Resistance Pattern ALK-TKIs

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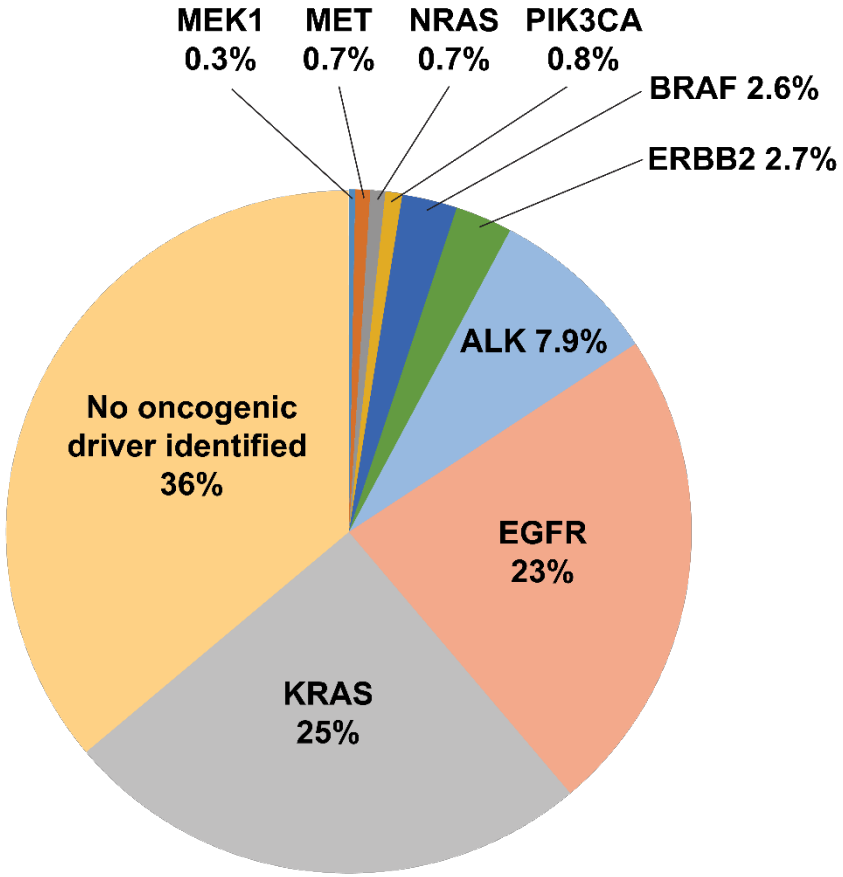
Incidence of *ALK* Mutation

ALK gene rearrangement in lung adenocarcinomas is the second most common (1.6%–11.7% of NSCLC) targetable genomic change after *EGFR* mutations.[1]

Mutations identified in the LCMC cohort[2]



Adapted from: Sholl LM, *et al. J. Thorac. Oncol*. 2015;10(5):768–777.

1. Bal A, *et al. APMIS*. 2016;124(10):832–838.
2. Sholl LM, *et al. J. Thorac. Oncol*. 2015;10(5):768–777.

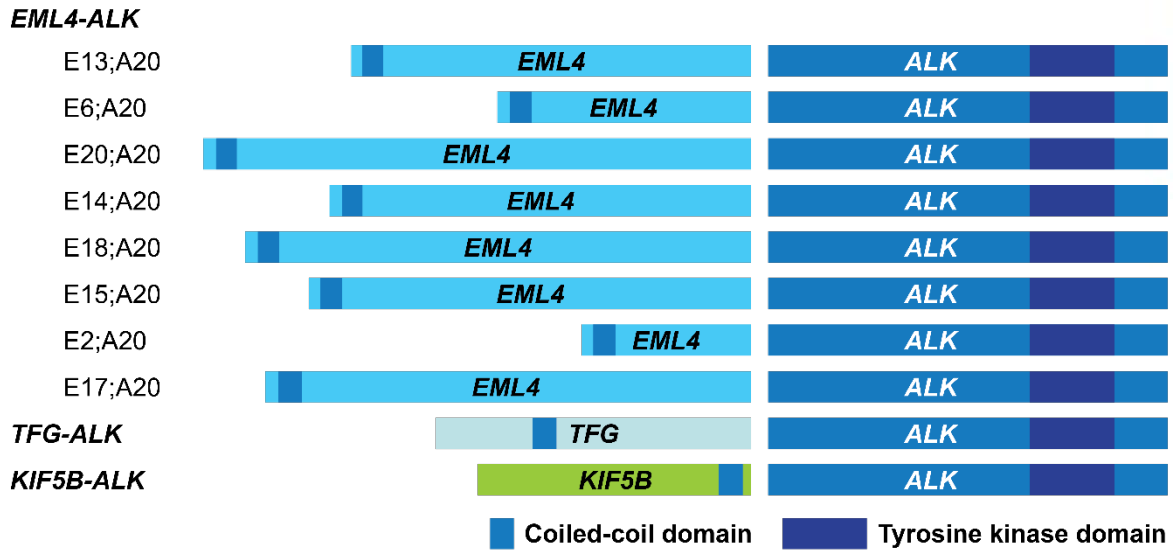
ALK: anaplastic lymphoma kinase; EGFR: Epidermal growth factor receptor; LCMC: Lung Cancer Mutation Consortium; NSCLC: Non-small–cell lung cancer.

ALK Rearrangements in Lung Cancer

Approximately 5% of all NSCLC cases:

- Typically, adenocarcinoma histology.
- Typically (but not always) nonsmokers or light former smokers.
- Tend to occur in younger patients
- Sensitive and specific diagnostic techniques available
- *EML4-ALK* and *EGFR* mutations are mutually exclusive

Different variants of *EML4-ALK* and non-*EML4* fusion partners



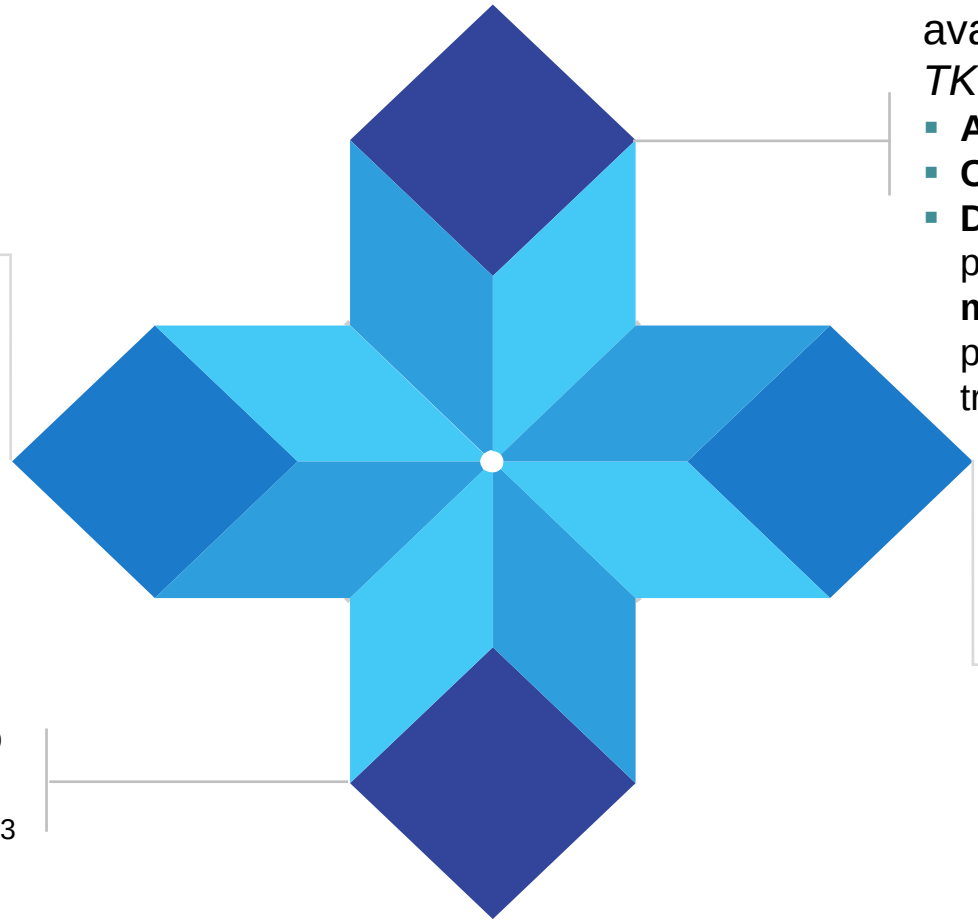
Adapted from: Sasaki T, *et al*. *Eur J Cancer*. 2010;46(10):1773–1780.

Sasaki T, *et al*. *Eur J Cancer*. 2010;46(10):1773–1780.

