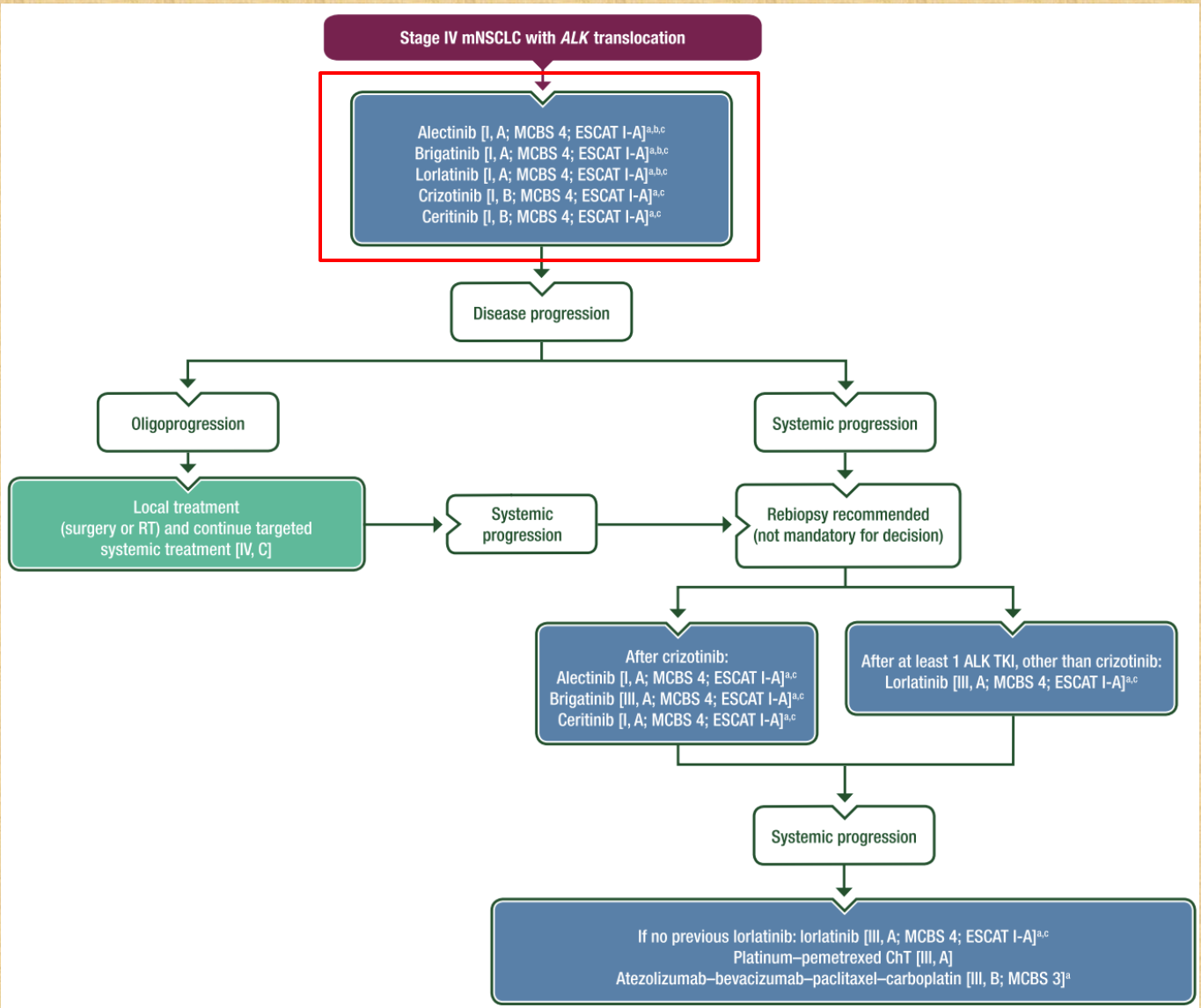


Fig. 1 Kaplan–Meier curves of OS Survival data in the total study population

Shimamura et al. BMC Cancer 2024

First-line ALK-TKIs options



- **Crizotinib** and **ceritinib** clearly «old generation» drugs
- **Brigatinib** suffers from EMA label of lorlatinib which restricts second-line use after alectinib or ceritinib
- **Ensartinib** not mentioned because only FDA (and China) approved in march 2024
- **Alectinib** and **Lorlatinib** most widely used supported by ALEX and CROWN phase 3 randomized trials versus crizotinib

Hendriks et al. Ann Oncol 2022

Did we need a new ALK inhibitor compared with crizotinib?

Key patient inclusion criteria
- Locally advanced or metastatic NSCLC
- ALK+
- No prior therapy
- ECOG PS 0–2

(n=275)

R 1:1

Foritinib 160 mg/day q3w (n=139)

Crizotinib 250 mg BID q3w (n=136)

Stratification
- ECOG PS (0/1 vs. 2)
- CNS metastases (yes vs. no)

PD/toxicity/ withdrawal/ death

Primary endpoint
- PFS (IRC assessed)

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

Outcomes	Foritinib (n=139)	Crizotinib (n=136)
ORR, n (%) [95%CI]	129 (92.8) [87.2, 96.5]	110 (80.9) [73.3, 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)

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)

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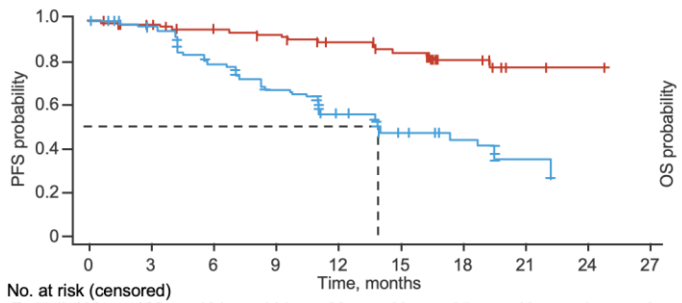
Progression-free survival

	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	

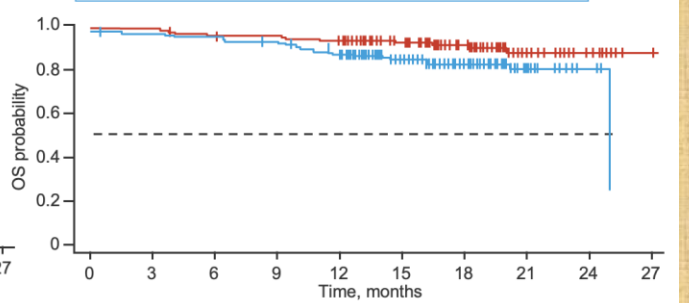


No. at risk (censored)

Foritinib	139 (0)	129 (7)	121 (12)	114 (16)	86 (40)	63 (59)	35 (85)	12 (107)	4 (115)	0 (119)	
Crizotinib	136 (0)	123 (10)	94 (18)	77 (21)	47 (39)	29 (51)	15 (64)	6 (70)	0 (75)	0 (75)	

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	



Foritinib	139 (0)	136 (1)	131 (2)	130 (3)	127 (3)	92 (37)	65 (63)	24 (102)	8 (118)	1 (125)	
Crizotinib	136 (0)	133 (2)	131 (2)	127 (3)	117 (5)	81 (38)	57 (62)	19 (98)	5 (112)	0 (116)	

Xiong et al. WCLC 2024

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer

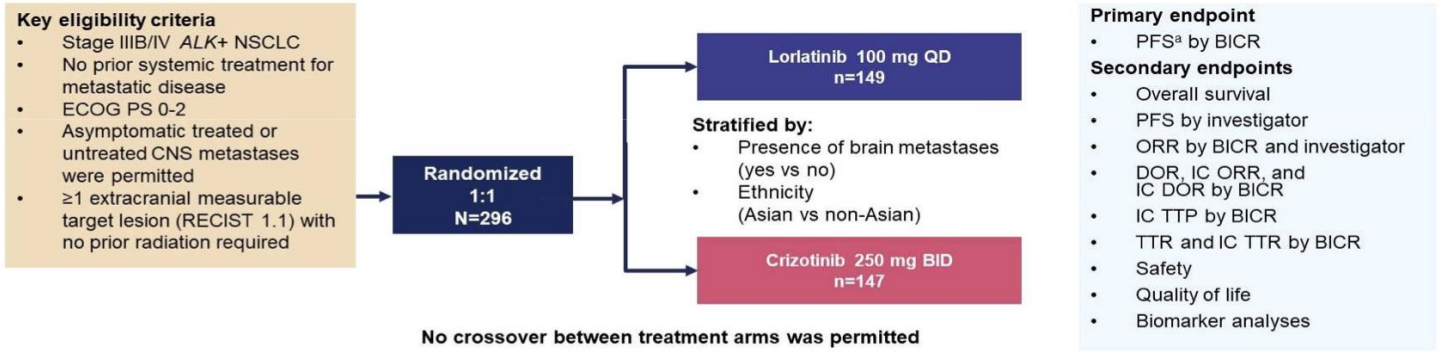
Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D., Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D., Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D., Gerson Peltz, M.D., M.P.H., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the CROWN Trial Investigators*

Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, *ALK*-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study

THE LANCET Respiratory Medicine

Prof Benjamin J Solomon, MBBS PhD [a] · Todd M Bauer, MD [b] · Prof Tony S K Mok, MD [c] · Prof Geoffrey Liu, MD [d] · Prof Julien Mazieres, MD [e] · Filippo de Marinis, MD [f] · Yasushi Goto, MD [g] · Prof Dong-Wan Kim, MD PhD [h] · Prof Yi-Long Wu, MD [i] · Prof Jacek Jassem, MD [j] · Froylán López López, MD [k] · Ross A Soo, MBBS PhD [l] · Alice T Shaw, MD PhD [m,†] · Anna Polli, BS [n] · Rossella Messina, PhD [n] · Laura Iadeluca, PhD [o,†] · Francesca Toffalorio, MD PhD [n] · Prof Enriqueta Felip, MD [p] Show less

CROWN: A Randomized Global Phase 3 Study

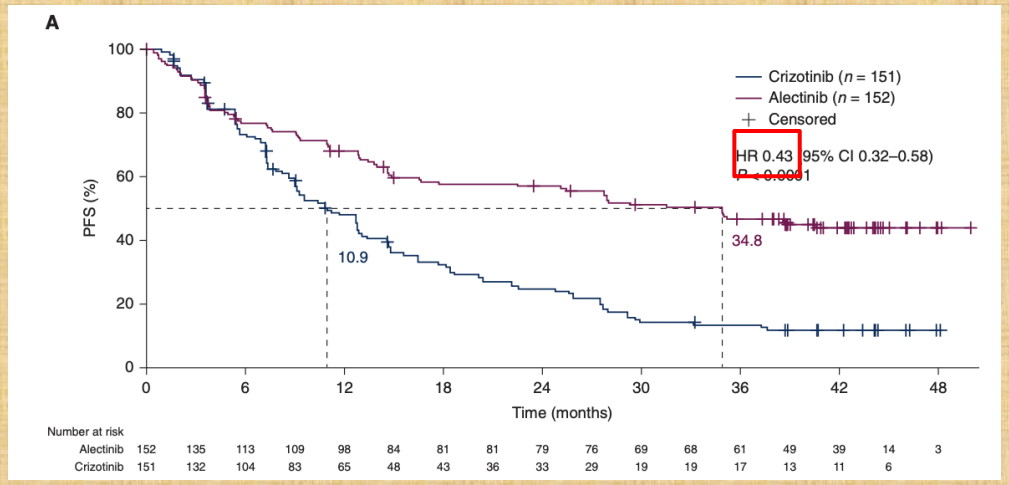


- **At the planned interim analysis, at 18.3 months of median follow-up in the lorlatinib arm, median PFS by BIRC was not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib, with an HR of 0.28 (95% CI, 0.19-0.41) and P<0.001[1]**
- **In a subsequent post-hoc analysis, at 3 years of follow-up, median PFS by BIRC was still not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (HR, 0.27 95% CI, 0.18-0.39)[2]**

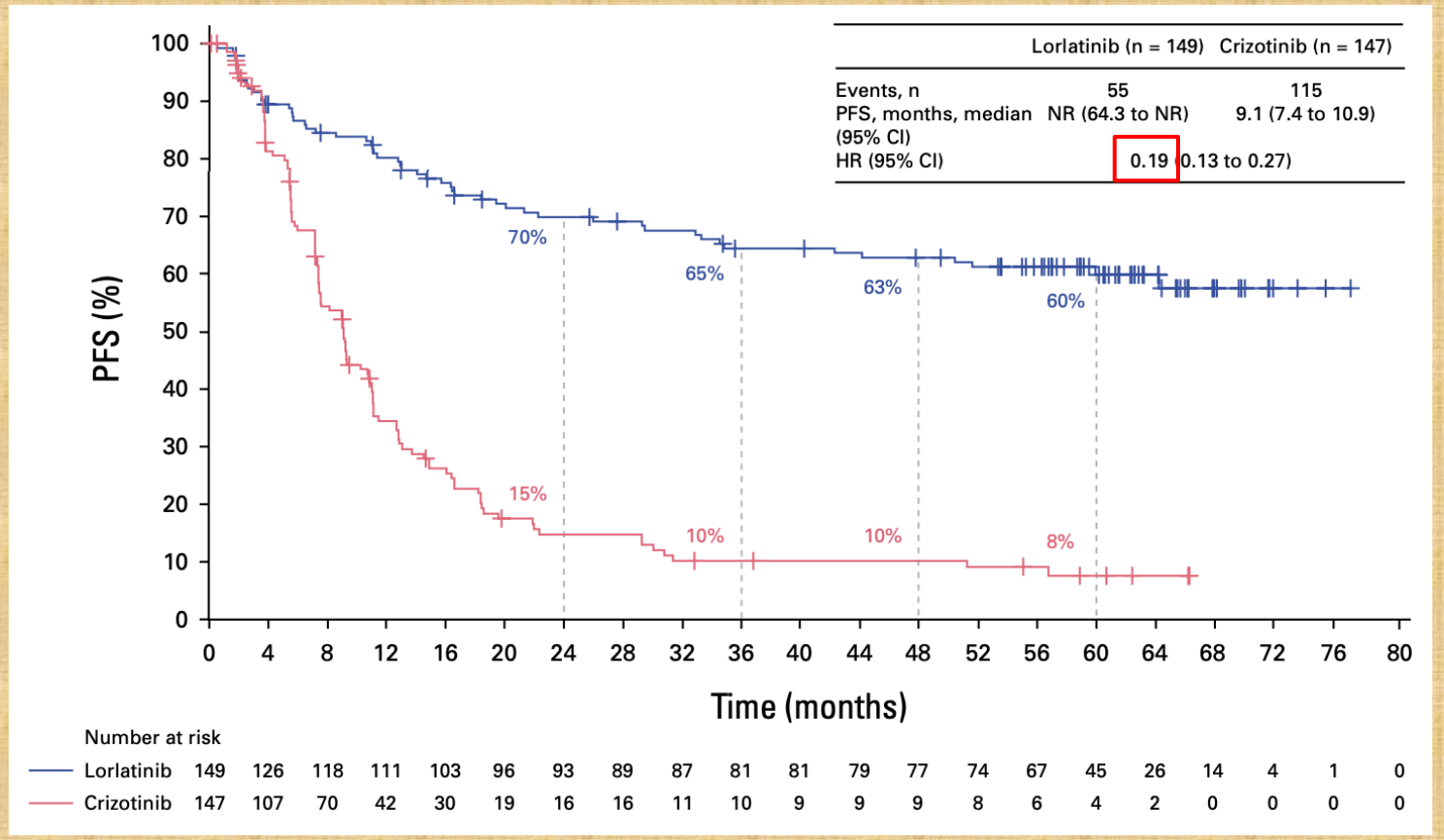
[1]Shaw et al. NEJM 2020; [2]Solomon et al. Lancet Respir Med 2023; Solomon et al. J Clin Oncol 2024

PFS: ALEX vs CROWN

Alectinib in ALEX: at a median follow-up of 48.2 months, mPFS 34.8 months – 5-yr PFS 35%



Lorlatinib in CROWN: at a median follow-up of 60.2 months mPFS not reached – 5-yr PFS 60%



