Management of First-Line *ALK*-Rearranged NSCLC

ALK: Anaplastic lymphoma kinase;
NSCLC: Non-small–cell lung cancer

Question to experts…

What is the incidence of *ALK* mutated *NSCLC* in your clinical practice?

What is the preferred testing platform at your center for *ALK NSCLC*?

Do the *ALK* variant translocations have an impact on outcomes or treatment selection?

ALK: Anaplastic lymphoma kinase; NSCLC: Non-small cell lung cancer.

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- Molecular Targets for Analysis (continued)
  - *ALK* (anaplastic lymphoma kinase) Gene Rearrangements: ALK is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the ALK kinase domain.
    - The most common fusion partner seen with ALK is echinoderm microtubule-associated protein-like 4 (EML4), although a variety of other fusion partners have been identified.
    - The presence of an *ALK* rearrangement is associated with responsiveness to oral ALK TKIs.
    - Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of an *ALK* rearrangement; however, these features should not be utilized in selecting patients for testing.
    - Testing Methodologies: FISH break-apart probe methodology was the first methodology deployed widely. IHC can be deployed as an effective screening strategy. FDA-approved IHC can be utilized as a stand-alone test, not requiring confirmation by FISH. Numerous NGS methodologies can detect *ALK* fusions. Targeted real-time PCR assays are used in some settings, although it is unlikely to detect fusions with novel partners.
  - *ROS1* (ROS proto-oncogene 1) Gene Rearrangements: ROS1 is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the ROS1 kinase domain.
    - Numerous fusion partners are seen with *ROS1*, and common fusion partners include: *CD74, SLC34A2, CCDC6*, and GOPC (*FIG*).
    - The presence of a *ROS1* rearrangement is associated with responsiveness to oral ROS1 TKIs.
    - Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of a *ROS1* rearrangement; however, these features should not be utilized in selecting patients for testing.
    - Testing Methodologies: FISH break-apart probe methodology can be deployed; however, it may under-detect the FIG-ROS1 variant. IHC approaches can be deployed; however, IHC for *ROS1* fusions has low specificity, and follow-up confirmatory testing is a necessary component of utilizing ROS1 IHC as a screening modality. Numerous NGS methodologies can detect *ROS1* fusions, although DNA-based NGS may under-detect *ROS1* fusions. Targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners.

National Comprehensive Cancer Network. (2022). *Non-Small Cell Lung Cancer (version 3.2022)*.
Retrieved from: J Natl Compr Canc Netw. 2022 May;20(5):497-530. doi: 10.6004/jnccn.2022.0025

Discussion Question

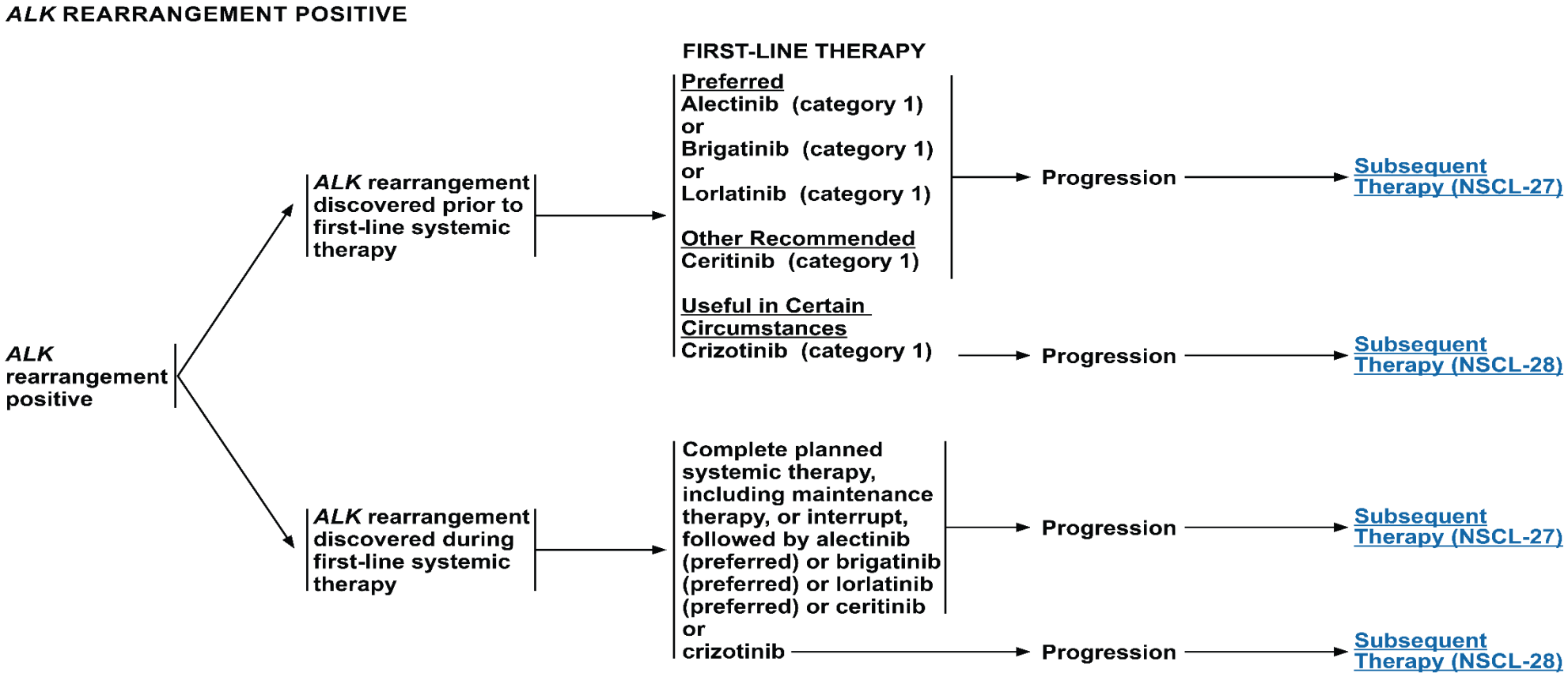
What are your impressions of the data from the CROWN trial?

How likely is it to impact your choice in the 1L setting in patients with and without brain metastasis?

1L: First line

Guideline Recommendation of Lorlatinib As First-Line Treatment

NCCN guidelines for first-line treatment of NSCLC



NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 3. 2022. March 16, 2022.

ALK: Anaplastic lymphoma kinase; NCCN: National Comprehensive Cancer Network; NSCLC: Non-small–cell lung cancer.

Discussion Question

What are your impressions of the CROWN AE data?

How is your experience of lorlatinib AE and how do you currently manage these AEs in practice?

In your experience, do you think AEs of lorlatinib will impact QoL in long term

Given that lorlatinib CNS AEs are reversible, are these a significant concern for 1L ALK+ NSCLC patients?

In 1L ALK+ NSCLC patients, how significant are the lipid profile related AEs?