ALK: anaplastic lymphoma kinase; *EGFR;* NSCLC: Non small cell lung cancer; TFG:TRK-fused gene.

Unmet Need in *ALK*-positive NSCLC

ALK-positive NSCLC patients are **generally young** (median age 51 years) and **non-smokers or light smokers.**[1]



CNS metastases occur in 20%-40% of untreated *ALK*-positive NSCLC patients leading to poor prognosis.[2,3]

Treatment challenge even with the availability of second-generation *ALK-TKIs*.[2,3,4,5,6,7]

- **ALK resistance mutations**
- **CNS metastases (inadequate penetration)**
- **Durable control of brain metastases** in patients with BM and **preventing brain metastases** in those without them at the point of diagnosis is a remaining unmet treatment need.

There is a need for additional *ALK-TKI*s that prevent the emergence of resistant subclones in untreated patients.[8]

1. Bang YJ. *Ther Adv Med Oncol*. 2011;3(6):279–291. 2. Toyokawa, G *et al. Cancer metastases Rev*. 2015;34(4):797–805. 3. Bauer TM, *et al. Target Oncol*. 2020;15(1)(02):55–65. 4. Solomon BJ, *et al. Lancet Oncol*. 2018;19(12):1654–1667. 5. Nagasaka M, Ge Y, Sukari A, Kukreja G, Ou SI. A user's guide to lorlatinib. Crit Rev Oncol Hematol. 2020 Jul;151:102969, 6. Guérin A, et al. *J Med Econ* 2015;18:312–22; 7. Tabbò F,et al. *Transl Lung Cancer Res* 2019;8:S290–S297; 8. Shaw AT, *et al. N Engl J Med*. 2020;383(21):2018–2029.

ALK: Ananaplastic lymphoma kinase; BM: Brain metastases; CNS: Central nervous system; NSCLC: Non small cell lung cancer; TKI: Tyrosine kinase inhibitor.

PFS Outcomes for ALEX, ALTA-1L, eXALT3, and CROWN Trials at Varying Levels of Data Maturity

ALEX: Alectinib vs Crizotinib
Enrollment: Aug 2014 – Jan 2016

Median duration of follow-up in experimental arm:

18.6 mo

1st interim analysis	Alectinib (n=152)	Crizotinib (n=151)
PFS (INV), months	**NR**	**11.1**
HR (95% CI)	**0.47 (0.34-0.65)**	
PFS (IRC), months	25.7	10.4
HR (95% CI)	0.50 (0.36-0.70)	

27.8 mo

2nd interim analysis	Alectinib (n=152)	Crizotinib (n=151)
PFS (INV), months	**34.8**	**10.9**
HR (95% CI)	**0.43 (0.32-0.58)**	
PFS (IRC), months	--	--
HR (95% CI)	--	

37.8 mo

Final Analysis	Alectinib (n=152)	Crizotinib (n=151)
PFS (INV), months	**34.8**	**10.9**
HR (95% CI)	**0.43 (0.32-0.58)**	
PFS (IRC), months	--	--
HR (95% CI)	--	
PFS (INV) rate at 36 months % (95% CI)	**46.4 (CI not available)**	**13.5 (CI not available)**

NEJM 2017 Peters et al.
JTO 2019 Camidge et al.
ESMO 2019 Mok et al.

ALTA-1L: Brigatinib vs Crizotinib
Enrollment: Apr 2016 – Aug 2017

Median duration of follow-up in experimental arm:

11.0 mo

1st interim analysis	Brigatinib (n=137)	Crizotinib (n=138)
PFS (INV), months	NR	9.2
HR (95% CI)	0.45 (0.30-0.68)	
PFS (IRC), months	**NR**	**9.8**
HR (95% CI)	**0.49 (0.33-0.74)**	

24.9 mo

2nd interim analysis	Brigatinib (n=137)	Crizotinib (n=138)
PFS (INV), months	29.4	9.2
HR (95% CI)	0.43 (0.31-0.61)	
PFS (IRC), months	**24.0**	**11.0**
HR (95% CI)	**0.49 (0.35-0.68)**	

40.4 mo

Final Analysis	Brigatinib (n=137)	Crizotinib (n=138)
PFS (INV), months	30.8	9.2
HR (95% CI)	0.43 (0.31-0.58)	
PFS (IRC), months	**24.0**	**11.1**
HR (95% CI)	**0.44 (0.35-0.66)**	
PFS (IRC) rate at 36 months % (95% CI)	**43.0 (34.0–51.0)**	**19.0 (12.0–27.0)**

NEJM 2018 Camidge et al.
JCO 2020 Camidge et al.
JTO 2021 Camidge et al.

eXALT3: Ensartinib vs Crizotinib
Enrollment: ? – Nov 2018

Median duration of follow-up in experimental arm:

23.8 mo

1st interim analysis	Ensartinib (n=143)	Crizotinib (n=147)
PFS (INV), months	-	-
HR (95% CI)	-	
PFS (IRC), months	**25.8**	**12.7**
HR (95% CI)	**0.51 (0.35-0.72)**	

27.6 mo

2nd interim analysis	Ensartinib (n=143)	Crizotinib (n=147)
PFS (INV), months	33.2	12.9
HR (95% CI)	0.45 (0.32-0.64)	
PFS (IRC), months	**31.3**	**12.7**
HR (95% CI)	**0.50 (0.36-0.71)**	

JAMA Oncol 2021 Horn et al.
World Lung 2020b Wu et al.

CROWN: Lorlatinib vs Crizotinib
Enrollment: Apr 2017 – Feb 2019

Median duration of follow-up in experimental arm:

18.0 mo

1st Interim analysis	Lorlatinib (n=147)	Crizotinib (n=149)
PFS (INV), months	NE	9.1
HR (95% CI)	0.21 (0.14, 0.31)	
PFS (IRC), months	**NE**	**9.3**
HR (95% CI)	**0.28 (0.19, 0.41)**	

36 mo

2nd Interim analysis	Lorlatinib (n=147)	Crizotinib (n=149)
PFS (INV), months	NE	9.1
HR (95% CI)	0.21 (0.14, 0.31)	
PFS (IRC), months	**NE**	**9.3**
HR (95% CI)	**0.27 (0.18, 0.39)**	
PFS (IRC) rate at 36 months % (95% CI)	**63.5** (54.6–71.1)	18.9 (11.8–27.4)

NEJM 2020 Shaw et al.
AACR 2022 Solomon et al.

Primary endpoints in bold

Cross-trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results.

And If It Wasn't Hard Enough To Choose One Agent First-line….

Overall efficacy

Overall Survival?

What's available second-line?

CNS activity?

Response rate?

Progression-free Survival?

Challenges for the second line treatment

- **Resistance mutation:**
  - Patients ultimately develop resistance to ALK TKI due to resistance mutations, which are around 53-71% [1, 2]
  - Amongst all resistance mutations, 29% of patients develop G1202R resistance which are difficult to treat mutation[1]
- **CNS Metastasis:**
  - Around 60% of ALK positive patients present with brain metastases upon progression after treatment with ALK inhibitor(s) and are associated with a poor prognosis[2]
- **Failure to use Subsequent therapy**

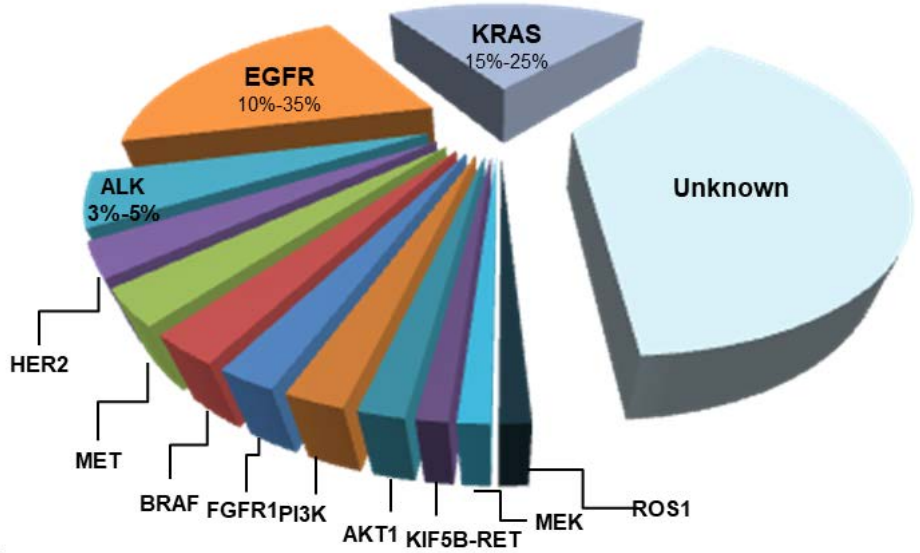
1. Gainor JF et al. Cancer Discov; 6(10); 1118–33. 2. Solomon et al. Lancet Oncol 2018; 19: 1654–67
Please see summary of prescribing information on last slide

Mechanisms of Acquired Resistance to ALK Inhibitors

- Progression on ALK Inhibitors

- Despite 1L ALK inhibitors demonstrating high activity in ALK-rearranged NSCLC, disease progression occurs in a median of ~10 to 25 months[1-5]
- Patterns of resistance may include isolated CNS progression and various forms of extracranial progression[5]
- Mechanisms implicated in acquired resistance to ALK inhibitors include[5,6]:
  - ALK amplifications
  - ALK mutations
  - Activation of oncogenic bypass pathways including those involving EGFR, HER2, MET, KIT, and InsR
  - Drug efflux pumps in the CNS

Frequency of Common Genetic Alterations in Advanced NSCLC[6,7]



Adapted from Thomas A et al. *Ann Oncol*. 2013;24(3):577-585

•CNS, central nervous system.