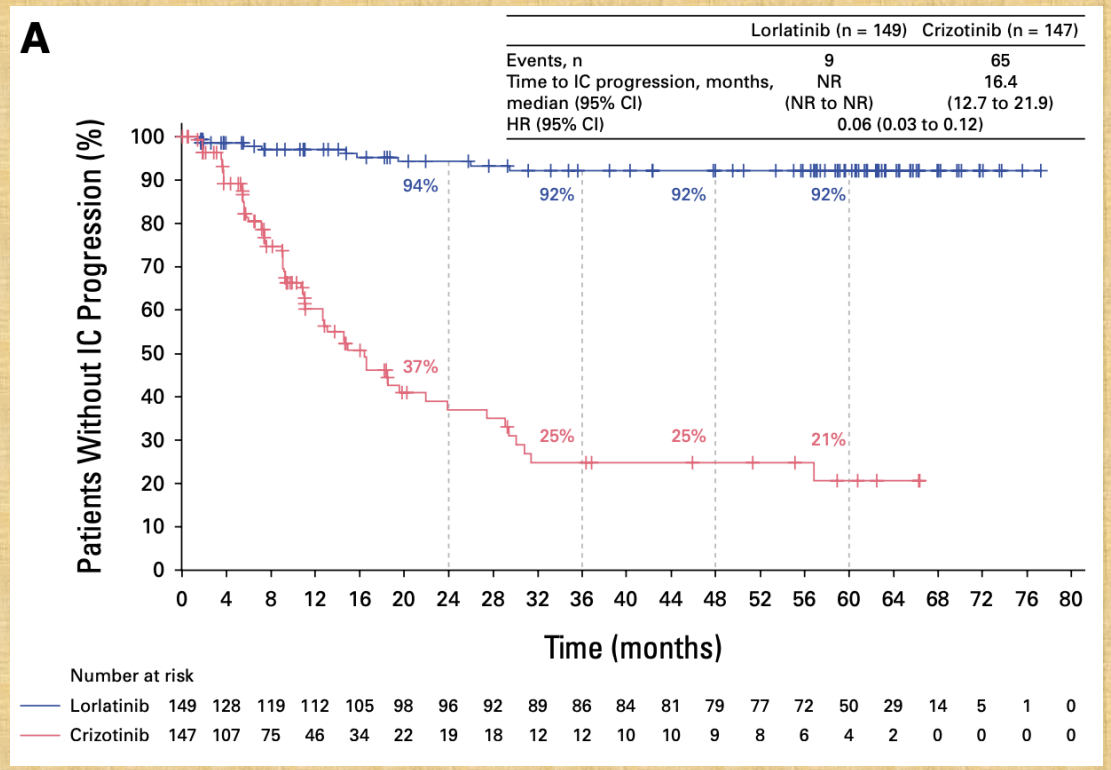
Mok et al. Ann Oncol 2020
Solomon et al. J Clin Oncol 2024

Study patients: ALEX vs CROWN

	ALEX	CROWN
	Alectinib vs crizotinib	Lorlatinib vs crizotinib
N	303	296
Asian	45%	44%
Screening brain mets	+	+
Baseline brain mets	40%	27%
Previous brain RT	14%	6%
Follow-up baseline brain imaging	mandatory in all pts	mandatory in all patients

CROWN: intracranial efficacy and safety

Time to intracranial progression was longer with lorlatinib than crizotinib (ITT population)

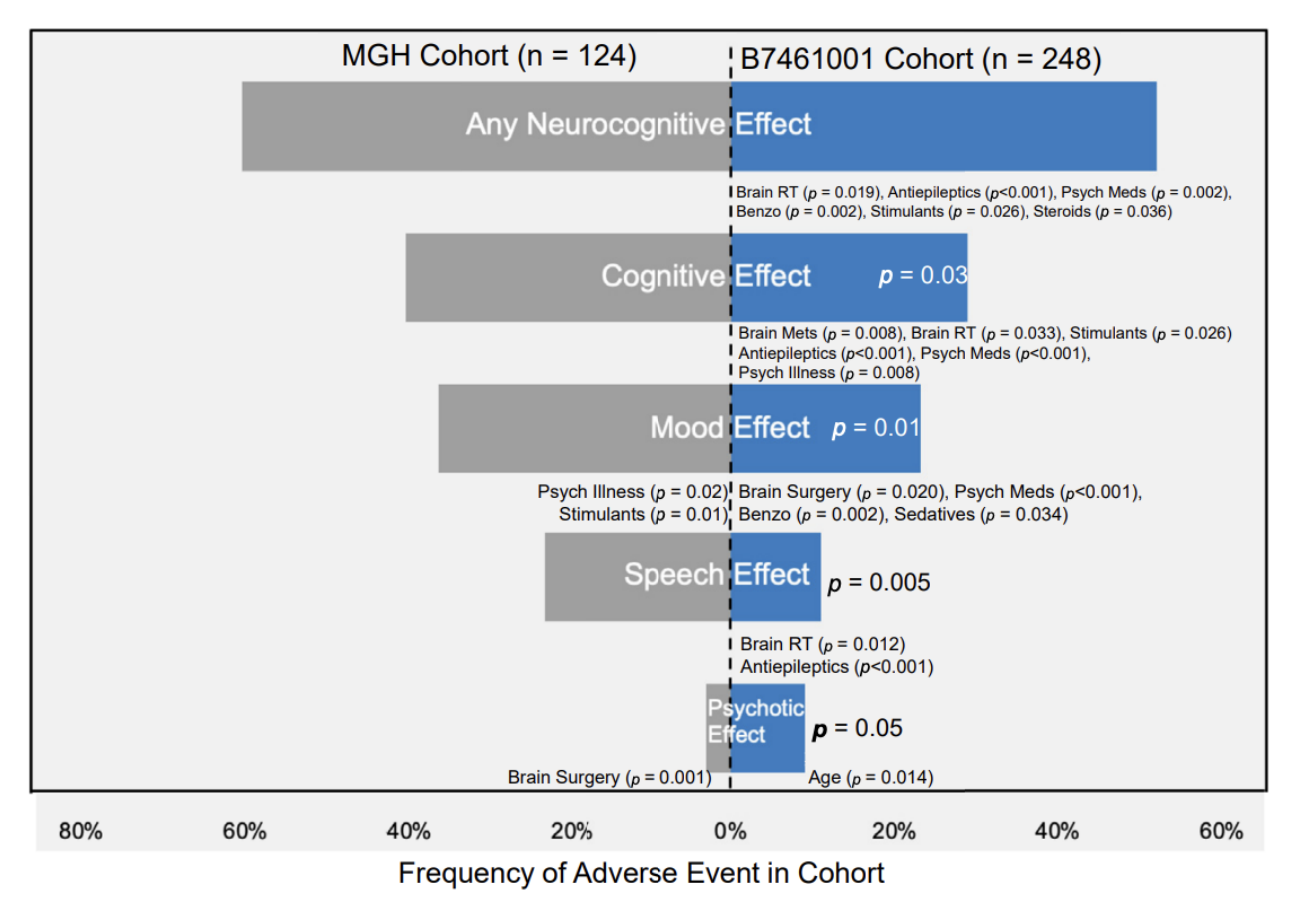


Lorlatinib adverse events

Adverse drug reactions	Lorlatinib (n = 149)	
	Any grade	Grade 3/4
Hypercholesterolemia	72%	19%
Hypertriglyceridemia	66%	23%
Edema	56%	4%
Weight increase	44%	20%
Peripheral neuropathy	40%	1%
Cognitive effects	26%	3%
Arthralgia	26%	1%
Hypertension	22%	11%
Diarrhea	22%	1%
Fatigue	19%[a]	1%[a]
Mood effects	17%	1%
Speech effects	5%	1%
Psychotic effects	5%	1%

Solomon et al. J Clin Oncol 2024
Solomon et al. Lancer Respir Med 2023

Can we predict the onset of neurocognitive adverse events?



Neurocognitive effects from lorlatinib are common. Lorlatinib-related NAEs may be influenced by multiple factors, including brain metastases, brain radiation, psychiatric illness, and use of neurotropic medications

Dagogo-Jack et al. J Thorac Oncl 2022

The Oncologist®

Lung Cancer

Clinical Management of Adverse Events Associated with Lorlatinib

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Lorlatinib • Non-small cell lung cancer • Safety • Drug therapy ma

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REVIEW

Recent Advances in the Management of Adverse Events Associated with Lorlatinib

ng Yan[1], Shanshan Chen[1], Wei Li[1], Dangang Shangguan[1,*], Zhihua She[3,*]

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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

Edurne Arriola[1] · Javier de Castro[2] · Rosario García-Campelo[3] · Beatriz Bernárdez[4] · Reyes Bernabé[5] · Jordi Bruna[6] · Manuel Dómine[7] · Dolores Isla[8] · Óscar Juan-Vidal[9] · Teresa López-Fernández[10] · Ernest Nadal[11] · Delvys Rodríguez-Abreu[12] · María Vares[13] · Úrsula Asensio[14] · Luis F. García[14] · Enriqueta Felip[15]

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anagement of adverse events associated

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Guidelines on the management of neurological AEs

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.

