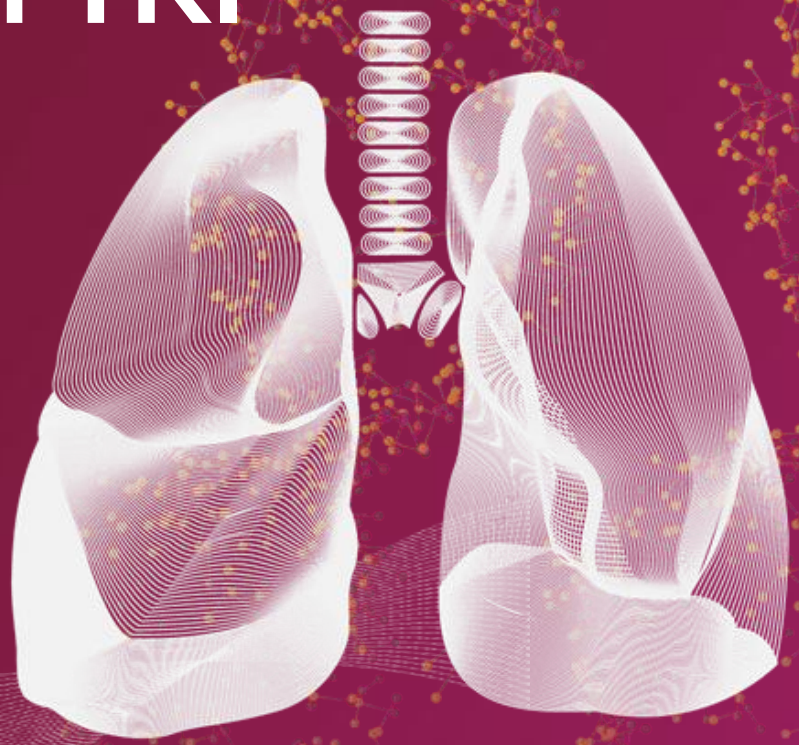
Selection of 1st line therapy in ALK+ mNSCLC: 1st or 2nd Gen TKI

Dr Naresh Somani MD,DM

Director Oncology &

HOD Medical Oncology

HCG cancer Centre & Somani Hospital , Jaipur

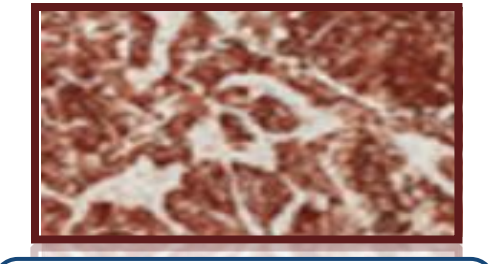


Molecular technologies

Tests performed on primary or metastatic tumor tissue, pleural fluid, or cytologic FFPE samples

FISH[1]

Fluorescent probes label and detect specific regions on a gene

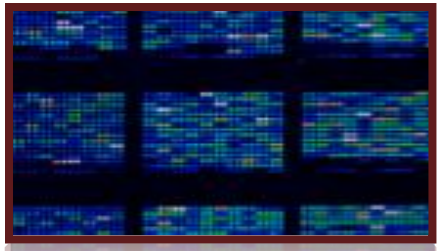


IHC[2]

Antibodies detect specific proteins expressed by cells

RT-PCR[3]

Many copies of DNA produced from minute quantities of RNA source material



NGS[4]