•1. Crizotinib prescribing informatio. New York, NY: Pfizer Inc.; 2019. 2. Ceritinib prescribing information. East Hanover, NJ: Novartis Pharmaceutical Corp.; 2019. 3. Alectinib prescribing information. Cambridge, MA: Takeda Pharmaceutical Company Ltd.; 2017. 4. Camidge DR et al. *N Engl J Med*. 2018;379(21):2027-2039 5. Rothenstein JM, et al. *Curr Oncol*. 2018;25(S1):S59-S67. 6. Thomas A et al. *Ann Oncol*. 2013;24(3):577-585. 7. Jordan et al. *Cancer Discov*. 2017;7(6):596-609.

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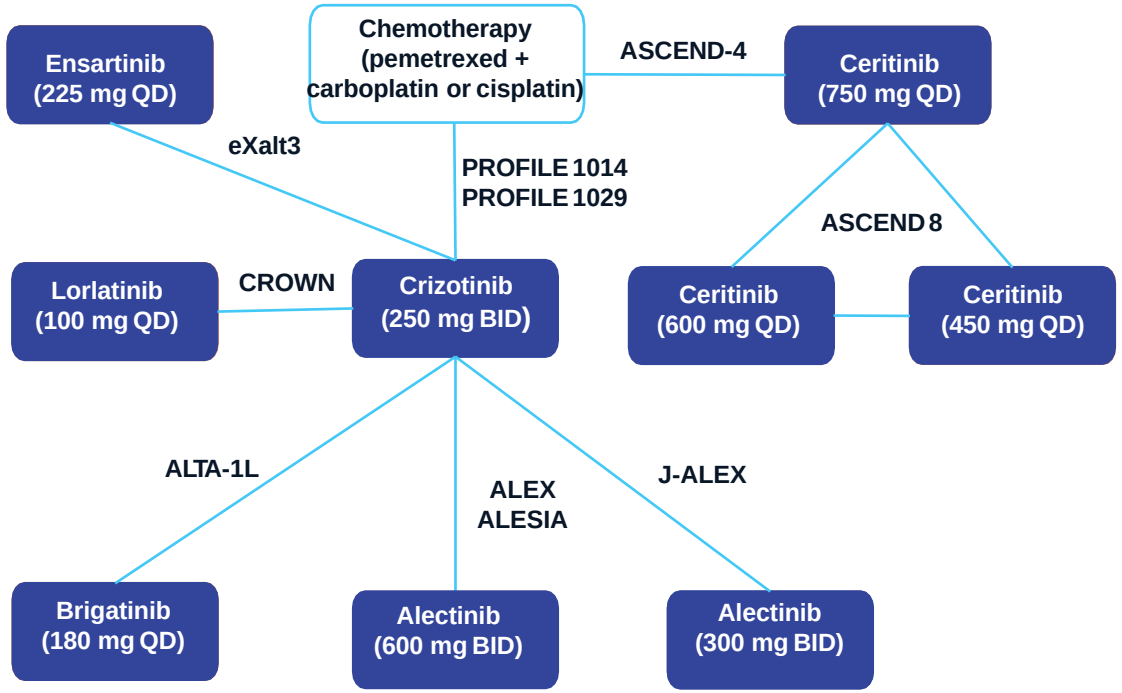
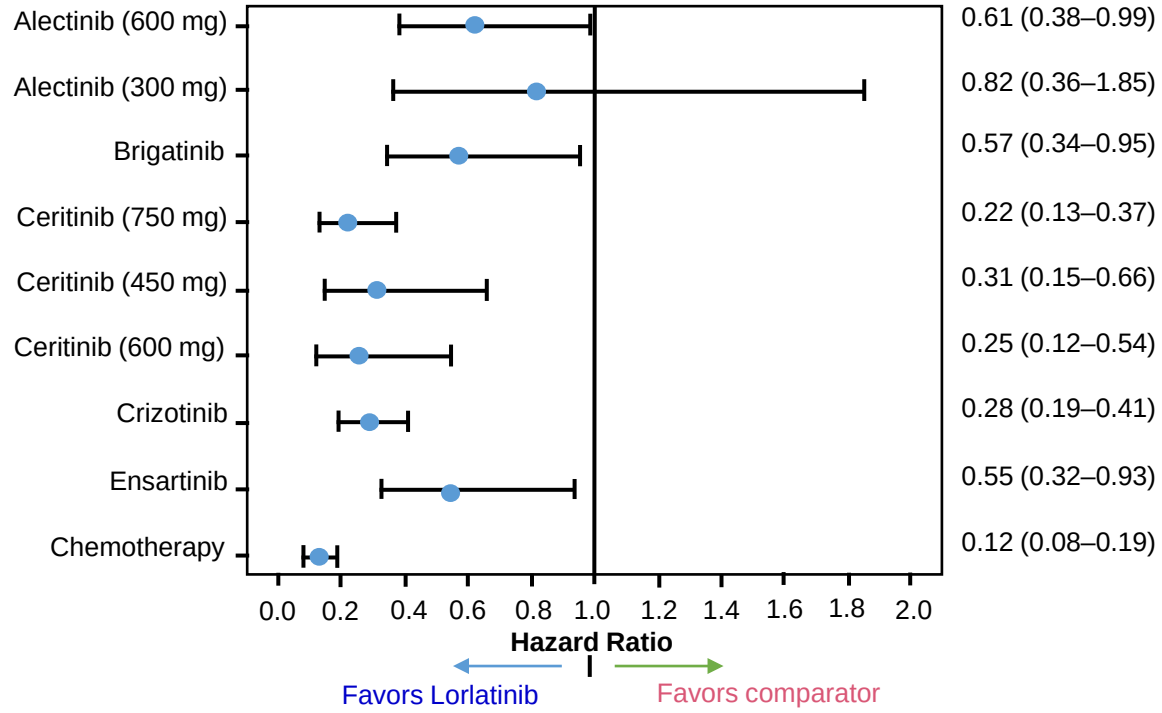
Lorlatinib Reduced Hazard of Progression Compared to Other Treatments in Meta-analysis

Network of evidence



Relative effect of lorlatinib compared to all treatments for PFS, HR (CrI)



Lorlatinib is an effective first-line treatment for ALK+ NSCLC when compared to crizotinib and other next-generation ALK-TKIs.

Gregory J, WCLC 2021, Presentation 2563. Available at: https://scientificpubs.congressposter.com/p/11n9yc3hxsy4rq70. Accessed on: 2 October 2021.

ALK: Ananaplastic lymphoma kinase; BID: Twice daily; CrI: Credible interval; FE: Fixed effects; HR: Hazard ratio; NSCLC: Non-small–cell lung cancer; PFS: Progression-free survival; QD: Once a day.