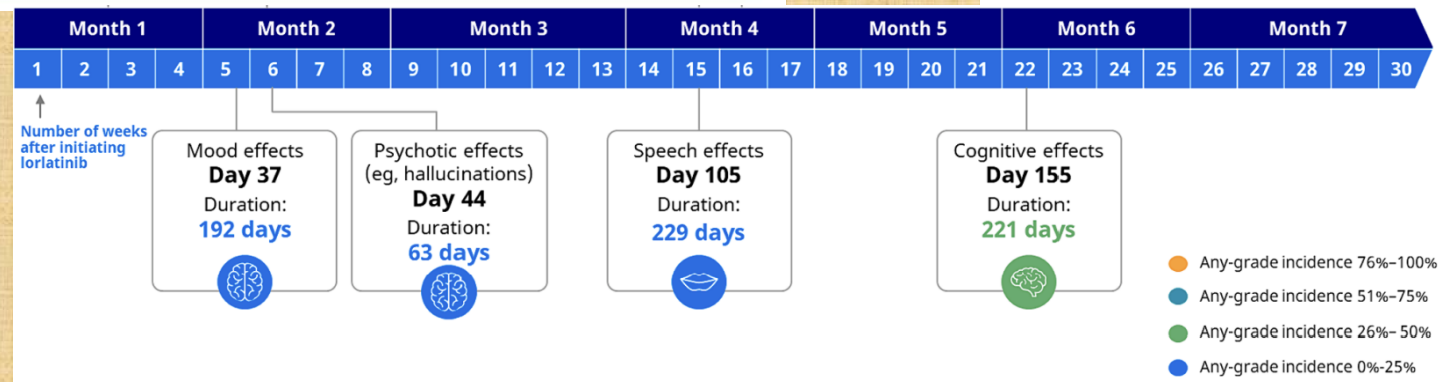
How to assess the occurrence of toxicity during treatment with lorlatinib

- 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)

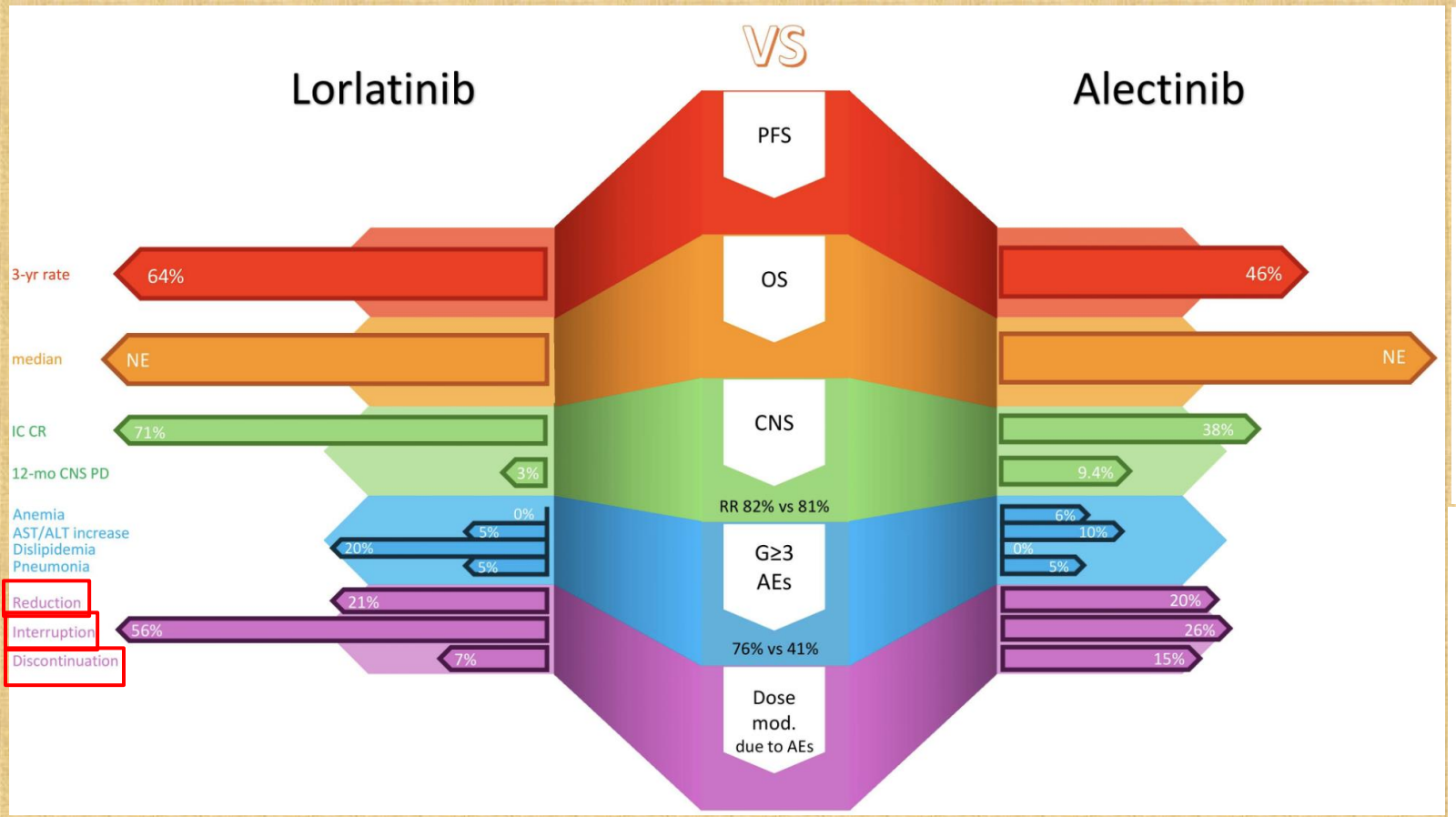
What to do if toxicity appears

- 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.