High-throughput sequencing using massively parallel sequencing technology

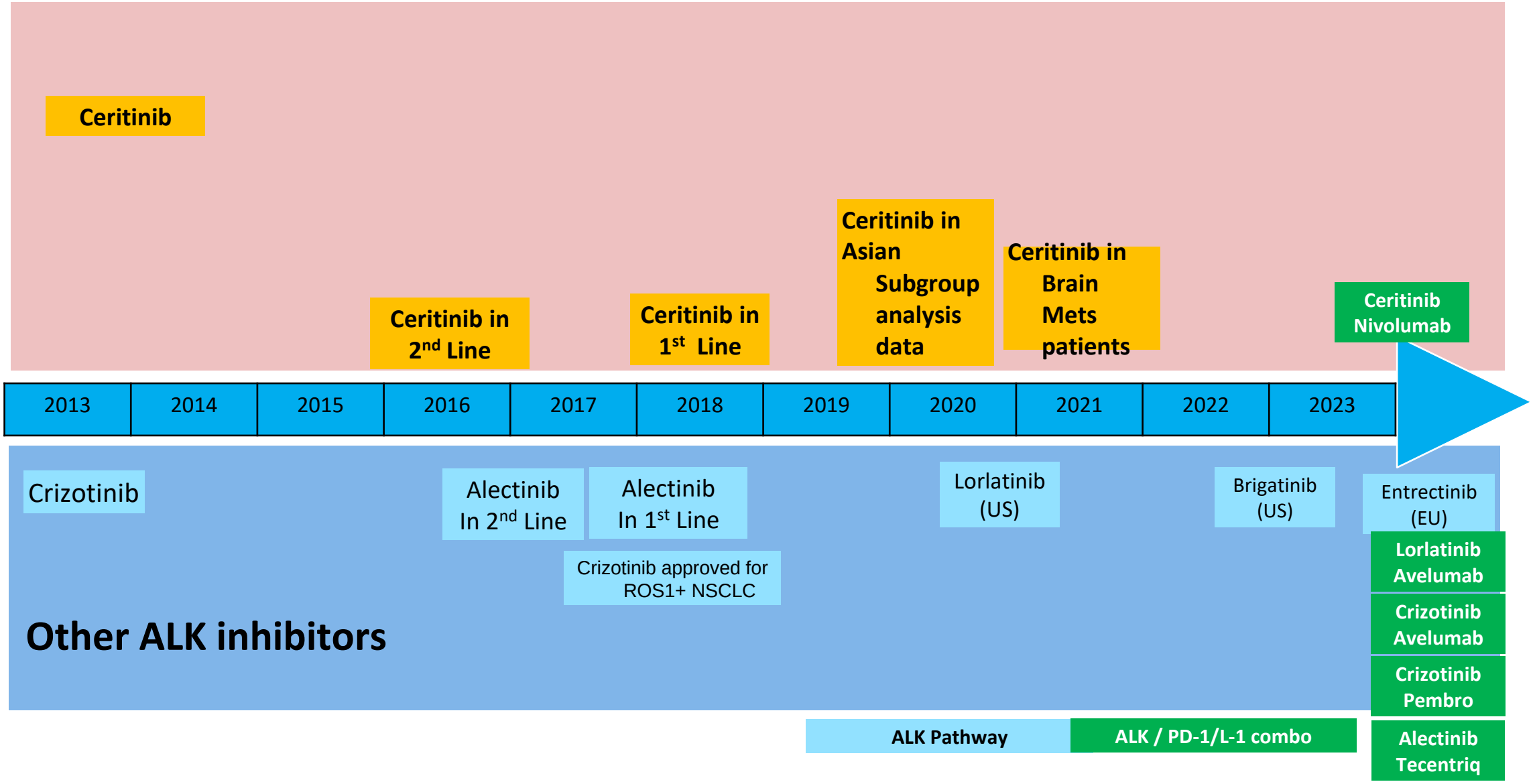
FFPE, formalin-fixed paraffin-embedded; FISH, fluorescence *in situ* hybridization; NGS, next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction

1. Vincent MD *et al. Curr Oncol* 2012;19:S33–S44; 2. Ramos-Vara JA. *Vet Pathol* 2005;42:405–426; 3. Peake I. *J Clin Pathol* 1989;42:673–676; 4. Grada and Weinbrecht. *J Invest Dermatol* 2013;133:e11