JOURNAL OF CHEMOTHERAPY
2022, VOL. 34, NO. 2, 87–96
https://doi.org/10.1080/1120009X.2021.1937782

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REVIEW

Comparison of lorlatinib, alectinib and brigatinib in ALK inhibitor–naive/untreated ALK-positive advanced non-small-cell lung cancer: a systematic review and network meta-analysis

Lida Wang[a], Zhixin Sheng[b], Junying Zhang[b], Jiwu Song[c], Lili Teng[d], Liping Liu[b], Qianpeng Li[b], Baohong Wang[b] and Bin Li[e]

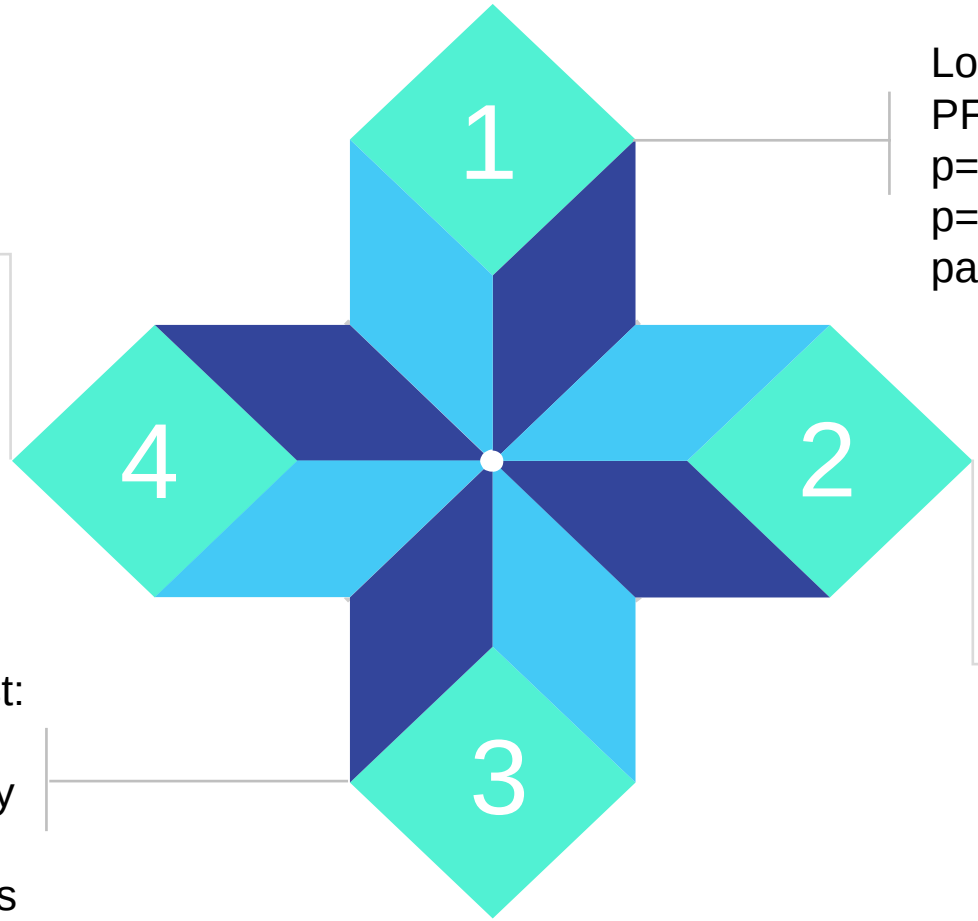
[a]Department of E.N.T, Weifang People's Hospital, Weifang, China; [b]Department of Hematology, Weifang People's Hospital, Weifang, China; [c]Department of Stomatology, Weifang People's Hospital, Weifang, China; [d]Infection Department, Weifang People's Hospital, Weifang, China; [e]Department of Respiration, Weifang People's Hospital, Weifang, China

In terms of PFS, the results indicated that lorlatinib was the best treatment choice for patients with ALK inhibitor-naïve or untreated (ALK inhibitor-naïve and chemotherapy-naive) *ALK*-positive, advanced NSCLC. Future head-to–head trials assessing the relative efficacy of lorlatinib, alectinib, and brigatinib are warranted.

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

Conclusion of Network Meta-analysis

In terms of PFS, the results indicated that lorlatinib was the best treatment choice for patients with ALK inhibitor-naïve or untreated *ALK*-positive advanced NSCLC



Lorlatinib significantly improved PFS than brigatinib (HR: 0.57, p=0.03) and alectinib (HR: 0.59, p=0.03) for ALK inhibitor-naïve patients.

Among lorlatinib, alectinib, brigatinib, and crizotinib, lorlatinib had the highest:

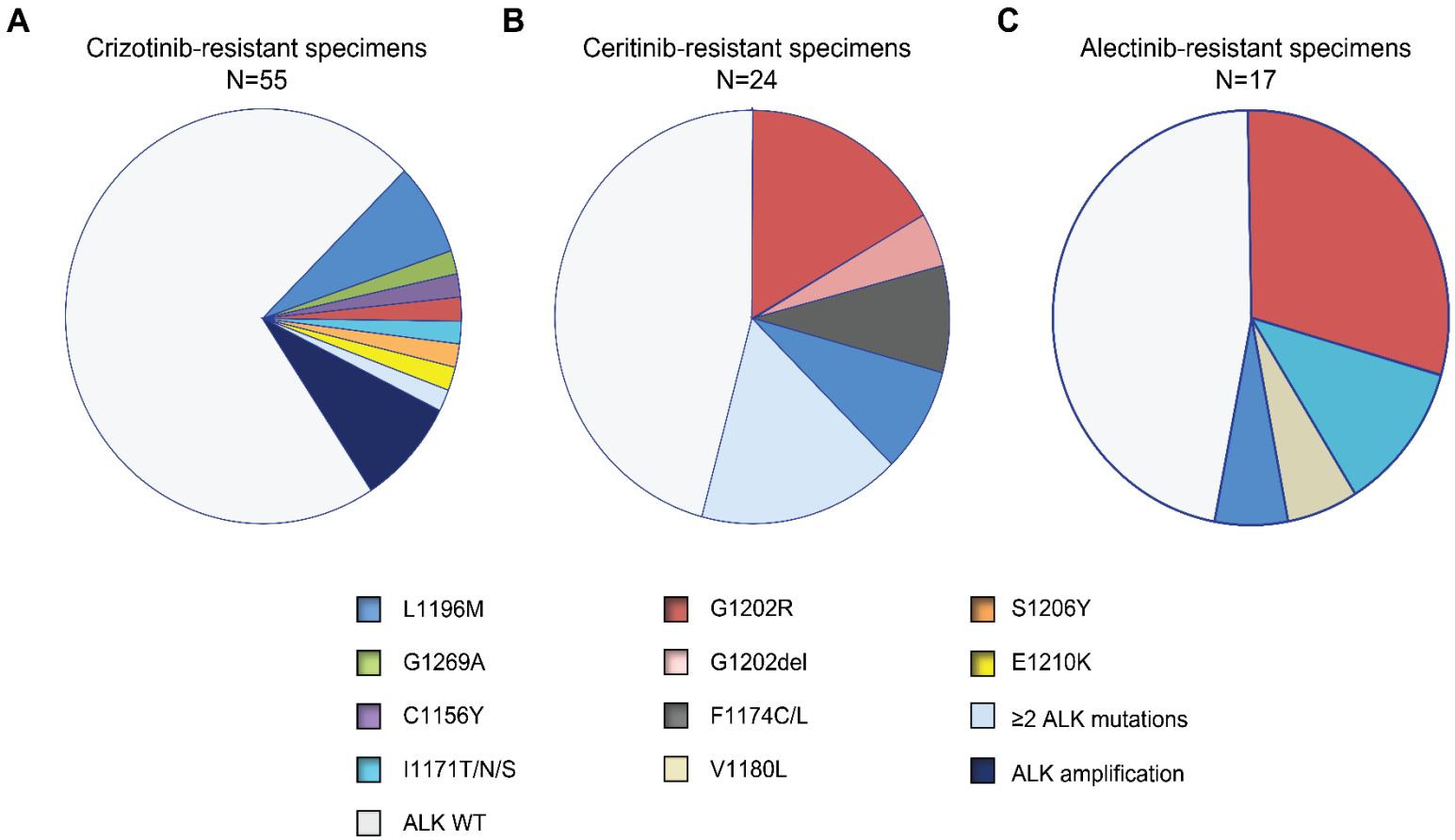
- Probability to reach the best overall confirmed response rates (probability of 48%)
- Intracranial confirmed response rates (probability of 44%)

No significant difference was found among them in OS and AE analysis.

AE: Adverse event; ALK: Ananaplastic lymphoma kinase; HR: Hazard ratio; NSCLC: Non-small–cell lung cancer; OS: Overall survival; PFS: Progression-free survival

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: Ananaplastic 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: Ananaplastic 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.**

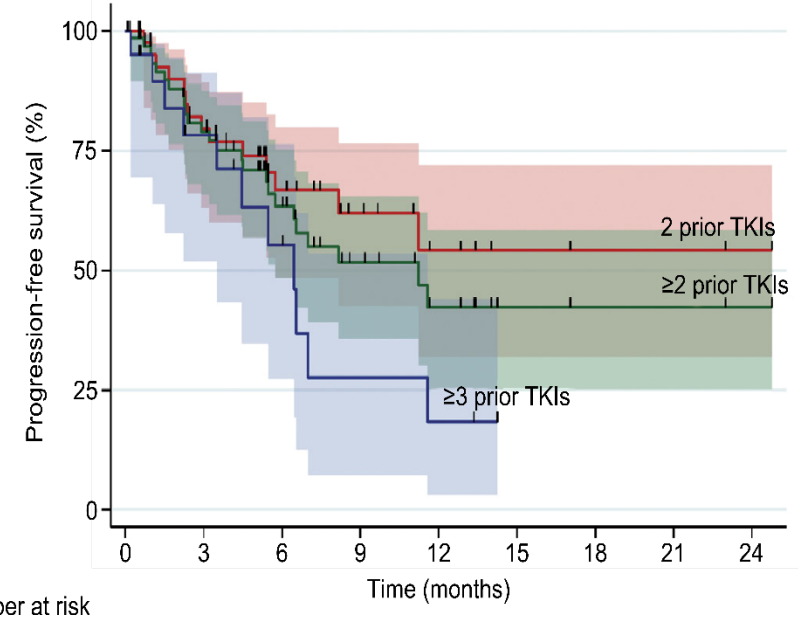
Gristina V, *et al. Pharmaceuticals (Basel)*. 2020;13(12):474.