AE: Adverse event; *ALK: Anaplastic lymphoma* kinase; CNS: Central nervous system; NSCLC: Non-small cell lung cancer; QoL: Quality of life

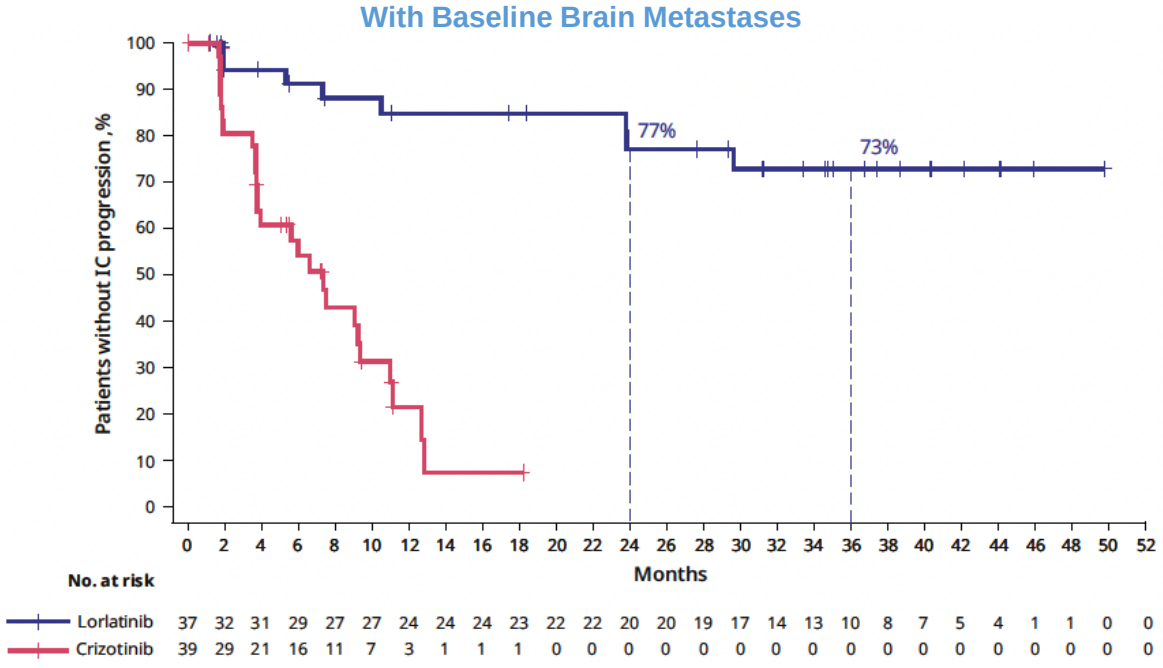
Abstract 979P

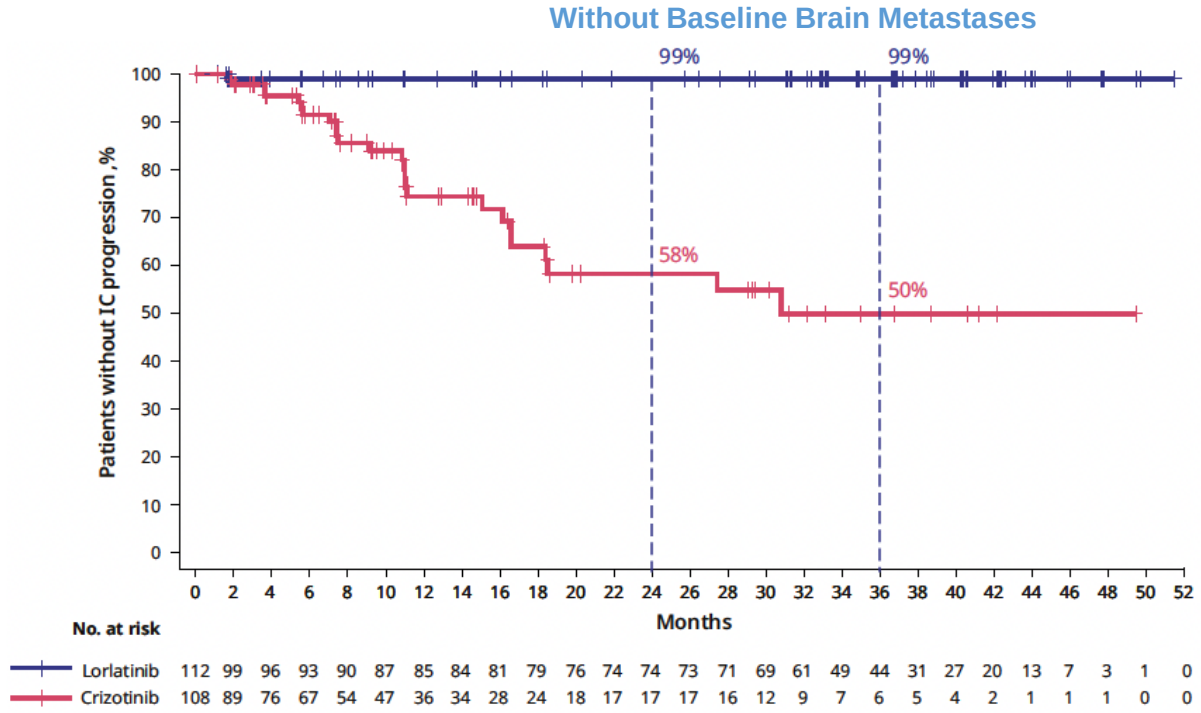
Long term Intracranial Safety and Efficacy analyses from the phase III CROWN study- Bearz et al.

Presented at the ESMO Congress 2022; September 9-13, 2022; Paris, France

Intracranial Efficacy and Safety Data

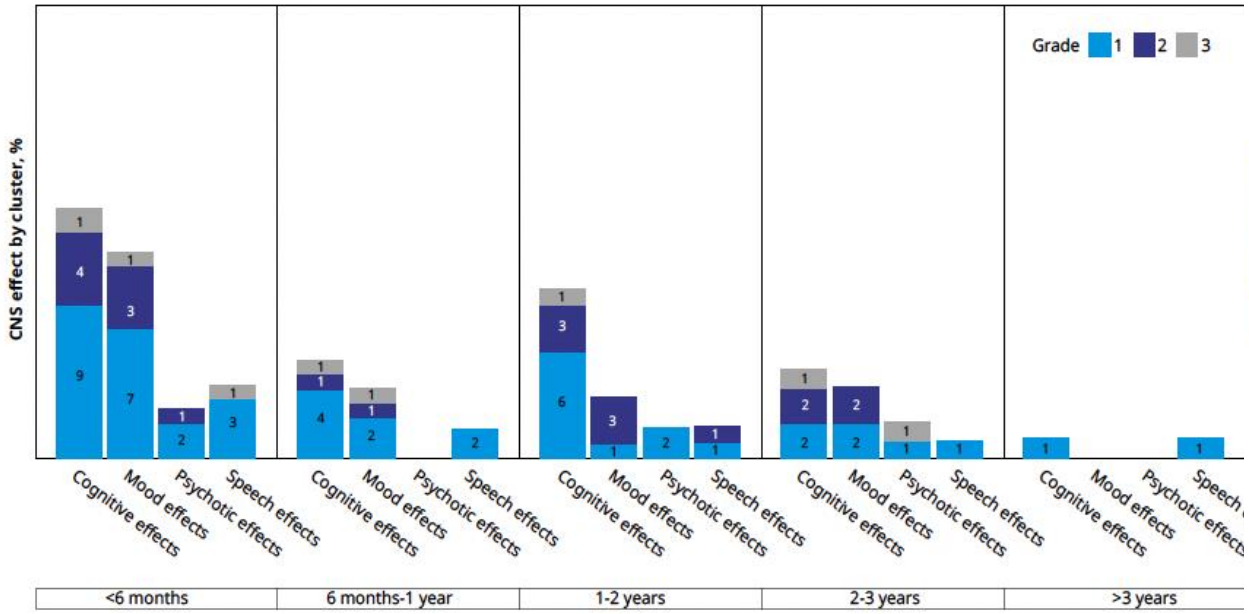
- Evaluation of long-term intracranial safety and efficacy of lorlatinib from the 3-year follow-up (data cutoff: September 20, 2021)
- Efficacy data already presented at AACR 2022