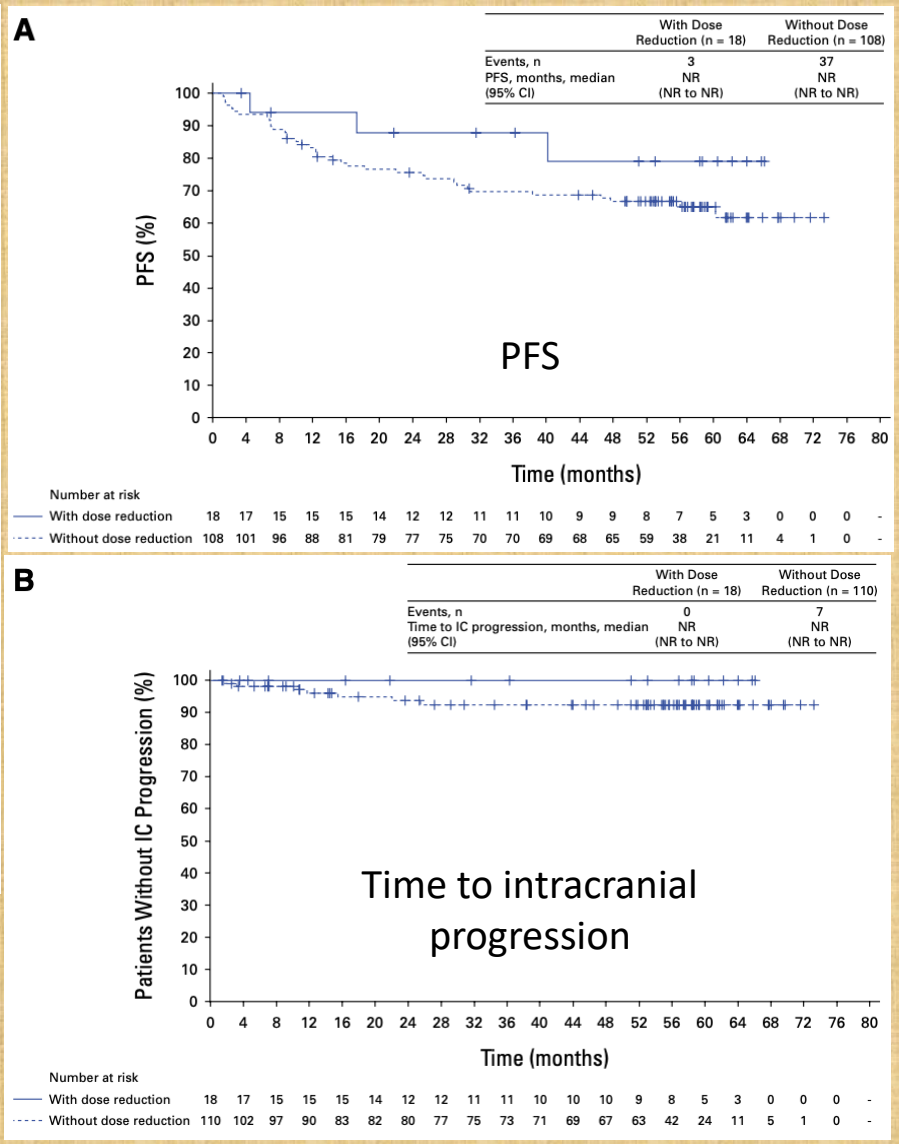


Arriola et al. Clin Drug Invest 2024
Liu et al. Lung Cancer 2024

Lorlatinib vs alectinib



Impact of dose reduction in the first 16 wks

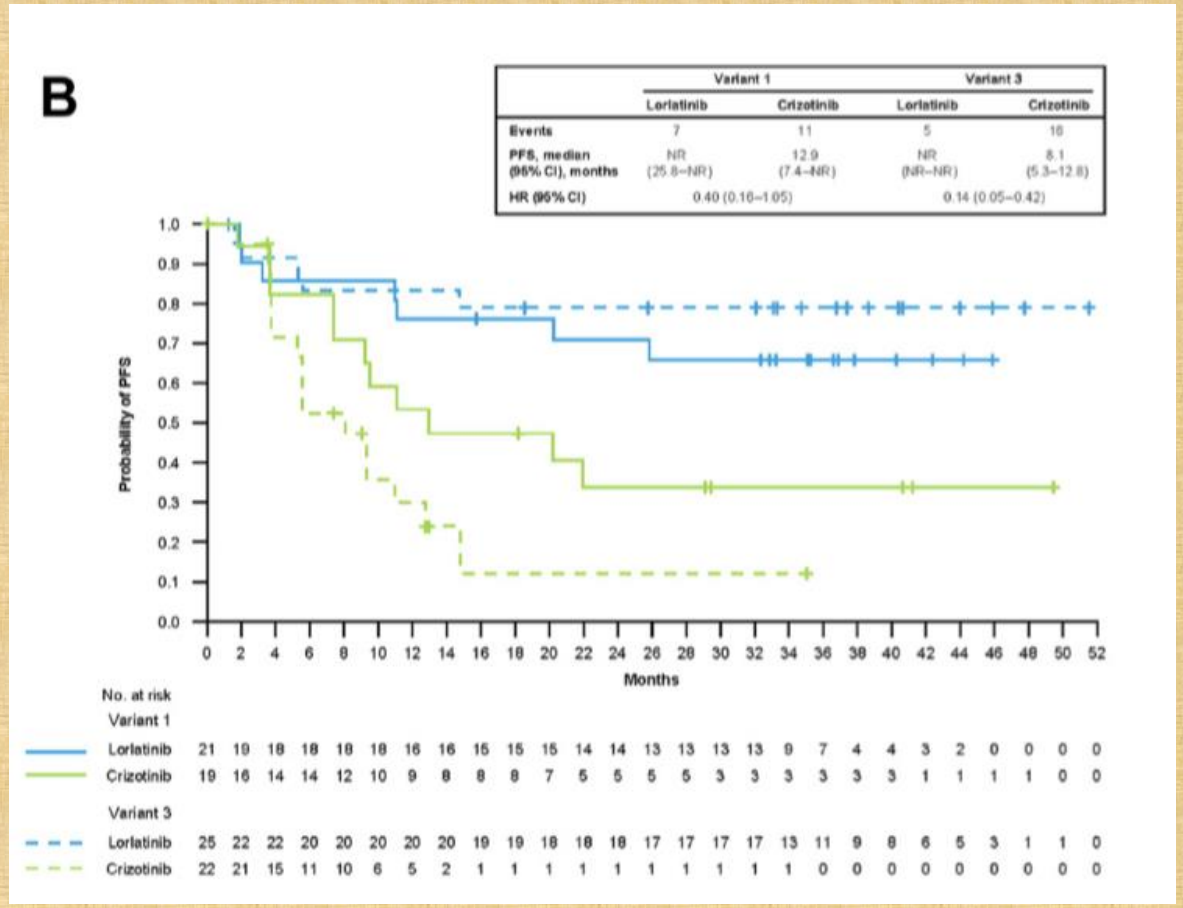


Attili et al. Cancers 2024

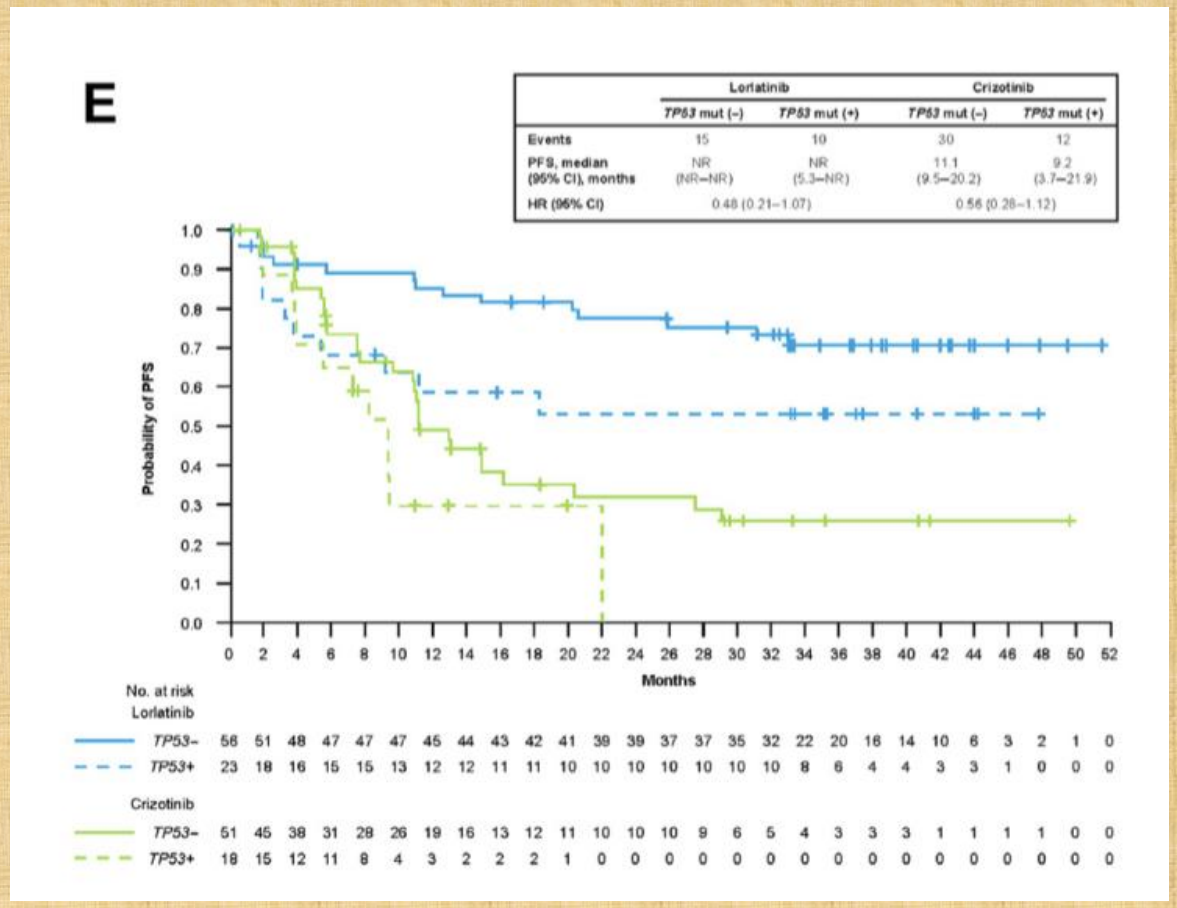
Solomon et al. J Clin Oncol 2024

TP53 rather type of variant impact on prognosis

Variant 1 vs variant 3



TP53 present vs absent



Bearz et al. J Thorac Oncol 2023