First line treatment of ALK rearranged NSCLC: spoilt for choices

- Crizotinib
- Ceretinib
- Alectinib
- Brigatinib
- Ensartenib
- Lorlatinib

Landscape: Advanced ALK+ NSCLC approvals

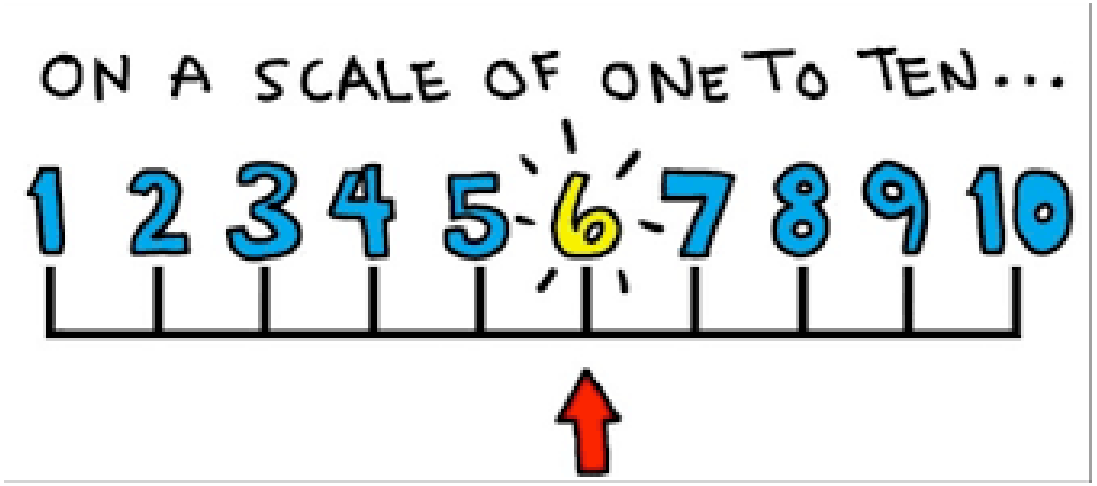


How do you decide??

- Progression free survival/overall survival
- CNS efficacy
- Toxicity profile
- Long term efficacy data
- Second line strategies
- Availability
- Cost cost cost…..

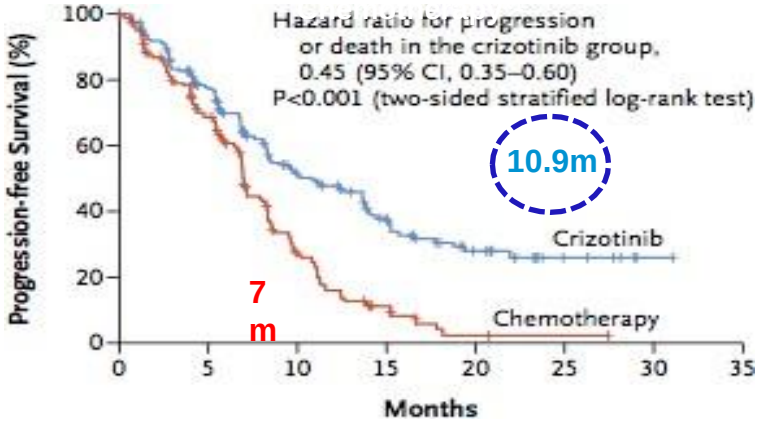
Rate them on a scale of 10….

- Progression free survival/overall survival
- CNS efficacy
- Toxicity profile
- Long term efficacy data
- Second line strategies
- Availability
- Cost cost cost…..