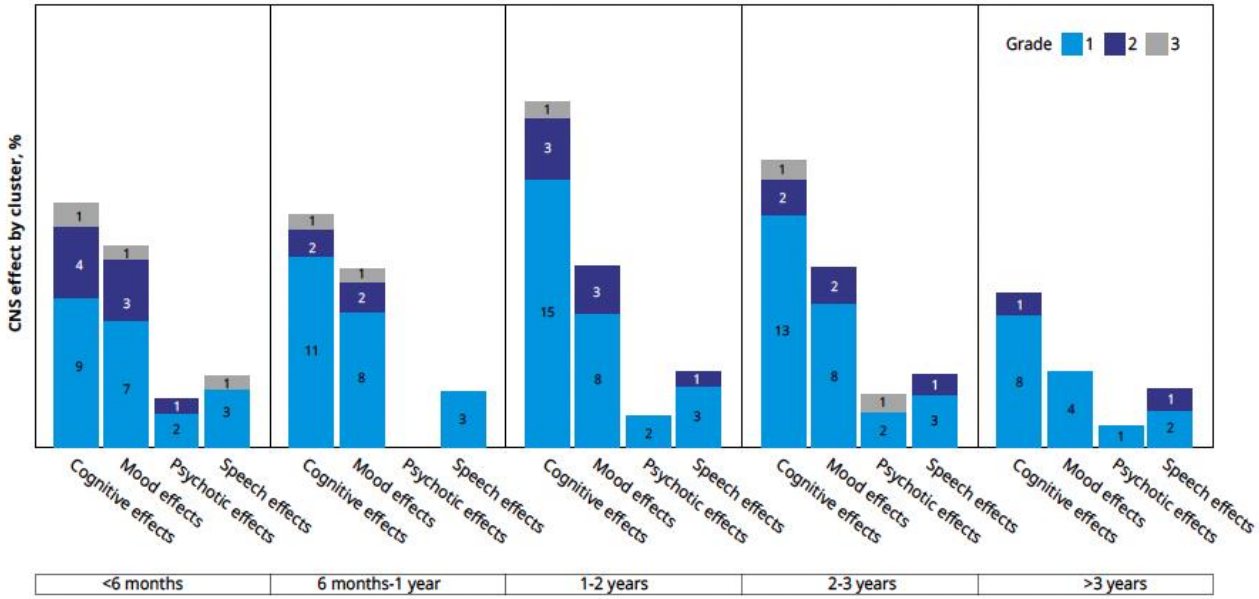


Intracranial Time to Progression by BICR

Incidence of treatment-emergent CNS AEs by time and grade



Prevalence of treatment-emergent CNS AEs by time and grade



- No Grade 4 CNS AEs
- Incidence of CNS AEs progressively reduces with time
- Predominantly Grade 1 AEs

Intracranial Safety Data

- Majority of the patients (59%) were managed without intervention
- CNS AEs led to only two patients permanently discontinuing treatment
- Long – term analysis confirmed that CNS AEs remained manageable over time and lorlatinib dose reduction did not impact intracranial efficacy.

Outcomes of treatment-emergent CNS AEs following dose management

Intervention	Outcome, n (%) n=103				
	Resolved	Partially resolved	Not resolved	Not applicable	Total
No intervention	32 (31)	1 (1)	28 (27)	0	61 (59)
Concomitant medication only	8 (8)	0	6 (6)	0	14 (14)
Dose reduction only	3 (3)	0	1 (1)	0	4 (4)
Dose interruption only	12 (12)	2 (2)	1 (1)	0	15 (15)
Dose reduction + dose interruption	2 (2)	0	0	0	2 (2)
Dose reduction + concomitant medication	0	0	0	0	0
Dose interruption + concomitant medication	1 (1)	0	3 (3)	0	4 (4)
Dose reduction + dose interruption + concomitant medication	0	1 (1)	0	0	1 (1)
Permanent treatment discontinuation	0	0	0	2 (2)	2 (2)
Total	58 (56)	4 (4)	39 (38)	2 (2)	103 (100)

Lorlatinib: Clinical Management of Common AEs And Dose Adjustment Guidelines

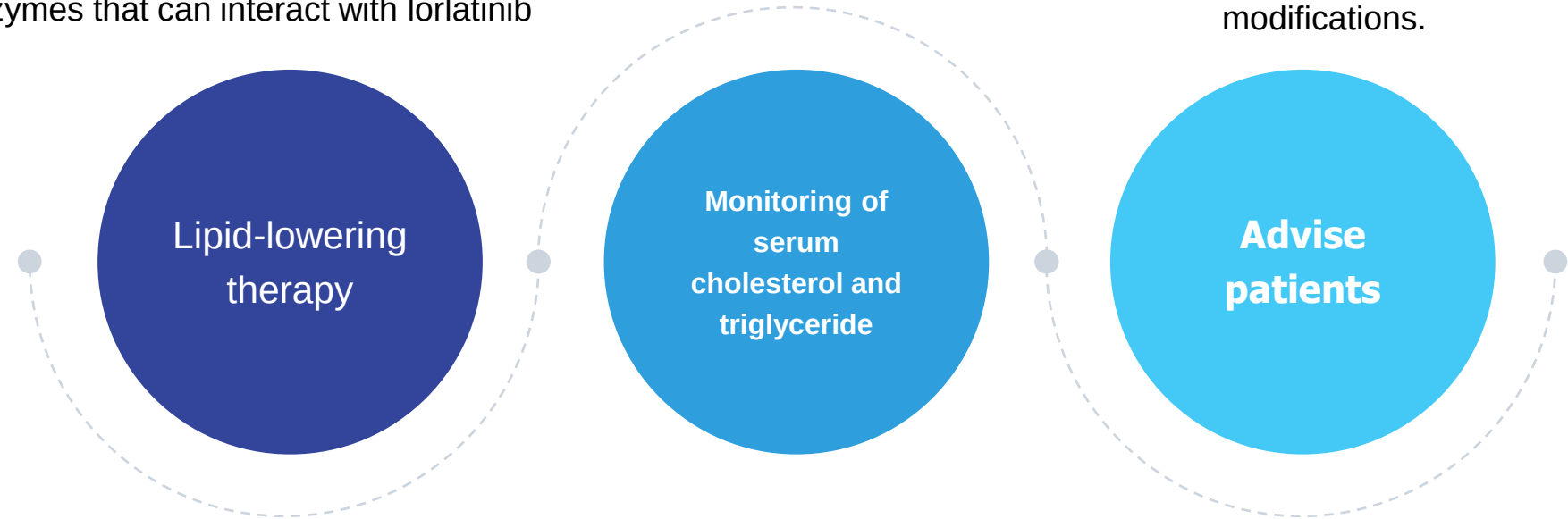
AE: Adverse Events

Therapy Management for Hyperlipidemia

Introduce or increase lipid-lowering therapy[a]

Pitavastatin, pravastatin or rosuvastatin should initially be considered based on their low involvement with specific CYP450 enzymes that can interact with lorlatinib

Advise patients that hyperlipidemia is managed and resolvable through lipid-lowering therapy and/or dose modifications.