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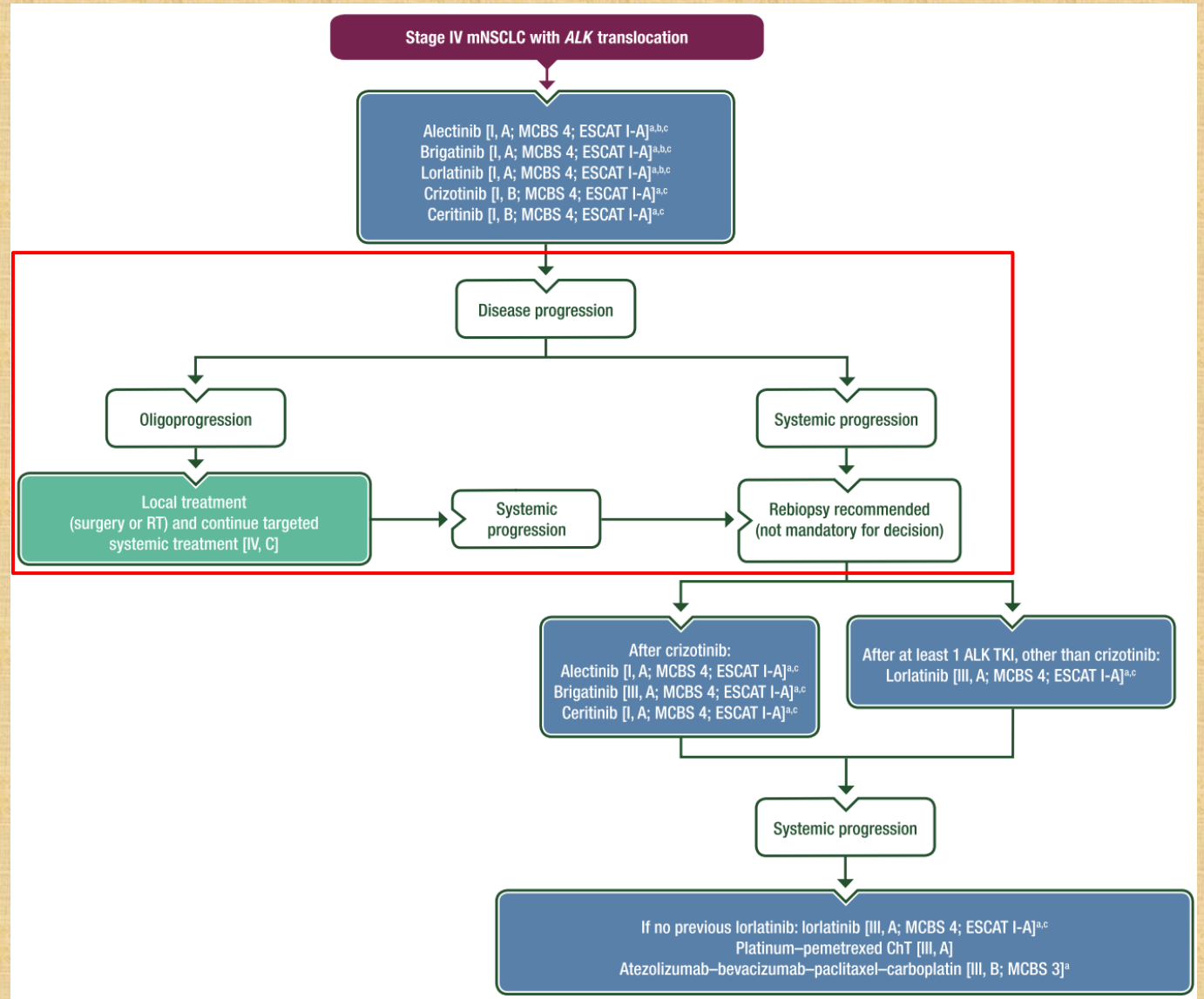
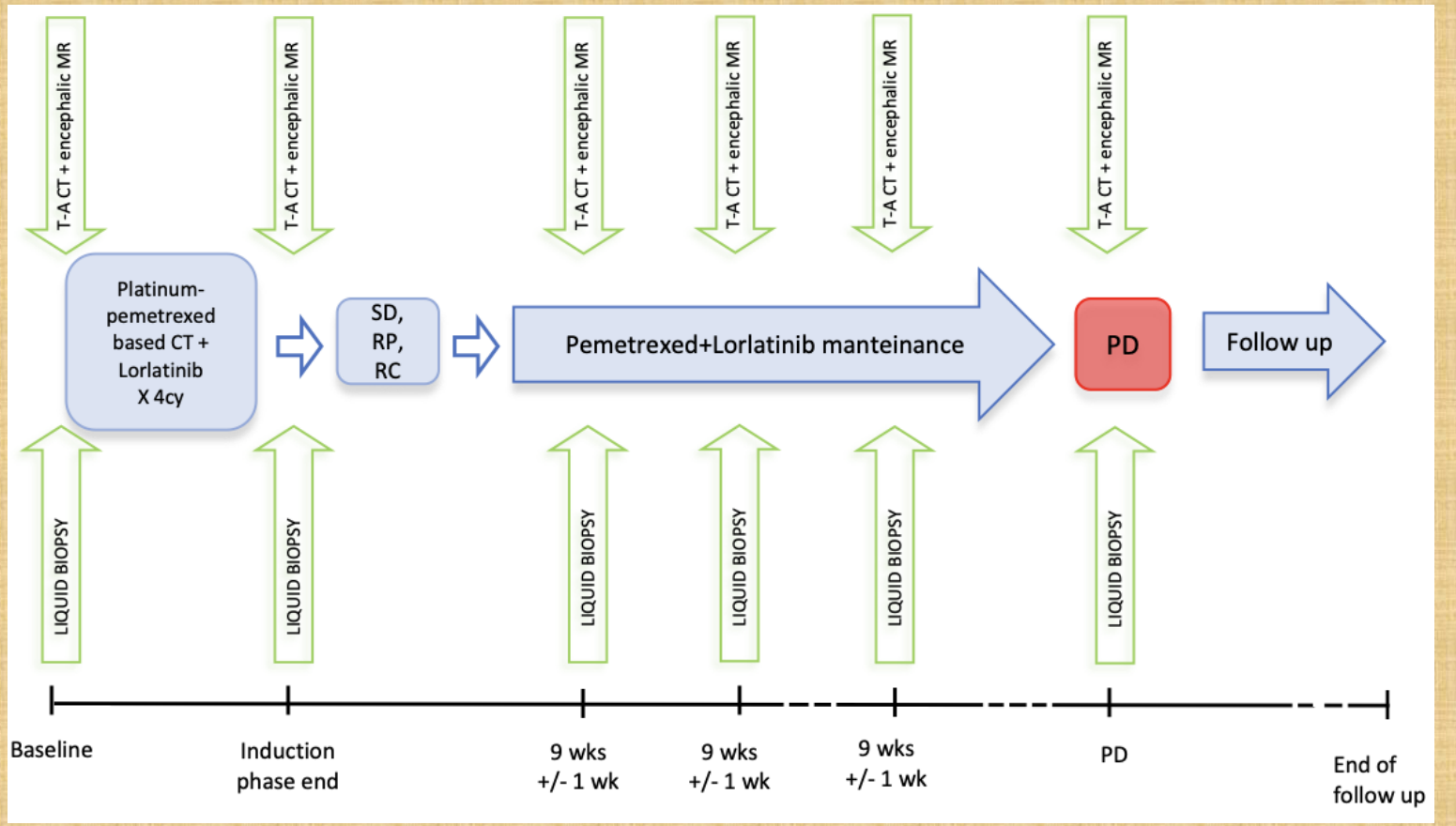
Management of ALK-TKI pretreated disease



- The **type of first-line agent** used impacts on treatment decision
  - If a 2nd gen. agent in 1st line > **lorlatinib**
  - If lorlatinib in 1st line > **platimum/pemetrexed**
- **Rebiopsy has a poor impact** on treatment decision
- **The type of disease progression** (oligo- vs systemic vs extra-cranial only) has an important impact on treatment decision