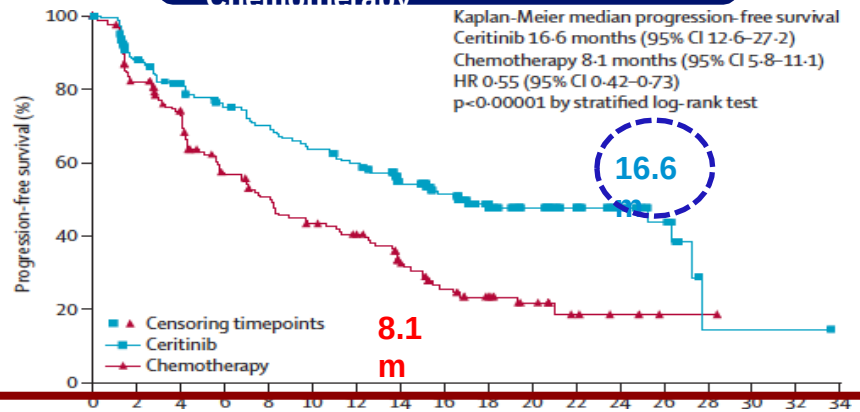


Randomised trials with first- and second-generation ALK-TKIs

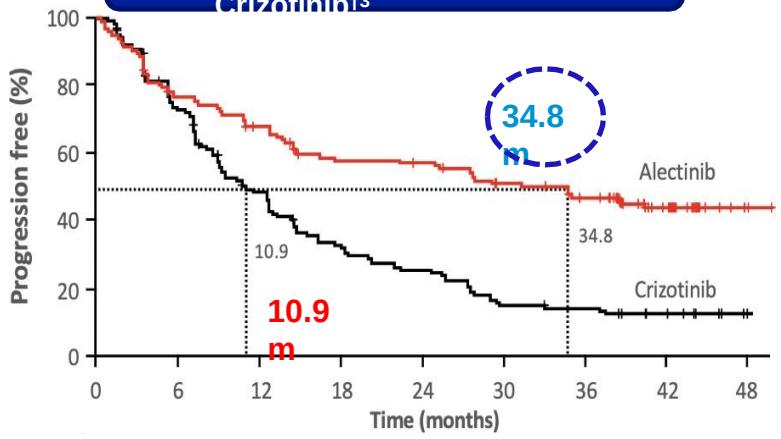
PROFILE 1014: Crizotinib vs



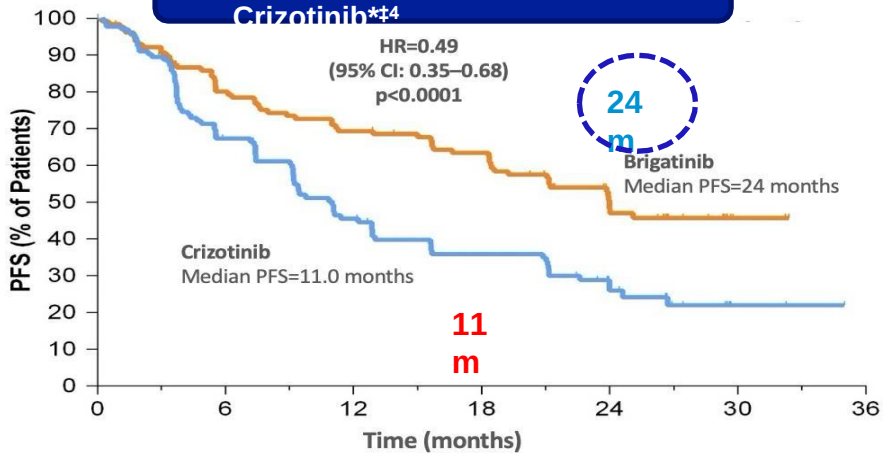
ASCEND 4: Ceritinib vs Chemotherapy*2



ALEX: Alectinib vs Crizotinib†3



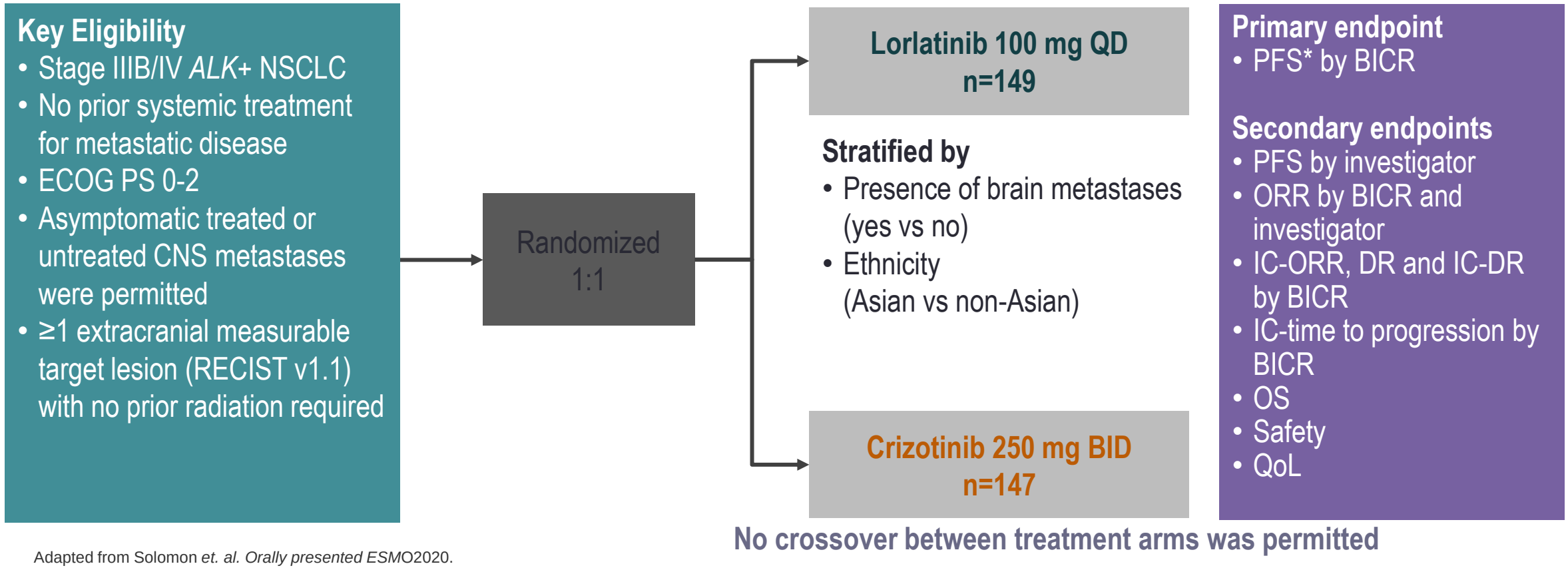
ALTA 1L: Brigatinib vs Crizotinib*‡4



*PFS assessed by independent review committee; †PFS assessed by investigator.
‡Brigatinib is currently not approved for use as a first line treatment option for ALK+ NSCLC in India.

1. Solomon B et al. *N Engl J Med* 2014; 371:2167–77; 2. Soria JC , et al. *Lancet* 2017;389(10072):917–29; 3. Mok T, et al. *Ann Oncol* 2020;31(8):1056–64; 4. Camidge R, et al. Presented at ESMO Asia 22–24 Nov 2019, Singapore.

CROWN Study Design



Adapted from Solomon *et. al. Orally presented ESMO*2020.