Make patients aware that regular monitoring of serum cholesterol and triglyceride levels is needed

For hyperlipidemia, serum cholesterol and triglyceride testing should be performed at baseline, 1 and 2 months after initiating treatment, and periodically thereafter.

[a]Administration of statins, fibrates or fish oils may be guided by information on differential metabolism by the CYP450 pathway.

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Bauer TM, *et al*. *The Oncologist 2019;24:1103–1110*.

CYP450: Cytochrome P450

Dose Modification Guidelines: Lorlatinib-related Hyperlipidemias

Dose modification guidelines for lorlatinib-related hyperlipidemias by severity

Severity	Guidance
Mild: Cholesterol ULN–300 mg/dL OR Triglycerides 150–300 mg/dL	▪ Introduce or modify lipid-lowering therapy ▪ Continue at the same lorlatinib dose
Moderate: Cholesterol >300–400 mg/dL OR Triglycerides >300–500 mg/dL	
Severe: Cholesterol >400–500 mg/dL OR Triglycerides >500–1,000 mg/dL	▪ Introduce lipid-lowering agent or increase dosage of ongoing lipid-lowering therapy, or change to a new lipid-lowering therapy ▪ Continue at the same lorlatinib dose without interruption
Life threatening: Cholesterol >500 mg/dL OR Triglycerides >1000 mg/dL	▪ Introduce lipid-lowering agent or increase dosage of ongoing lipid-lowering therapy, or change to a new lipid-lowering therapy ▪ Withhold lorlatinib dose until hyperlipidemia is moderate or mild before rechallenging at same dose while maximizing lipid-lowering therapy ▪ If severe hyperlipidemia recurs despite maximal lipid-lowering therapy, reduce lorlatinib dose by one dose level (by 25 mg)

Bauer TM, *et al*. *The Oncologist.* 2019;24:1103–1110 .

ULN: Upper limit of normal.

Lorlatinib-related CNS Effects

01

CNS effects: Changes in cognitive function, mood and speech.

Generally mild in severity, intermittent, and improved or resolved upon dose modifications.

02

These ADRs were reported at a frequency of 39.7% (n=117), with 11.9% of patients experiencing >1 type of CNS effect.

03

Baseline CNS metastases were present in 71.8% (84 of 117) of patients with CNS effects.

04

A total of 24 patients required ≥1 dose modification as a result of CNS effects:

- 15 of these patients experienced resolution in their CNS effects.
- The median time to resolution of CNS effects was 12.5 days (range, 2–112).
- Recurrence of CNS effects upon rechallenge at the same and reduced dose occurred in 6 and 7 of patients, respectively.

Bauer TM, *et al*. *The Oncologist.* 2019;24:1103–1110 .

ADR: Adverse drug reaction; CNS: Central Nervous System

Dose Modification Guidelines: Lorlatinib-Related CNS Effects

Dose modification guidelines for lorlatinib-related central nervous system effects by CTCAE grade[a]

CTCAE grade	Guidance
Grade 1: Mild	• Continue at the same dose or withhold dose until recovery to baseline • Rechallenge at the same dose or reduce dose by one dose level (by 25 mg)
Grade 2: Moderate OR Grade 3: Severe	• Withhold dose until AE is grade ≤1 • Rechallenge at one reduced dose level (by 25 mg)
Grade 4: Life-threatening/urgent intervention indicated	• Permanently discontinue lorlatinib

Adapted from: Bauer TM, *et al*. *The Oncologist 2019;24:1103–1110*.

Instruct patients and caregivers to report any changes in cognitive function, mood, or speech

[a]Based on CTCAE (v4.03).

Bauer TM, *et al*. *The Oncologist.* 2019;24:1103–1110 .

CNS: Central Nervous System; CTCAE: Common terminology criteria for adverse events; AE: Adverse events.

Question to Experts..

Do you re-biopsy every *ALK*-mutated patient at progression?

Do you believe there is an unmet need in this area? What can be done better for the best patient outcomes?

Do you believe in sequencing TKIs or do you think the most potent agent should be used upfront?

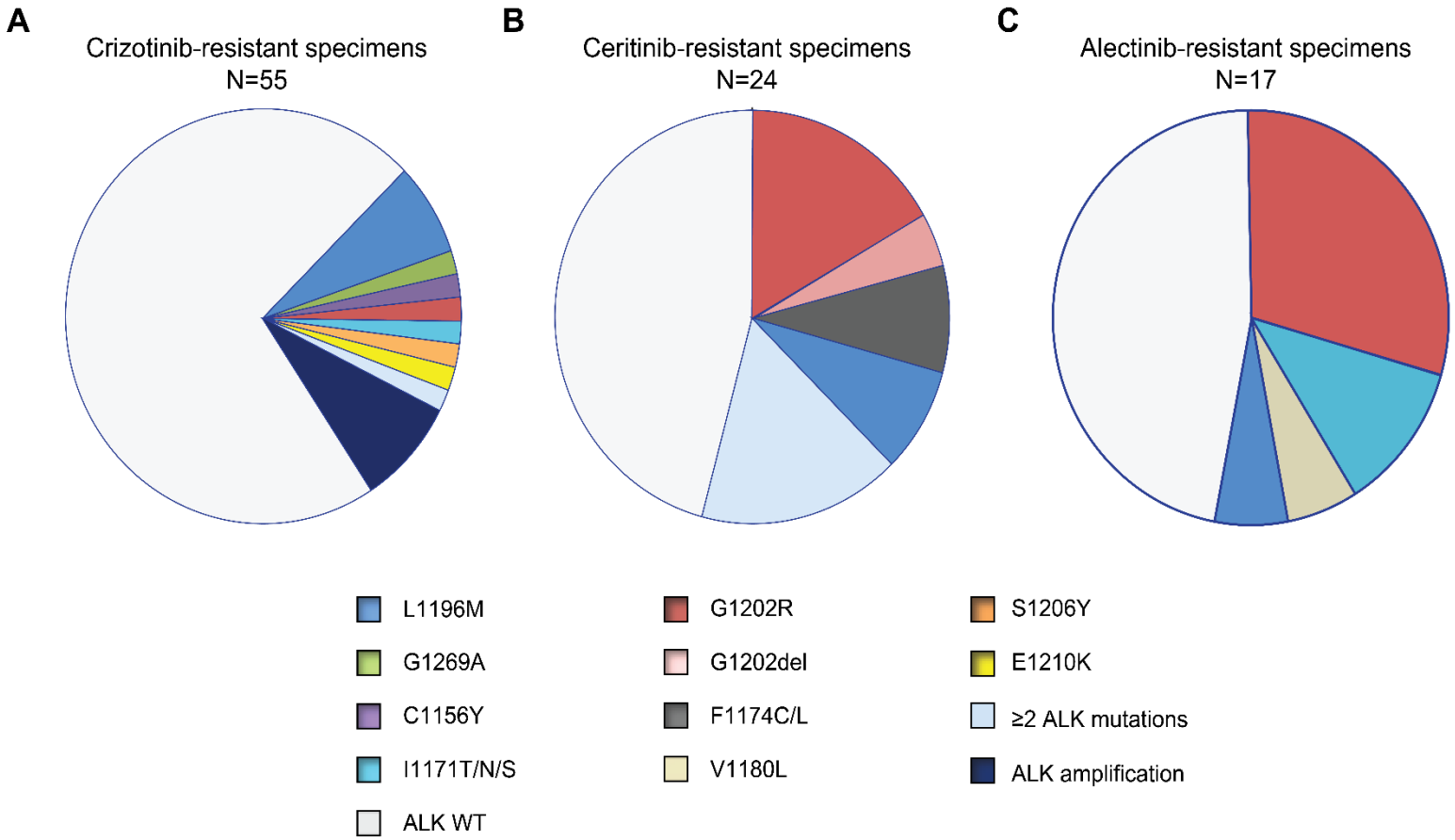
ALK: Anaplastic lymphoma kinase; TKI: Tyrosine kinase inhibitors.