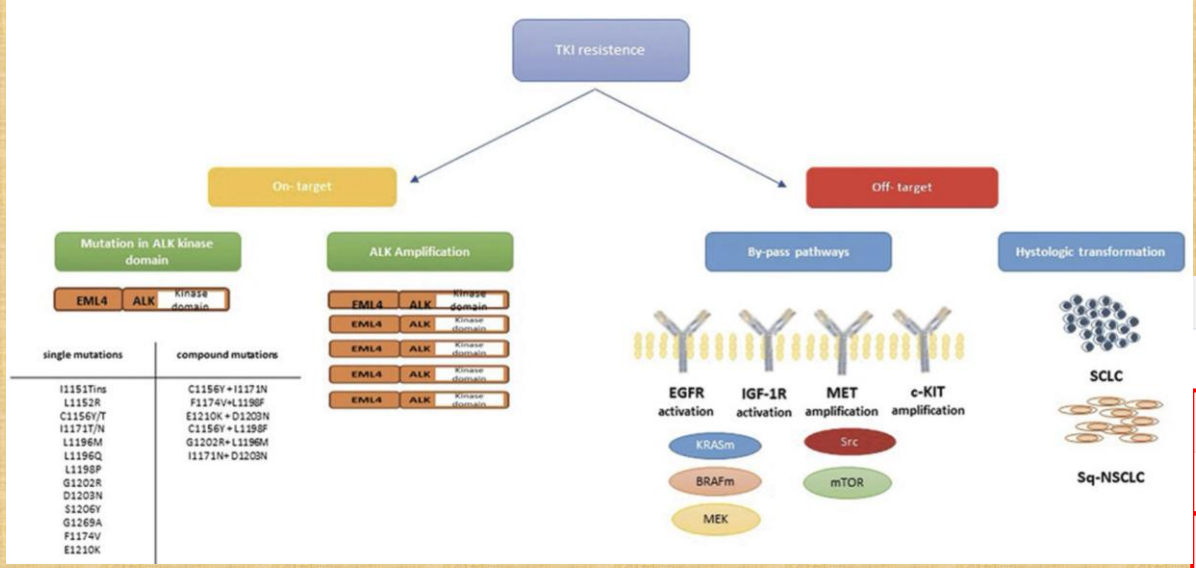
Hendriks et al. Ann Oncol 2022

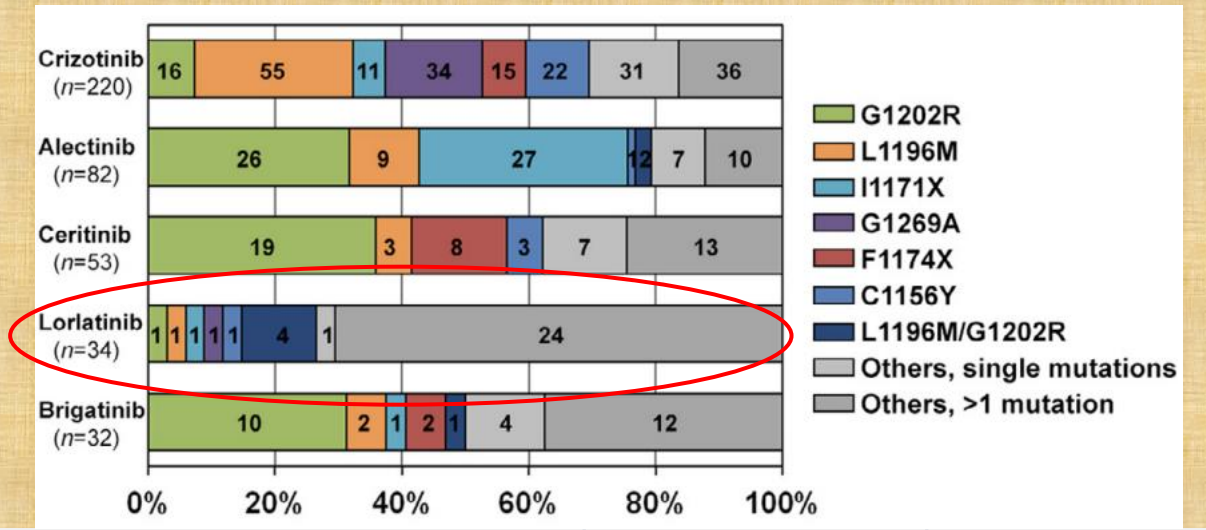
Extracranial progression only on lorlatinib: treatment beyond progression + platinum/pemetrexed?



NCT06378892

First-line treatment influences resistance mechanisms





Resistance Mechanism	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)

Gemelli et al. Exp Rev Anticancer Ther 2024; Koopman et al. Clin Lung Cancer 2022 Solomon et al. J Clin Oncol 2024

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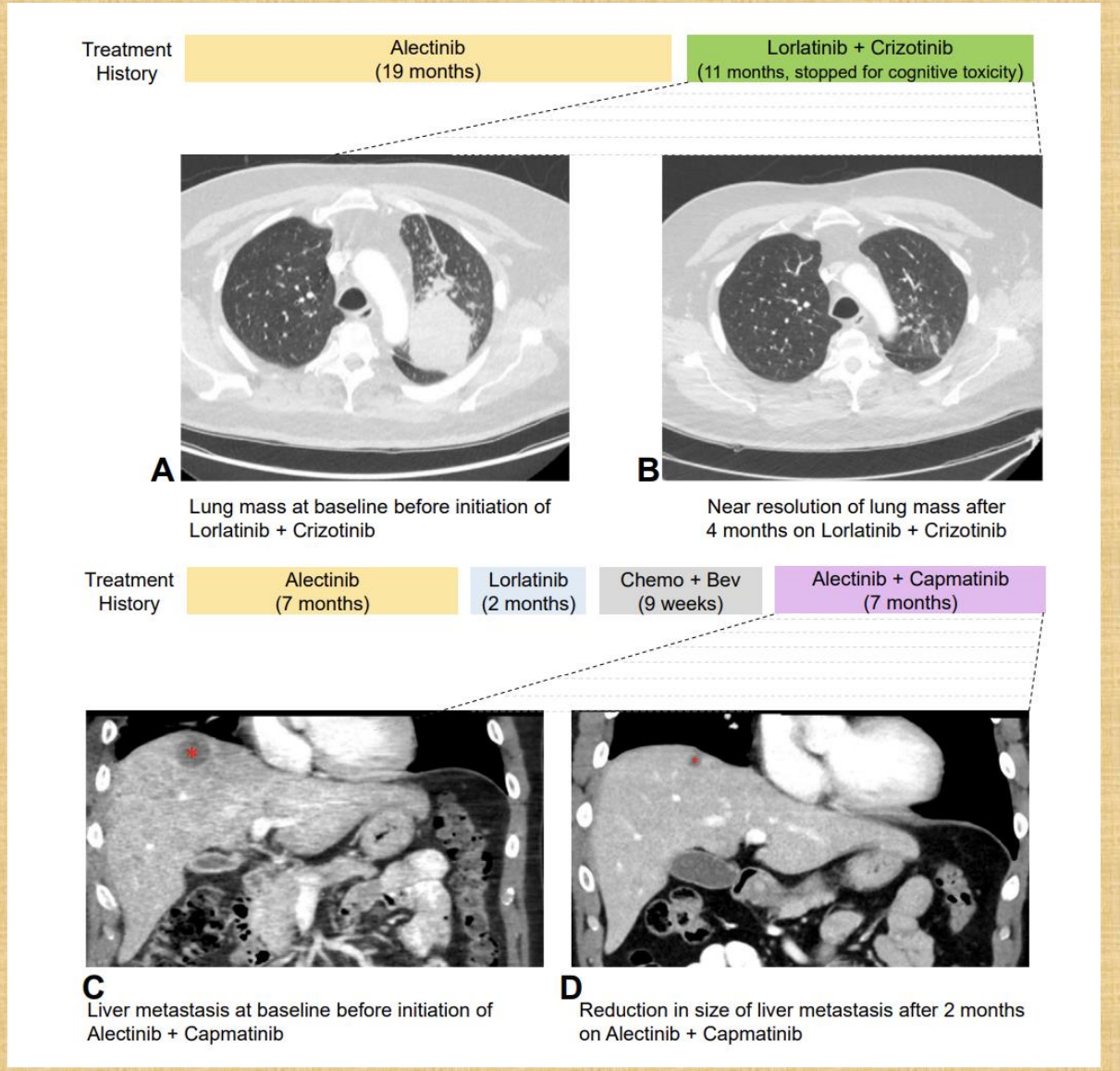
MET-TKI + an ALK-TKI in MET-mediated acquired resistance



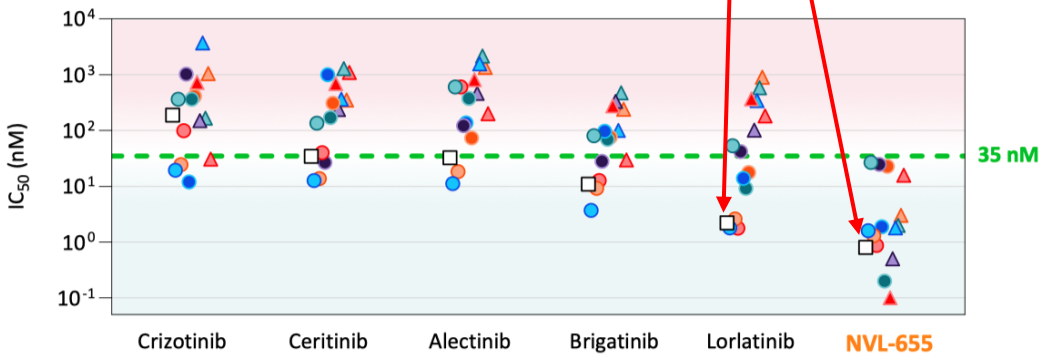
Dagogo-Jack JTO CCR 2023

NVL-655 in ALK+ solid tumors

More potent than lorlatinib

ALK Fusion and ALK Single/Compound Mutation Activity

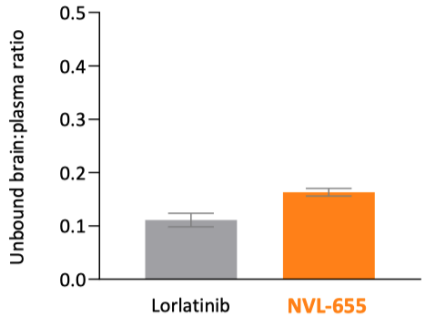
Potent activity (IC_{50} = 0.1 – 30 nM) against ALK-driven cell lines, including ALK single and compound mutants



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

Brain Penetrance

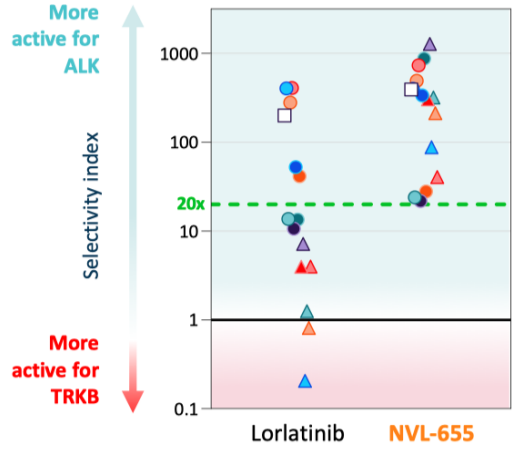
Preclinical pharmacokinetic data similar to lorlatinib