ALK: Ananaplastic 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



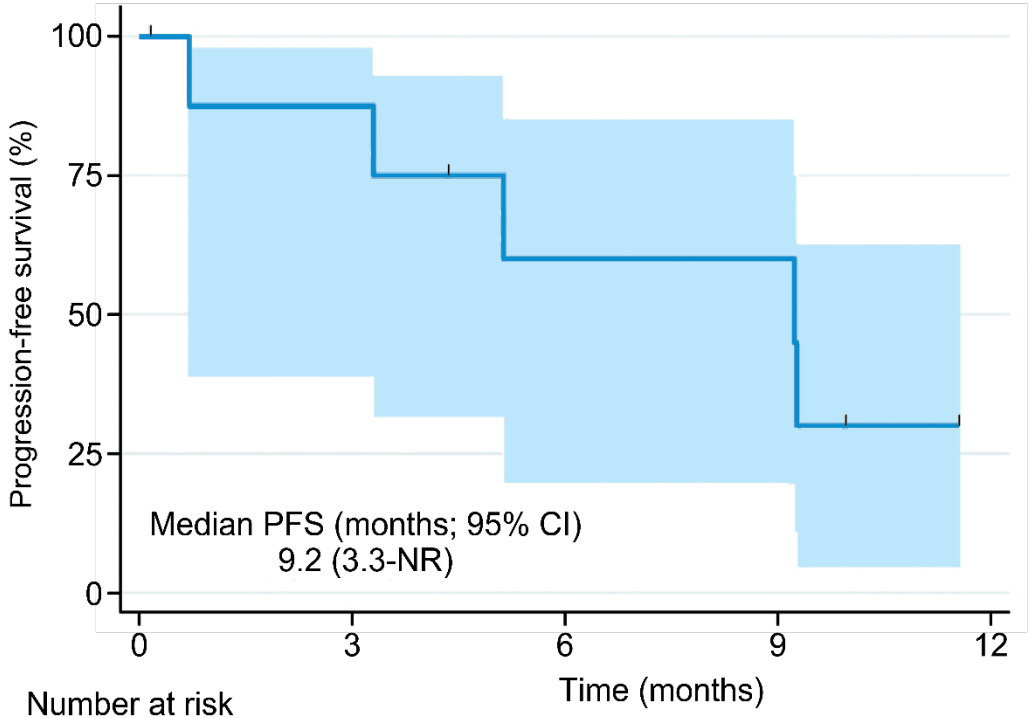
	Median PFS (months; 95% CI)
2 prior TKIs	NR (4.5-NR)
≥2 prior TKIs	11.2 (4.5-NR)
≥3 prior TKIs	6.5 (3.6-11.6)

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

Sequencing of ALK-TKI Generations Lead to More *ALK* Resistance Mutations

Clonal evolution of resistance to sequential *ALK*-targeting therapies.[1,2]

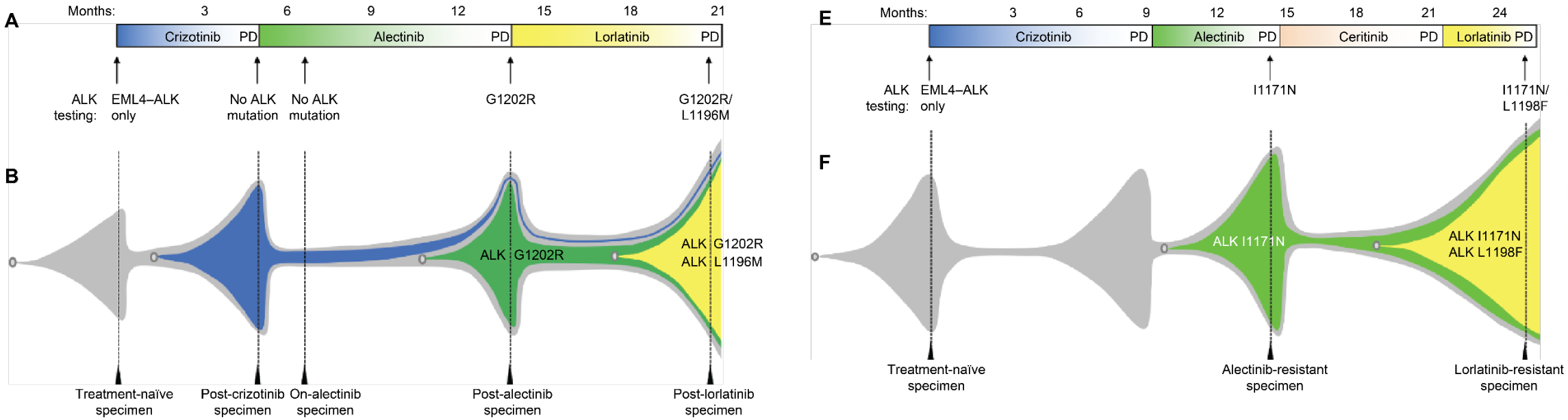


Image adapted from Yoda S, Lin JJ, *Cancer Discov.* 2018;8(6):714–729.

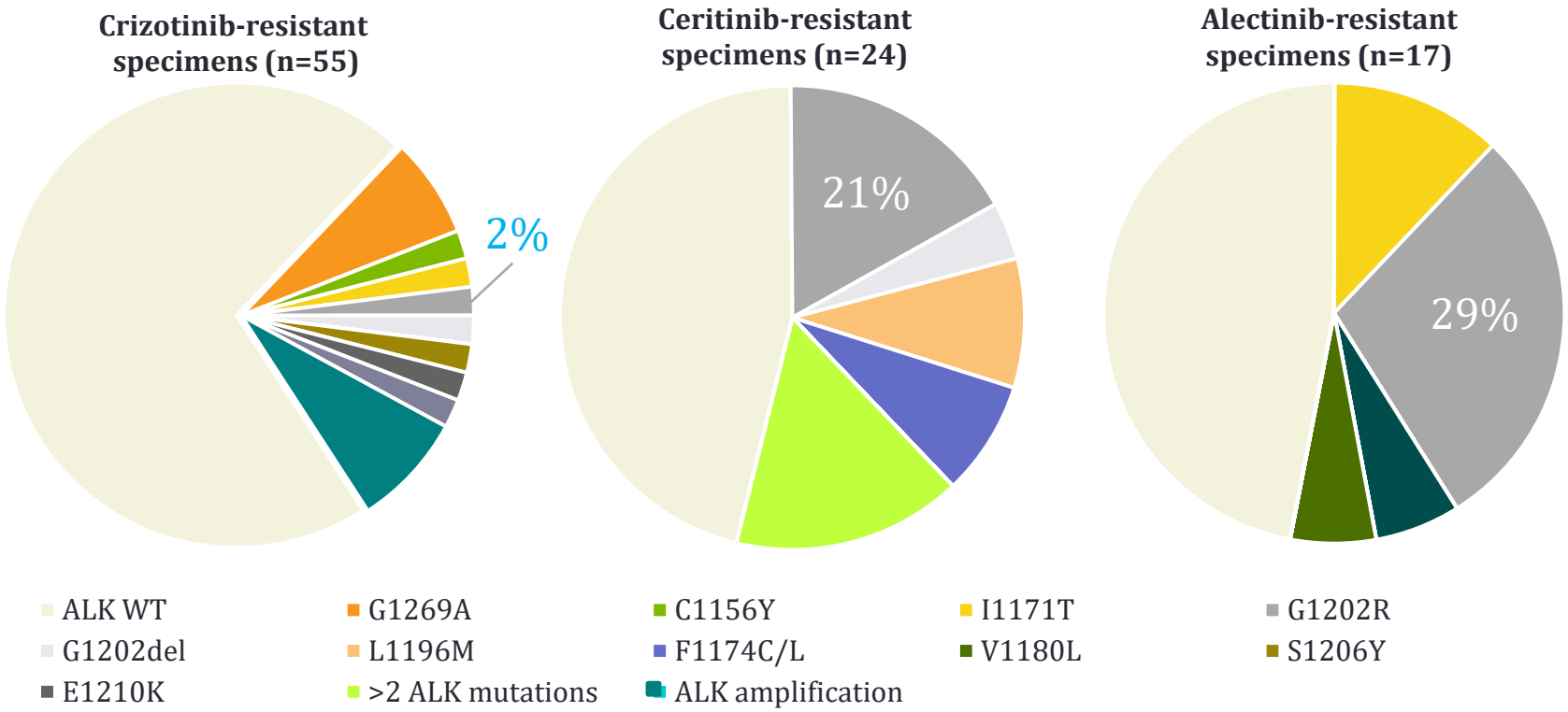
As more generations of *ALK*-TKI were sequenced, more "monster" *ALK* resistance mutations appeared.[2]