Resistance Pattern After ALK-TKIs

ALK: Anaplastic lymphoma kinase;
TKI: Tyrosine kinase inhibitors.

Resistance to Second-Generation ALK TKIs is Driven by Mutations

Resistance to 2nd-generation ALK-TKIS is largely driven by secondary ALK kinase domain mutations, particularly G1202R



Gainor JF, *et al. Cancer Discov.* 2016;6(10):1118–1133.

ALK: Anaplastic lymphoma kinase;
TKI: Tyrosine kinase inhibitors.

Lorlatinib: A Potent Third-generation ALK-TKI

Lorlatinib is a potent third-generation ALK-TKI with broad-spectrum activity against *ALK* resistance mutations.

- Secondary mutations in the ALK kinase domain can induce resistance to first- and second-generation ALK-TKIs.
- *ALK* G1202R confers resistance to the available first- and second-gen ALK-TKIs.
- **Lorlatinib exhibits broad-spectrum activity against most known *ALK* resistance mutations including *ALK* G1202R.**

IC_{50} ≤50 nM IC_{50} >50–<200 nM IC_{50} ≥200 nM

Cellular ALK Phosphorylation Mean IC_{50} (nM)					
Mutation Status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
Parental BA/F3	763.9	885.7	890.1	2774.0	11293.8
V1	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	50.1	58.8	95.8	5.2
D1203N	116.3	35.3	27.9	34.6	11.1
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0

1. Gainor JF, *et al. Cancer Discov.* 2016;6(10):1118–1133.
2. Johnson TW, et al. *J Med Chem*. 2014;57(11):4720−4744.

ALK: Anaplastic lymphoma kinase; IC_{50}: Half-maximal inhibitory concentration; N: Not done; ROS1: c-Ros Oncogene 1; TKI: Tyrosine kinase inhibitor.

Resistance Mechanisms Associated With ALK-TKIs

ALK-positive patients progress due to different mechanisms of resistance, which are classified as *ALK*-dependent and ALK-independent.

	ALK-independent resistance mechanism	ALK-dependent resistance mechanisms
Crizotinib	*EGFR* overexpression and IGF-1R activation	Amplification of the *ALK* fusion gene; L1196M, G1269A/S, I1151Tins, L1152P/R, C1156Y/T, I1171T/N/S, F1174C/L/V, V1180L, G1202R, S1206C/Y, S1206C/Y, E1210K mutation acquisition
Ceritinib	c-*MET* gene amplification; activating mutation of MEK and *PIK3CA* mutations	G1202R, F1174C/L/V, G1202del, I1151Tins, L1152P/R, C1156Y/T
Alectinib	c-*MET* gene amplification and *PIK3CA* mutations	G1202R, I1171T/N/S, V1180L, L1196M
Brigatinib*	Not reported	E1210K + S1206C, E1210K + D1203N, G1202Ra
Lorlatinib	NF2 loss of function mutations	L1198F + C1156Yc, L1196M/D1203N, F1174L/G1202R, C1156Y/G1269A

***Brigatinib is currently not approved for use as a first-line treatment option for ALK+ NSCLC in India.**

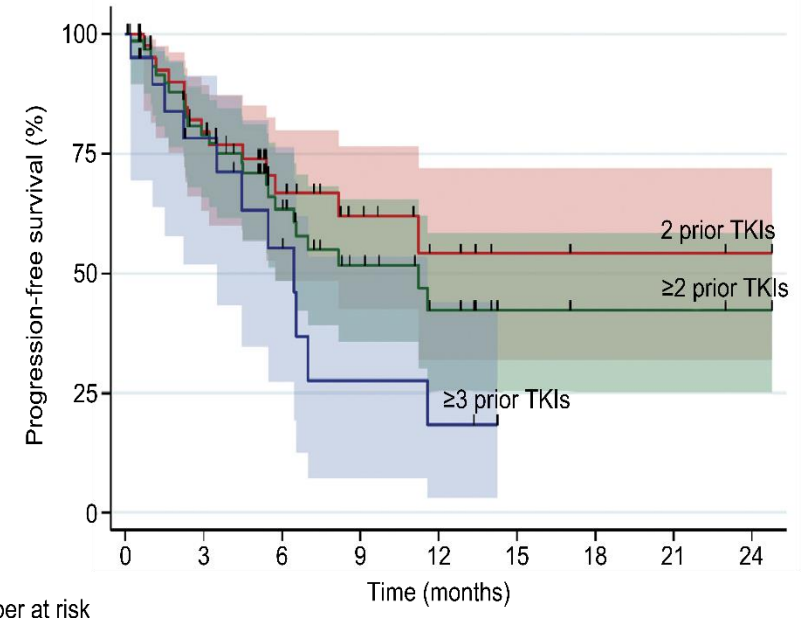
Gristina V, *et al. Pharmaceuticals (Basel)*. 2020;13(12):474.

ALK: Anaplastic lymphoma kinase; EGFR: Epidermal growth factor receptor; IGF-1R: Insulin growth factor-1 receptor; NSCLC: Non-small–cell lung cancer; TKI: Tyrosine kinase inhibitors.

Diminishing PFS with More Prior Lines of ALK-TKIs

Lorlatinib PFS in by lines of prior ALK-TKIs

A



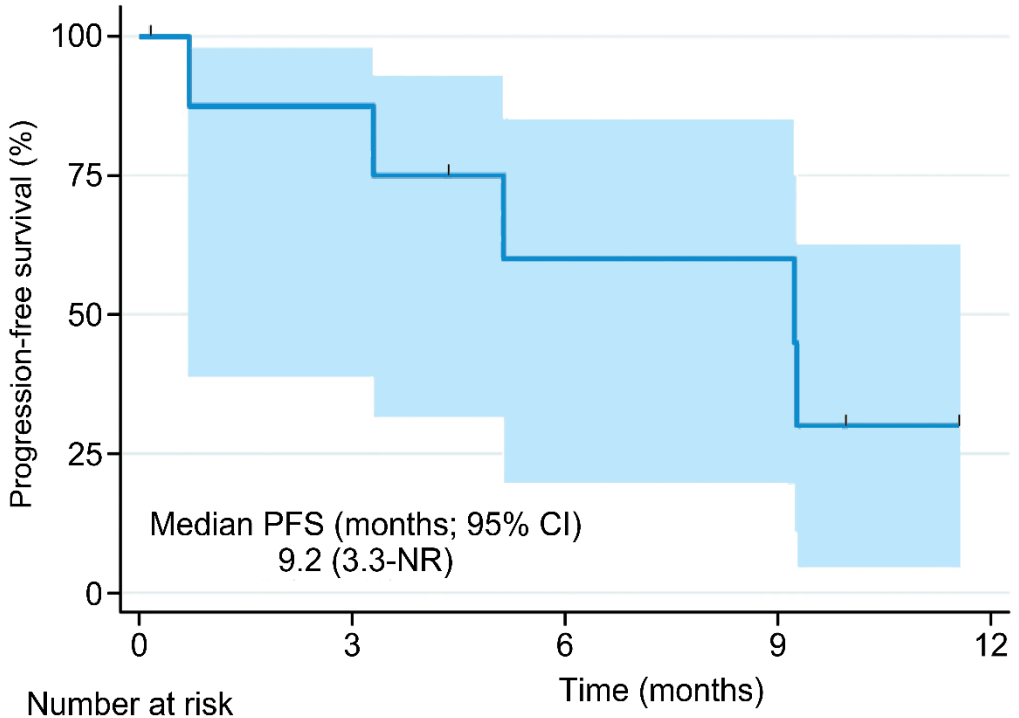
	Median PFS (months; 95% CI)
2 prior TKIs	NR (4.5-NR)
≥2 prior TKIs	11.2 (4.5-NR)
≥3 prior TKIs	6.5 (3.6-11.6)