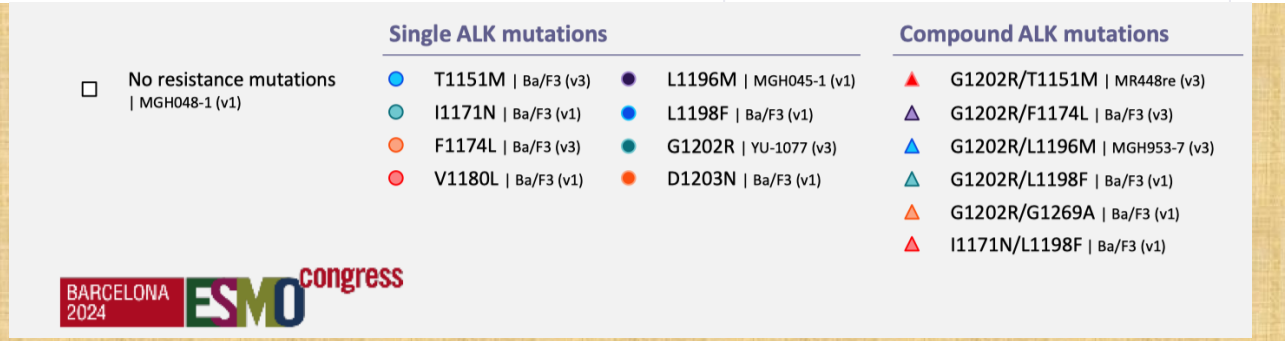
Wistar Han rats
10 mg/kg, single dose PO
1-hour timepoint

Avoidance of TRK Inhibition

Selective inhibition of ALK and ALK mutants over TRK



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



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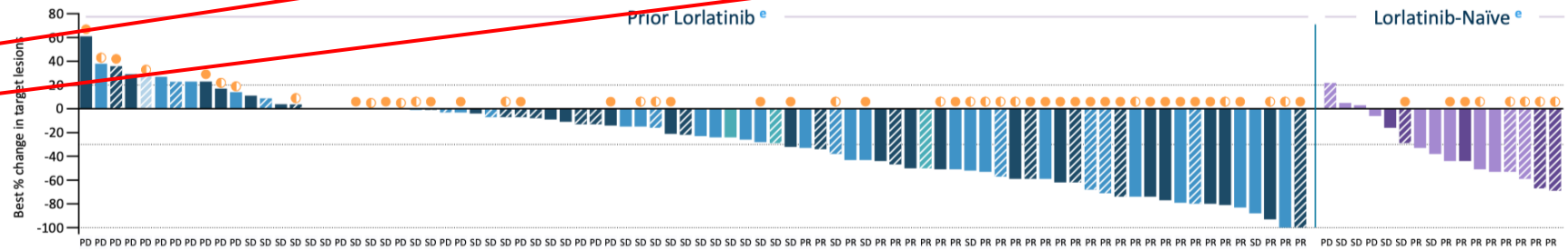
NVL-655 in ALK+ solid tumors: efficacy

Particularly active in presence of ALK resistance mutations, coumpound mutations (4th gen agent), after 2nd gen TKIs in lorlatinib-naive pts

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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NVL-655 in ALK+ solid tumors: toxicity

- 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%)

RP2D selected as 150 mg QD

- MTD not reached through 200 mg QD
- No clear dose-toxicity relationship through 150 mg QD dose level
- 150 mg QD maintained steady state plasma levels at or above the target efficacy thresholds
  (ALK fusions + ALK single/compound mutations in periphery and in the CNS)

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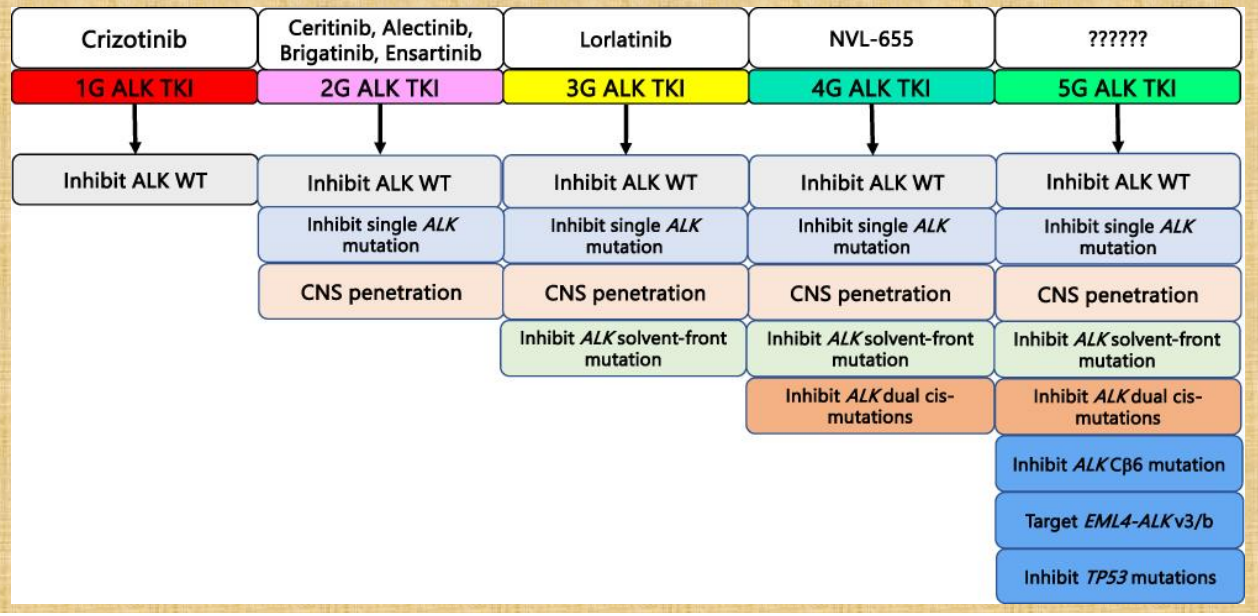
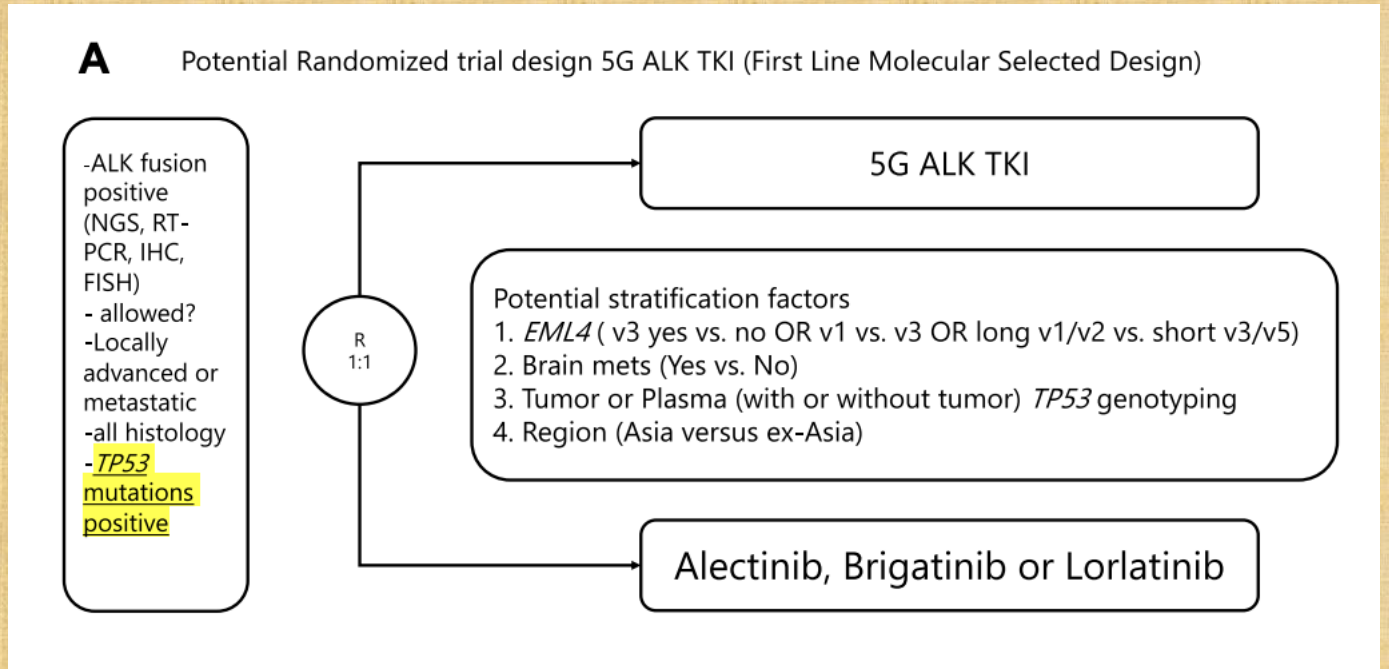
Envisioning the future of treatment for ALK+ disease





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Thanks for your attention

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