1. Yoda S, Lin JJ, *Cancer Discov.* 2018;8(6):714–729.
2. Ou SH S04.02. Presented at IASLC TTLC 2021

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

Resistance upon progression with second-generation ALK TKIs

Frequency and distribution of ALK-resistance mutations*



*If a specimen is listed as having ≥2 ALK resistance mutations, the individual mutations are not separately represented in the charts

Compared with crizotinib, there were more resistance mutations after treatment with second-generation ALK inhibitors, including the difficult-to-treat G1202R mutation

Gainor JF, et al. *Cancer Discov* 2016;6:1118–33.

Lorlatinib covers the broadest range of ALK resistance mutations

- Secondary mutations in the ALK kinase domain can induce resistance to first- and second-generation ALK TKIs1
- Lorlatinib has broad-spectrum potency against most known ALK resistance mutations, including ALK G1202R1,2
- ALK positive patients also develop compound mutations upon ***sequential treatment*** with ALK inhibitors

	Cellular ALK Phosphorylation Mean IC_{50} (nM)			
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Lorlatinib**
EML4-ALK	38.6	4.9	11.4	2.3
C1156Y	61.9	5.3	11.6	4.6
I1171N	130.1	8.2	397.7	49.0
I1171S	94.1	3.8	177.0	30.4
I1171T	51.4	1.7	33.6	11.5
F1174C	115.0	38.0[a]	27.0	8.0
L1196M	339.0	9.3	117.6	34.0
L1198F	0.4	196.2	42.3	14.8
G1202R	381.6	124.4	706.6	49.9
G1202del	58.4	50.1	58.8	5.2
D1203N	116.3	35.3	27.9	11.1
E1210K	42.8	5.8	31.6	1.7
G1269A	117.0	0.4	25.0	10.0

IC_{50} < 50 nM
IC_{50} ≥ 100 < 200 nM
IC_{50} ≥ 200 nM

IC_{50}, half-maximal inhibitory concentration

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

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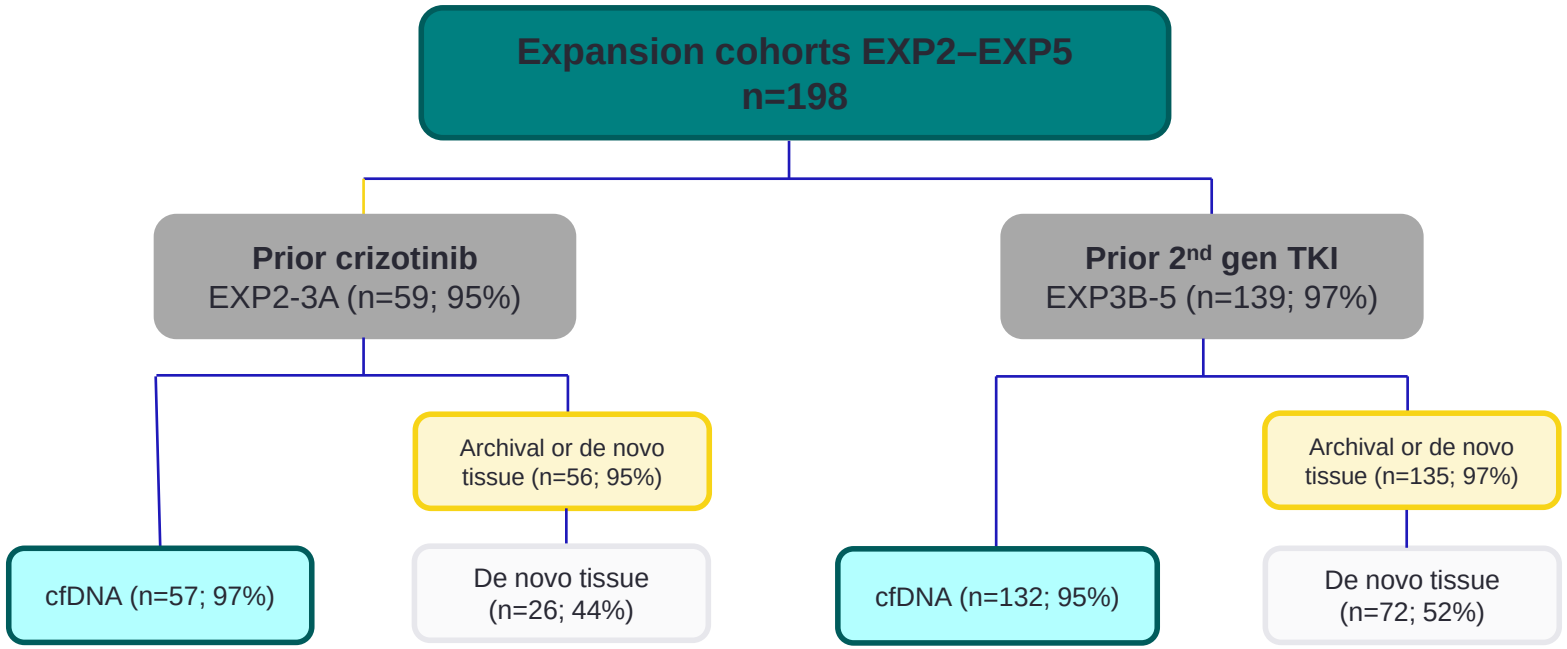
ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced ALK-Positive NSCLC

Alice T. Shaw, Benjamin J. Solomon, Benjamin Besse, Todd M. Bauer, Chia-Chi Lin, Ross A. Soo, Gregory J. Riely, Sai-Hong Ignatius Ou, Jill S. Clancy, Sherry Li, Antonello Abbattista, Holger Thurm, Miyako Satouchi, D. Ross Camidge, Steven Kao, Rita Chiari, Shirish Gadgeel, Enriqueta Felip and Jean-François Martini

Shaw AT, *et al*. J Clin Oncol 37:1370-1379.

Flow chart of study population

- 198 patients were enrolled into expansion cohorts EXP2–EXP5 only, depending on prior treatment
- Cohorts EXP1 and EXP6 were not included in the present analysis



Adapted from Shaw AT, *et al.* J Clin Oncol 37:1370-1379.

Shaw AT, *et al.* J Clin Oncol 2019 37:1370-1379.

Please see summary of prescribing information on last slide

Resistance mutation is not a predictor of 2nd /3rd gen ALK TKI efficacy in patients progressed on Crizotinib

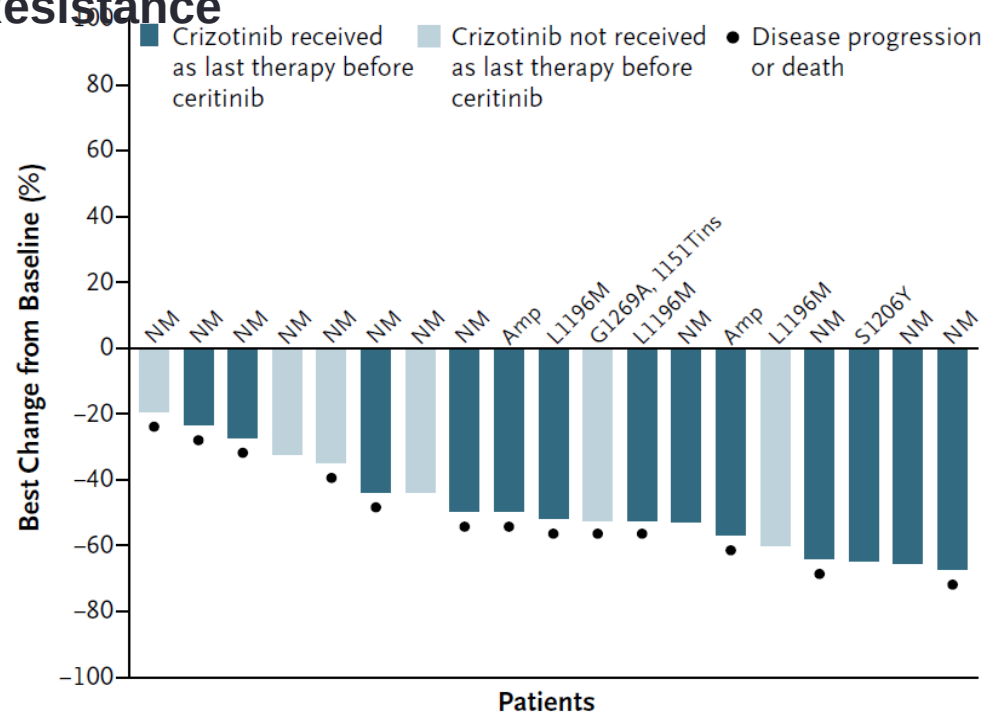
- Second-generation inhibitors are generally effective **even in the absence of crizotinib-resistant *ALK*** mutations, likely reflecting incomplete inhibition of ALK by crizotinib in many cases[1]
- Activity of ceritinib in patients whose tumors had progressed during crizotinib treatment may be independent of the underlying mechanism of acquired resistance [2]