Number at risk

2 prior TKIs	45	30	18	11	6	3	2	2	1
≥2 prior TKIs	66	43	24	14	8	3	2	2	1
≥3 prior TKIs	21	13	6	3	2	0	0	0	0

Image adapted from Zhu VW, *et al*. *J Thorac Oncol.* 2020;15(9):1484−1496.

B



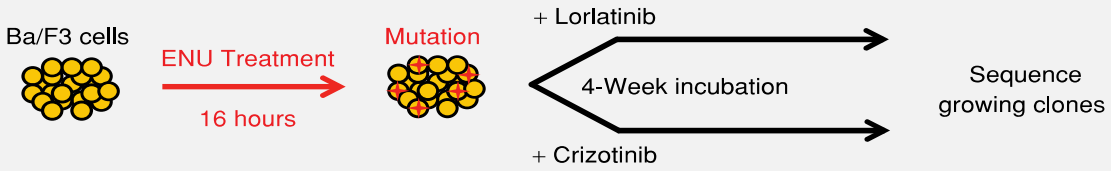
Number at risk

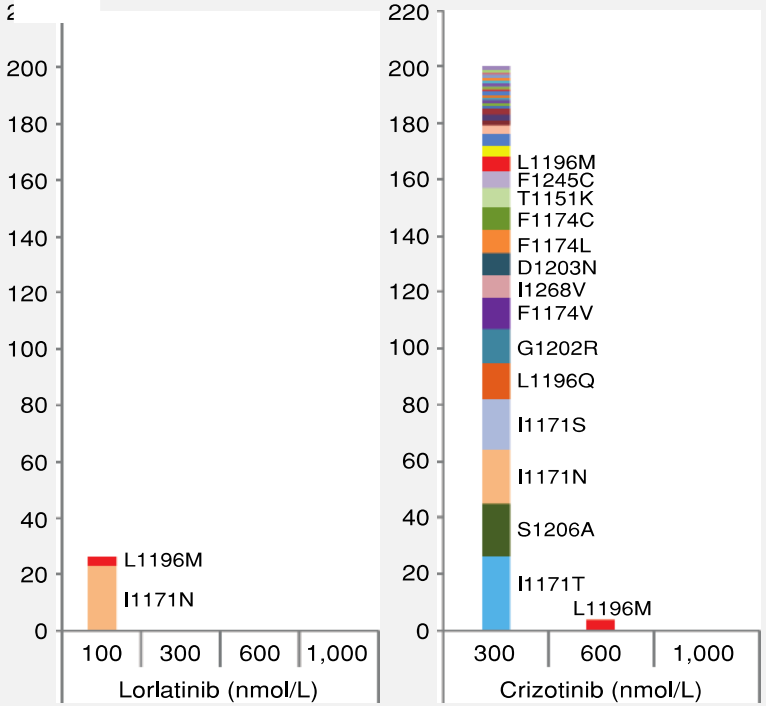
9	7	4	4	0

1. Zhu VW, *et al*. *J Thorac Oncol.* 2020;15(9):1484−1496.
2. Ou SH S04.02. Presented at IASLC TTLC 2021

ALK: Anaplastic lymphoma kinase; CI: Confidence interval; NSCLC: Non-small–cell lung cancer; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitors.

Rationale for Upfront Use of Pan-Inhibitory Agent





Crizotinib (nmol/L)

	300	600
I1171T	26	0
I1171N	19	0
S1206A	19	0
I1171S	18	0
L1196Q	13	0
G1202R	12	0
F1174V	11	0
F1174C	8	0
F1174L	8	0
D1203N	8	0
I1268V	8	0
T1151K	7	0
F1245C	6	0
L1196M	5	4
T1151M	4	0
Y1239H	4	0
L1152R	3	0

Crizotinib (nmol/L)

	300	600
L1152P	2	0
F1174I	2	0
E1210K	2	0
Q1129K	1	0
Q1129V	1	0
T1151R	1	0
C1156F	1	0
C1156R	1	0
E1161N	1	0
M1166K	1	0
I1170S	1	0
I1171V	1	0
F1174S	1	0
L1198F	1	0
L1198I	1	0
S1206F	1	0
G1269A	1	0
Y1278H	1	0

Lorlatinib (nmol/L)

	100
I1171N	23
L1196M	3

Lorlatinib suppresses the emergence of single *ALK* resistance mutations

Upfront Lorlatinib could significantly delay or suppress on-target resistance

Summary of the type and number of ALK kinase domain mutations identified in the mutagenesis screen using Ba/F3 cells harboring non-mutant EML4-ALK (either variant 1 or variant 3)

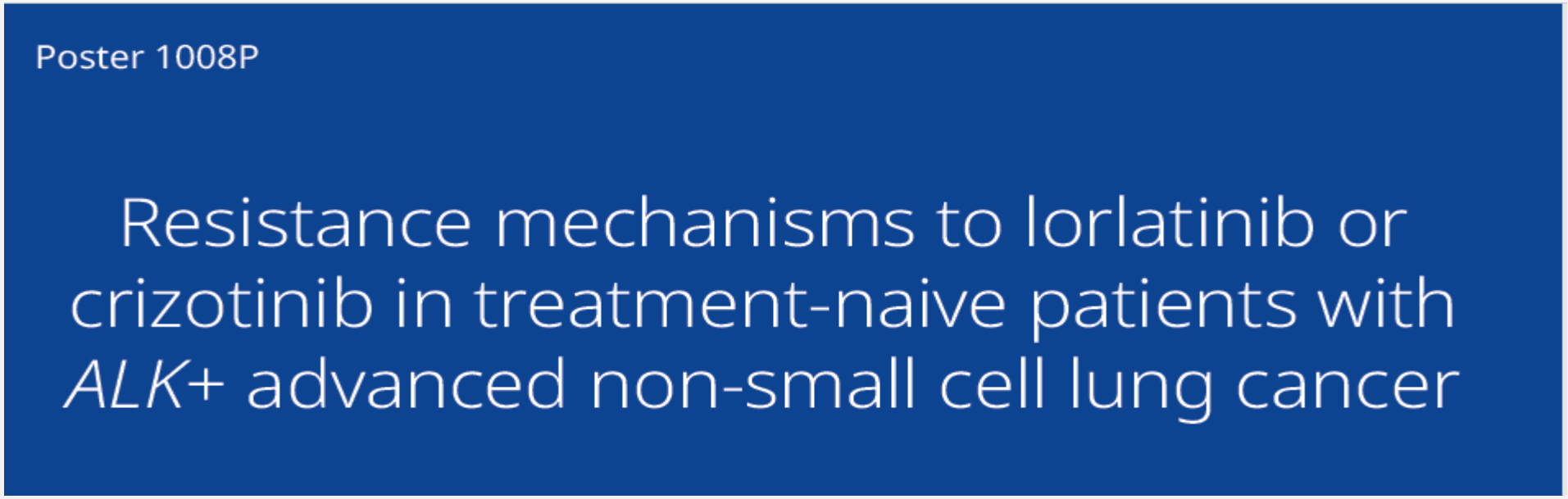
See summary of prescribing information on last page

Yoda S et al., Cancer Discover 2018;8:714-29

Discussion Question

What therapy would you prefer at progression on ALK inhibitor?

1L: First line



Enriqueta Felip,[1] Jean-Francois Martini,[2] Julien Mazieres,[3] Dong-Wan Kim,[4] Deborah Shepard,[2] Anna Polli,[5] Geoffrey Liu,[6] Filippo de Marinis,[7] Francesca Toffalorio,[5] Yasushi Goto,[8] Benjamin J. Solomon[9]

Presented at the ESMO Congress 2022; September 9-13, 2022; Paris, France

Methodology

- Analysis part of CROWN trial

- Plasma samples collected at baseline, on study (weeks 4 and 24), and at end of treatment (EOT) and analyzed by a validated ctDNA NGS assay

- Resistance mechanisms explored included *ALK*-dependent and *ALK* independent bypass alterations :
  - *RTK*
  - *MAPK*
  - *PI3K*
  - Cell cycle & Other genes

- PFS by blinded independent central review (BICR) was based on the September 20, 2021, data cutoff

Distribution of EML4::ALK variants at baseline

Variant	Lorlatinib n=134	Crizotinib n=129
EML4::ALK v1/v2, n (%)	27 (20)	28 (22)
EML4::ALK v3, n (%)	18 (13)	23 (18)
EML4::ALK other, n (%)	15 (11)	9 (7)

Summary of potential resistance mechanisms against Lorlatinib or Crizotinib

Resistance mutation at EOT	Lorlatinib n=26	Crizotinib n=80
New single *ALK* mutation, n (%)	0	6 (8)
ALK compound mutation, n (%)	0	2 (2)
Bypass mechanism, n (%)[a]	9 (35)	10 (12)
MAPK pathway aberration	3 (12)	1 (1)
PI3K/mTOR/PTEN pathway aberration	2 (8)	0
RTK pathway aberration	4 (15)	5 (6)
Cell cycle pathway aberration	2 (8)	5 (6)
Other mutation, n (%)	9 (35)	15 (19)

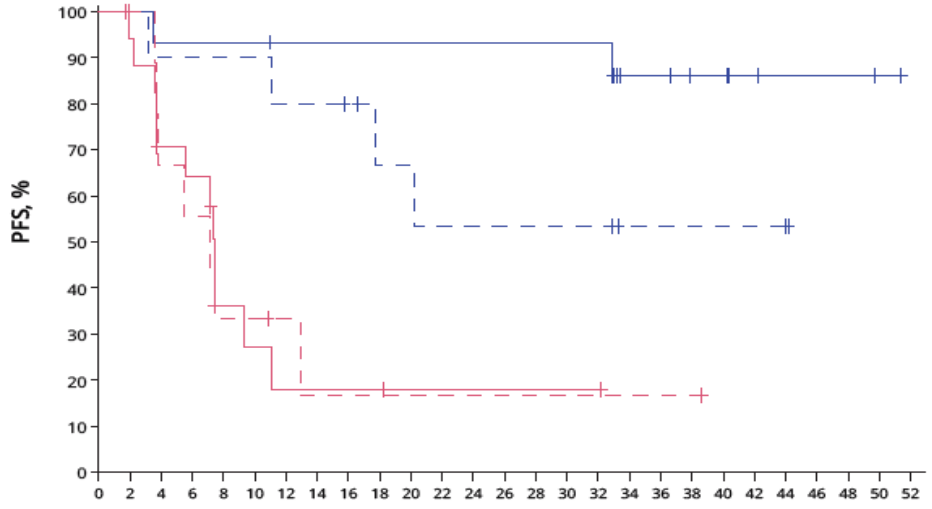
[a]Each sample could harbor >1 bypass mechanism.

PFS based on BICR

Figure 2: PFS based on BICR by *EML4::ALK* variant subtype with or without *TP53* mutations

A. Patients who had *EML4::ALK* v1/v2

	Lorlatinib		Crizotinib	
	TP53 mut (-) n=15	*TP53* mut (+) n=12	*TP53* mut (-) n=19	*TP53* mut (+) n=9
Events, n	2	4	12	7
PFS, median (95% CI), months	NR (NR-NR)	NR (17.7-NR)	7.4 (3.7-11.1)	7.2 (3.8-12.9)
HR (95% CI)	0.23 (0.04-1.31)		0.99 (0.39-2.54)	



No. at risk

Lorlatinib

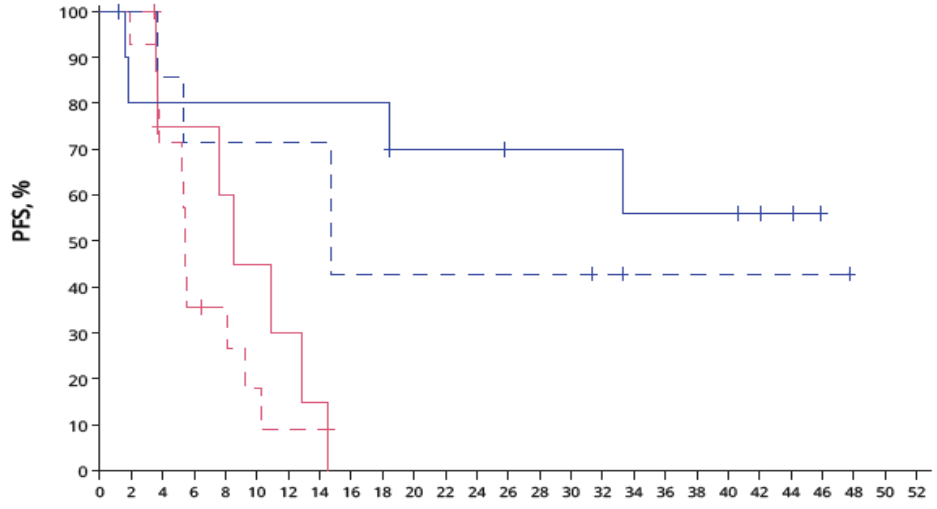
TP53 mut (-)	15	15	14	14	14	14	13	13	13	13	13	13	13	13	13	13	7	7	5	5	3	2	2	2	1	0
TP53 mut (+)	12	10	9	9	9	9	8	8	7	5	5	4	4	4	4	4	2	2	2	2	2	2	0	0	0	0

Crizotinib

TP53 mut (-)	19	16	11	10	4	3	2	2	2	2	1	1	1	1	1	1	1	0	0	0	0					
TP53 mut (+)	9	9	6	5	3	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	0					

B. Patients who had *EML4::ALK* v3

	Lorlatinib		Crizotinib	
	TP53 mut (-) n=10	*TP53* mut (+) n=8	*TP53* mut (-) n=9	*TP53* mut (+) n=14
Events, n	4	4	7	12
PFS, median (95% CI), months	NR (18.4-NR)	14.8 (5.3-NR)	8.5 (3.7-12.8)	5.4 (3.7-9.2)
HR (95% CI)	0.55 (0.13-2.30)		0.66 (0.25-1.73)	



No. at risk

Lorlatinib

TP53 mut (-)	10	8	8	8	8	8	8	8	8	8	6	6	6	5	5	5	5	4	4	4	4	3	2	0	0	
TP53 mut (+)	8	7	6	5	5	5	5	5	3	3	3	3	3	3	3	3	2	1	1	1	1	1	1	1	0	

Crizotinib

TP53 mut (-)	9	9	5	5	4	3	2	1	0																	
TP53 mut (+)	14	13	10	5	4	2	1	1	0																	

HR, hazard ratio.