ASCEND 1

- Repeat biopsy = 19 patients progressed on crizotinib
  ALK gene amplification = 2
  secondary resistance mutations = 5
  No detectable mutation = 12

- Tumor regression was observed in all the patients, regardless of molecular status.
- Confirmed responses were seen in 6 of 7 patients with *ALK* gene amplification or mutation and in 7 of 12 patients without *ALK* alteration

Correlation of Response to Ceritinib with *ALK* Gene Alteration among Patients with Crizotinib Resistance



1. Gainor JF, et al. *Cancer Discov* 2016;6:1118–33., 2. Shaw et al. N Engl J Med 2014;370:1189-97

Efficacy: Patients previously treated with crizotinib (EXP2-3A)

Outcome measure (n=59)		Plasma genotyping[a]		Tissue genotyping	
		ALK-mutation positive (n=11)	*ALK*-mutation negative (n=44)	*ALK*-mutation positive (n=11)	*ALK*-mutation negative (n=43)
ORR, % (95% CI)	73 (60–84)	73 (39–94)	75 (60–87)	73 (39–94)	74 (59–87)
Median DOR, months (95% CI)	NR (8.4–NR)	NR (5.6–NR)	NR (6.8–NR)	NR (NR–NR)	16.6 (6.8–NR)
Median PFS, months (95% CI)	11.1 (8.2–NR)	NR (1.7– NR)	12.5 (8.2–NR)	NR (2.6–NR)	12.5 (6.9–NR)

Adapted from Shaw AT, *et al*. J Clin Oncol 37:1370-1379.

In crizotinib-resistant patients, the efficacy of lorlatinib was comparable in patients with and without *ALK* mutations

- [a]Plasma sample failed cfDNA analysis in two patients. NR, not reached.

Shaw AT, *et al*. J Clin Oncol 2019 37:1370-1379.

Clinical efficacy of 2nd generation ALK inhibitors in crizotinib resistant patients

	Ceritinib		Alectinib		Brigatinib	
Reference	Kim et al. Lancet Oncol 2016	Crino et al. JCO 2016	Ou et al. JCO 2016	Shaw et al. Lancet Oncol 2016	Gettinger et al. Lancet Oncol 2016	Kim et al JCO 2017 (ALTA) 90mg/ 90*-180mg
Patients (N)	163	140	138	87	70	112 / 110
ORR (%)	56	38	50	48	71	45 / 54
Median PFS (mths)	6.9	5.7	8.9	8.1	13.4	9.2 / 12.9 16.7 mths**

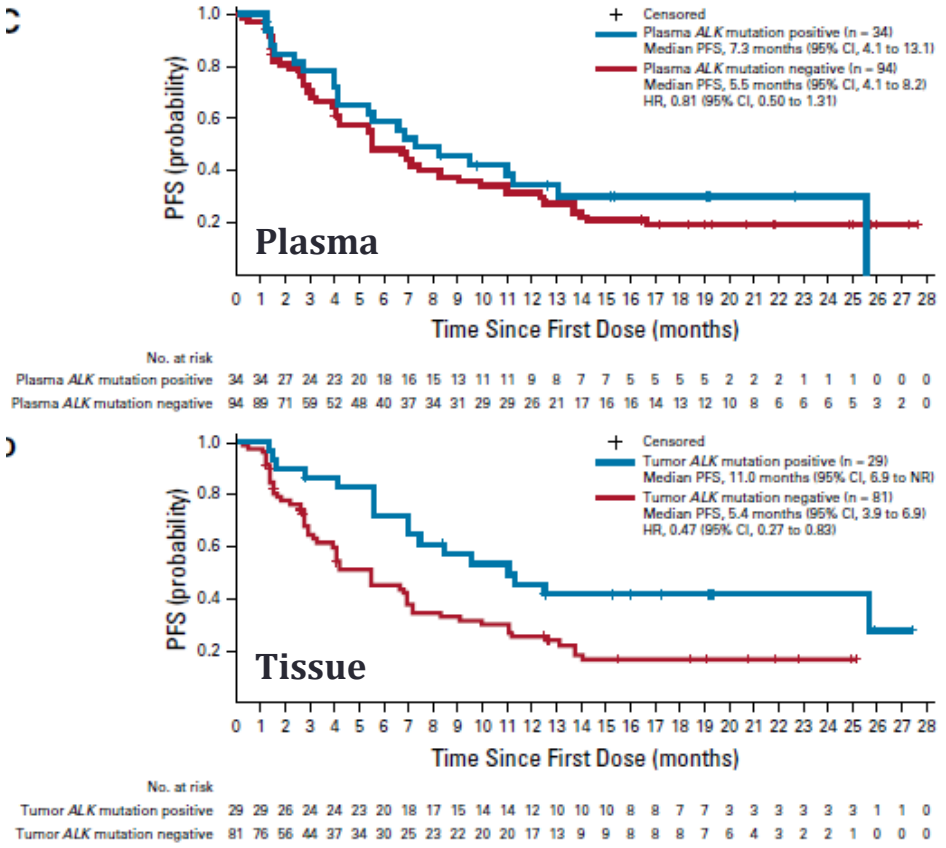
90mg 7 day run in then increase to 180mg

**Updated analysis of ALTA ORR for Brigatinib on 180mg dose Ahn et al. JTO 2017

MUNICH 2018 ESMO congress

Efficacy: Patients previously treated with ≥1 second-generation TKI(s) (EXP3B-5)

Outcome measure (n=139)		Plasma genotyping[a]		Tissue genotyping	
		ALK-mutation positive (n=34)	*ALK*-mutation negative (n=94)	*ALK*-mutation positive (n=29)	*ALK*-mutation negative (n=81)
ORR, % (95% CI)	40 (32–49)	62 (44–78)	32 (23–42)	69 (49–85)	27 (18–38)
Median DOR, months (95% CI)	7.1 (5.6–24.4)	7.0 (4.3–24.4)	7.1 (5.2–NR)	24.4 (6.9–NR)	4.3 (4.1–12.6)
Median PFS, months (95% CI)	6.9 (5.4–8.2)	7.3 (4.1–13.1)	5.5 (4.1–8.2)	11.0 (6.9–NR)	5.4 (3.9–6.9)



- The ORR to lorlatinib after a prior second-generation ALK TKI differed depending on *ALK* mutation status
- DOR and mPFS did not differ significantly depending on *ALK* mutation status when determined by plasma genotyping, but did differ significantly when determined by tissue genotyping
  - These differences were more pronounced when tissue genotyping was limited to *de novo* biopsies

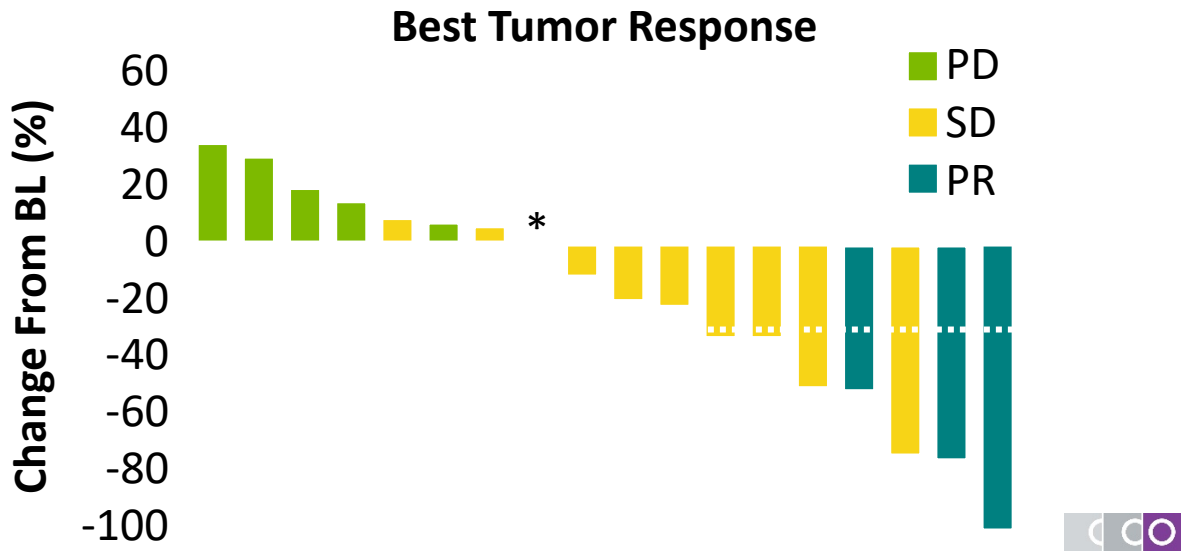
[a]Plasma sample failed cfDNA analysis in four patients. NR, not reached.

Shaw AT, *et al*. J Clin Oncol 2019 37:1370-1379.

Limited Role of Other Second-Generation ALK TKIs After PD on First-line Alectinib

- **Ceritinib**[1]
  - Retrospective analysis of 35 patients with *ALK*+ NSCLC treated with ceritinib
  - ORR: 44% (all patients)
    - **16% in 9 patients who received ceritinib immediately after alectinib**

- **Brigatinib**[2]
  - Retrospective analysis of 22 patients with alectinib-refractory *ALK*+ NSCLC treated with brigatinib
  - ORR: 17%; median PFS: 4.4 mos



*Patient with 0% change from BL.

1. Yoshida. In Vivo. 2018;32:1587. 2. Lin. J Thorac Oncol. 2018;13:1530.

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Clinical Efficacy of Alectinib in Patients with ALK-Rearranged Non-small Cell Lung Cancer After Ceritinib Failure

Table I. *Details of anaplastic lymphoma kinase (ALK) rearrangement-positive patients treated with alectinib after ceritinib failure.*

Patient no.	Age (years)	Gender	Stage	ALK inhibitor treatment sequence	PFS on Ce (months)	Response to Ce	Duration between Ce and Al (months)	Treatment before Al	Lesion description	Response after Al	Resistance mutation in *ALK*
1.	68	M	IV	Ce	22.4	PR	0	Ce	Pleural effusion, and dissemination	PD	-
2.	55	F	IIIB	Cr→Ce	11.9	PR	0	Ce	Pulmonary	PD	Negative
3.	71	M	IV	Ce→Cri	9.4	PR	5.8	Cr	CNS, liver, Pleural effusion, and dissemination	PD	-
4.	29	M	IV	Cr→Ce→Cr	3.0	SD	0	Ce	Mediastinal LN and pleural effusion	PD	G1269A
5.	37	M	IV	Cr→Ce	4.1	PR	0	Ce	Liver	PR	-
6.	51	M	Rec	Ce→Cr	1.7	PD	21.2	Cr	CNS, Bone	PR	-
7.	39	M	IV	Cr→Ce→Cr	7.1	PR	0	Ce	Pulmonary and pleural effusion	PD	-
8.	63	M	IV	Ce	7.5	PR	11.9	Pem	Pulmonary	SD	Negative

M, Male; F, female; Ce, ceritinib; Cr, crizotinib; Al, alectinib; PFS, progression-free survival; PR, partial response; SD, stable disease; PD, progressive disease; Rec, postoperative recurrence, Pem, pemetrexed; LN, lymph nodes; CNS, central nervous system.

Among the eight study patients, two (25%) had PR, one (12%) had SD, and five (63%) had PD. The median PFS was 3.6 months (95% confidence interval=0-7.1 months)

Oya, Yuko et al Clinical Efficacy of Alectinib in Patients with ALK-Rearranged Non-small Cell Lung Cancer After Ceritinib Failure VL - 37 DO - 10.21873/anticanres.12103 JO - Anticancer research

Efficacy according to type of *ALK* mutation

- Lorlatinib demonstrated antitumor activity against all five of the most common *ALK* mutations

ALK mutation	N	ORR, % (95% CI)	Median DOR, months (95% CI)	Median PFS, months (95% CI)
G1202R/del	28	57 (37–76)	7 (6.1–24.4)	8.2 (5.6–25.6)
F1174X	12	42 (15–72)	NR (5.7–NR)	7.4 (2.8–NR)
L1196M	12	67 (35–90)	NR (5.2–NR)	NR (2.8–NR)
G1269A	9	89 (52–100)	NR (5.6–NR)	NR (8.2–NR)
I1171X	8	75 (35–97)	4.2 (2.8–4.2)	5.5 (4.1–6.9)

Adapted from Shaw AT, *et al.* J Clin Oncol 37:1370-1379.

- Lorlatinib was effective against ALK G1202R/del, the most common mutation detected, which has previously demonstrated resistance to both first- and second-generation ALK inhibitors

- Patients with at least one on-study target lesion assessment were included. If any assessment procedures differed from or were not interchangeable with the procedure at screening, the change from baseline could not be calculated and is not displayed. NR, not reached.

Shaw AT, *et al.* J Clin Oncol 2019 37:1370-1379.

Efficacy according to number of *ALK* mutations

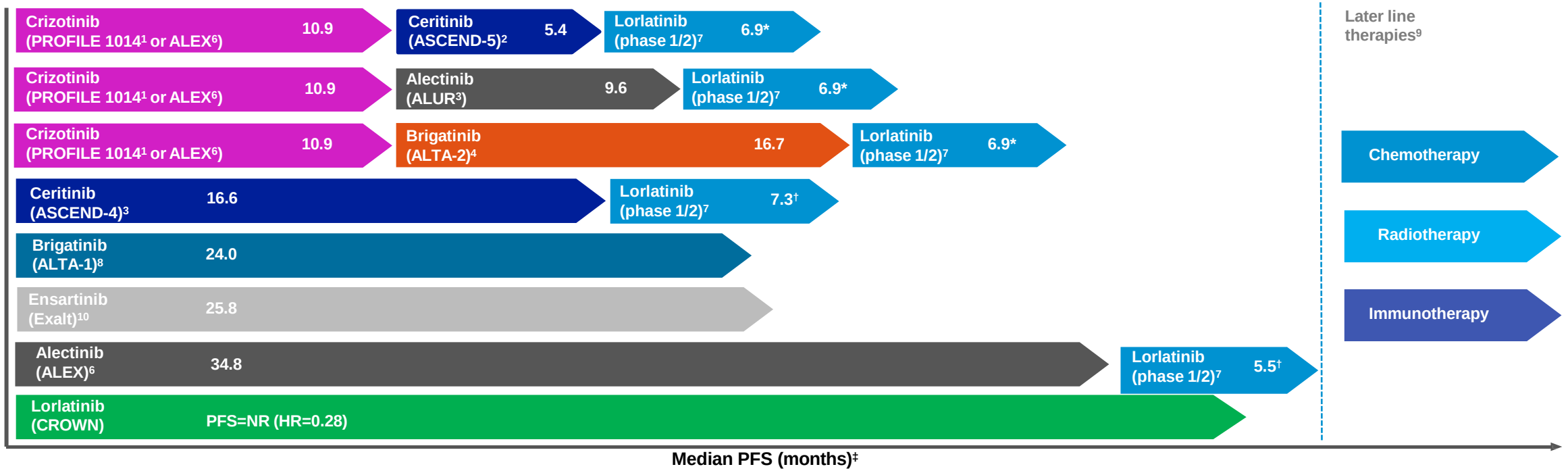
- Among patients with detectable *ALK* mutations, approximately one-third of patients had more than one *ALK* mutation
- When efficacy of lorlatinib among patients in EXP3B to EXP5 who harbored either one *ALK* mutation or >1 *ALK* mutation was compared,
  - ORR trended higher among patients with one *ALK* mutation only, compared with patients with >1 *ALK* mutation (75% versus 56%, respectively)
  - Median duration of response was longer in patients with one *ALK* mutation only, compared with patients with >1 *ALK* mutation (24.4 months versus 6.1 months, respectively)

In patients who failed ≥1 second-generation ALK inhibitor(s), the number of *ALK* resistance mutations may affect the efficacy of lorlatinib, but larger studies are required to validate this finding.

Shaw AT, *et al*. J Clin Oncol 2019 37:1370-1379.

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: Ananaplastic 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, loratinib 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: Ananaplastic lymphoma kinase; IC: Intracranial; NSCLC: Non-small–cell lung cancer; PFS: Progression-free survival; QoL: Quality of life

Thank You