Conclusion

- Treatment-naive patients who started ALK therapy had better outcomes if they harbored EML4 - ALK variants 1 or 2 (v1/v2) (regardless of TP53 mutation status) compared with those with EML4-ALK variant 3 (v3) and TP53 mutations

- Lorlatinib was effective against all EML4-ALK variants, however v3 with TP53 mutation fared worse

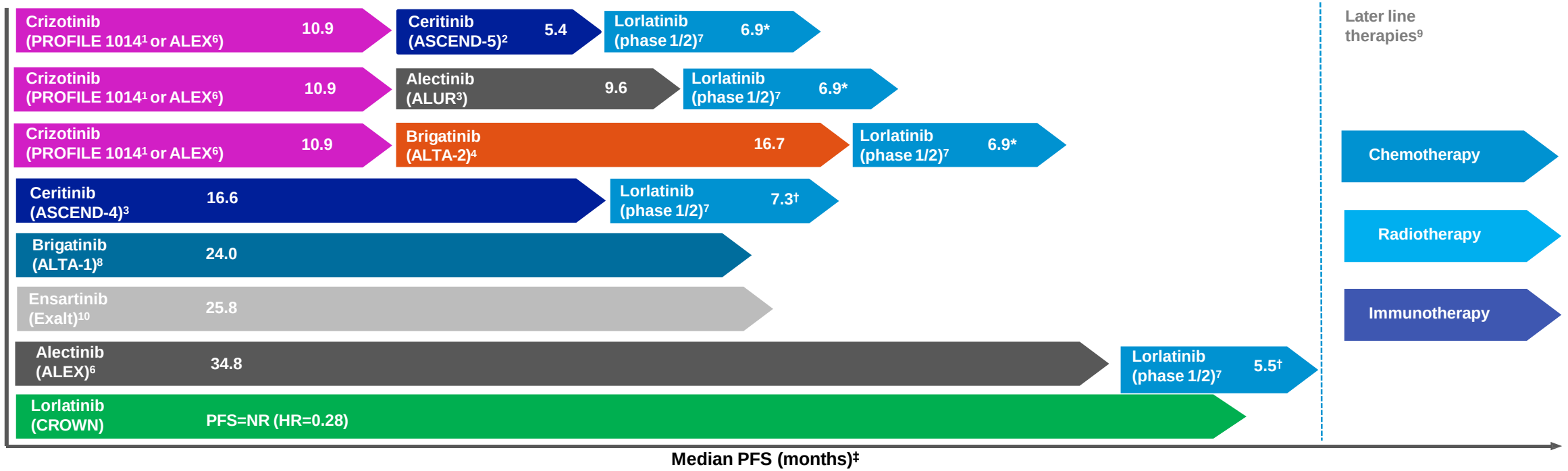
- Bypass mechanism aberrations were the main resistance response to lorlatinib treatment

- Emerging new ALK mutations were not detected at the end of lorlatinib treatment

- New combination strategies may be needed to overcome mechanisms of resistance to lorlatinib

Rapidly Evolving Clinical Evidence on ALK+ NSCLC Defines Treatment Sequence for Patients

The rapidly evolving ALK+ NSCLC landscape and a growing body of clinical evidence is defining the treatment sequence for patients.



*Data are from the EXP4 and EXP5 groups (two or three prior ALK TKIs ± chemotherapy); †Lorlatinib PFS data following ceritinib or alectinib in any line; ‡Adapted and updated from Ferrera, et al. 20189. **Brigatinib is currently not approved for use as a first-line treatment of ALK+ NSCLC in Singapore; Ensartinib is an investigational agent not yet approved in the first-line treatment of ALK+ NSCLC in Singapore; Lorlatinib is currently not approved for use as a first-line treatment option for ALK+ NSCLC in Singapore.** For illustration purposes only; note that cross-trial comparisons should be interpreted with caution due to the differences in study design, size, patient population, and data maturity; the IMpower150 regimen is not currently approved in the US

1. Solomon BJ, *et al*. *N Eng J Med.* 2014;371(23):2167–2177. 2. Shaw A, *et al*. *Lancet Oncol*. 2017;18(12):1590–1599. 3. Novello S, *et al*. *Ann Oncol*. 2018;29(6):1409–1416. 4. Huber RM, *et al. J. Clin. Oncol.* 2018;36(15):9061–9061. 5. Soria JC, *et al*. *Lancet.* 2017;389(10072):917–929. 6. Camidge DR, *et al. J Thorac Oncol*. 2019;14(7):1233–1243. 7. Besse B, *et al. J. Clin. Oncol.* 2018;36(15):9032–9032 8. Camidge DR, *et al. N Engl J Med*. 2018;379(21):2027–2039. 9. Ferrara R, *et al. J Thorac Oncol*. 2018;13(1):27–45. 10. Horn, L. IASLC WCLC 2020 Presidential Symposium.

ALK: Anaplastic lymphoma kinase;
NSCLC: Non-small– cell lung cancer;
PFS: Progression-free survival.

Key Takeaways

In treatment-naive ALK+ NSCLC, compared to crizotinib in first-line, lorlatinib resulted in a significantly':[1–3]

- Longer PFS
- Higher overall and IC response rates
- Improved global QoL

The safety profile of lorlatinib was similar to that reported in previous studies[1-3]

Although grade 3/4 AEs were more frequent with lorlatinib than crizotinib, the majority were asymptomatic and readily managed[4]

With sequential ALK inhibitor treatment, approximately 35% of patients will develop compound *ALK* resistance mutations on lorlatinib with a solvent front. *ALK* G1202R-containing compound mutations, which may become the most common on-target resistance mechanism, and are predominantly refractory to all known ALK inhibitors.[1]

These results support the use of lorlatinib as an effective first-line therapy for patients with advanced *ALK*+ NSCLC.

1. Shaw AT, *et al. Lancet Oncol*. 2017;18:1590–1599; 2. Solomon BJ, *et al*. *Lancet Oncol*. 2018;19:1654–1667; 3. Shaw AT, *et al*. *Lancet Oncol*.2019;20:1691–1701; 4. Bauer TM *et al. Oncol*. 2019; 24:1103–1110.

AE: Adverse event; ALK: Anaplastic lymphoma kinase; IC: Intracranial; NSCLC: Non-small–cell lung cancer; PFS: Progression-free survival; QoL: Quality of life.

Thank You