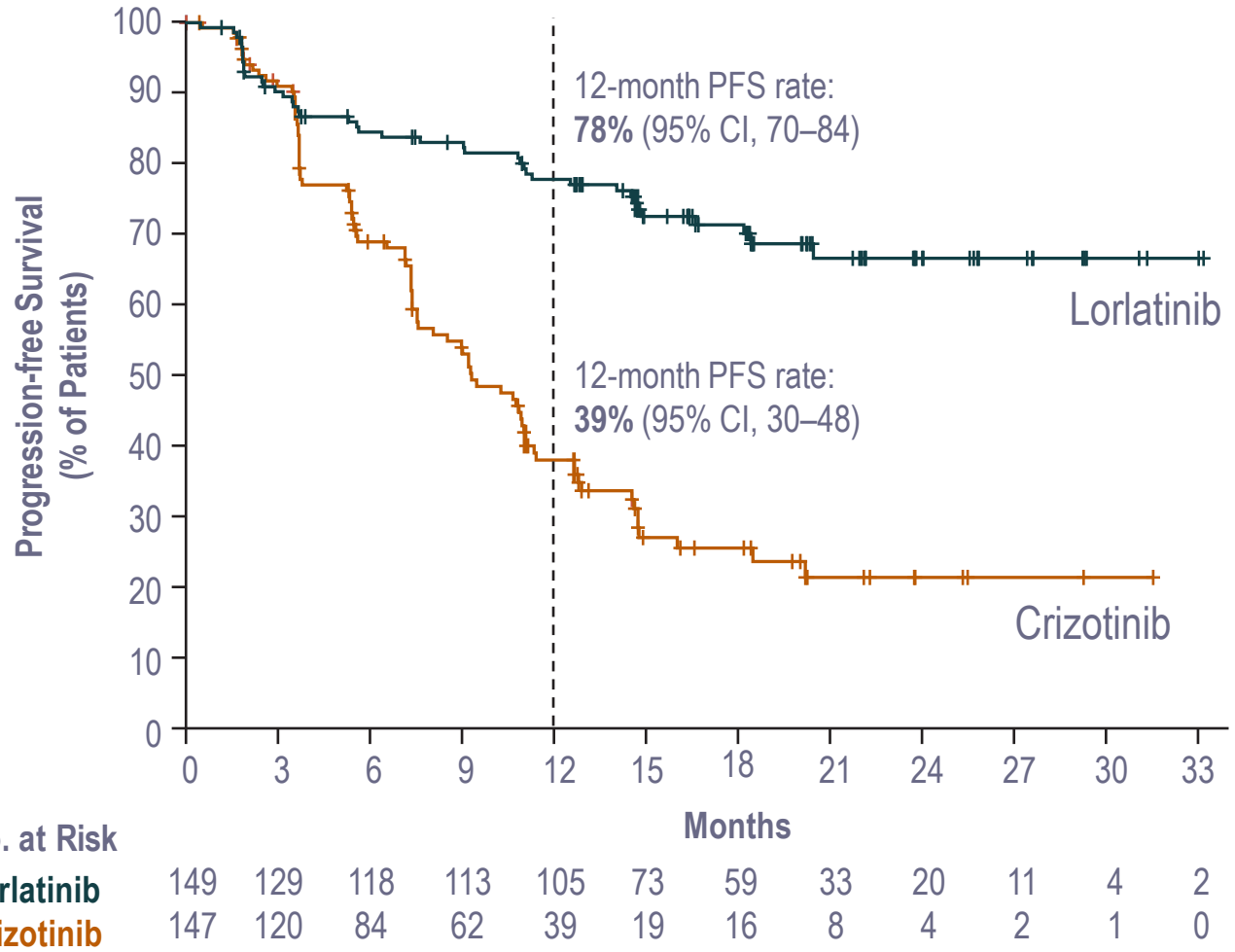
■ *Defined as the time from randomization to RECIST-defined progression or death due to any cause.

BICR, blinded independent central review; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.
ClinicalTrials.gov number, NCT03052608

Solomon et al. Orally presented at European Society of Medical Oncology (ESMO) Virtual Congress; Sep19-21,2020.

Please see summary of prescribing information on last slide

Primary Endpoint: PFS by BICR



Adapted from Solomon *et. al. Orally presented ESMO*2020.

	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	41 (28)	86 (59)
Median PFS, months (95% CI)	NE (NE–NE)	9.3 (7.6-11.1)
HR (95% CI) 1-sided P value*	**0.28** (0.19-0.41) <0.001	

*By stratified log-rank test.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival

Solomon et al. Orally presented at European Society of Medical Oncology (ESMO) Virtual Congress; Sep19-21,2020.

Please see summary of prescribing information on last slide

Comparison of First-Line ALK TKI Studies

ALK TKI	Comparator Arm	# of patients	ORR (%) *Investigator Assessed	Median PFS	Intracranial ORR (%)	CNS CR Rate
Ceritinib ASCEND-4	Chemo	376	72.5 vs 26.7	16.6 vs 8.1	72.7 vs 27.3	---
Alectinib ALEX	Crizotinib	303	*82.9 vs 75.5	25.7 vs 10.4 (HR 0.50)	81 vs 50	38%
Brigatinib ALTA-1L	Crizotinib	275	74 vs 62	24.0 vs 11.0 (HR 0.49)	78 vs 26	11%
Ensartinib exALT	Crizotinib	290	75 vs 67	25.8 vs 12.7 (HR 0.51)	64 vs 21	---
Lorlatinib CROWN	Crizotinib	296	76 vs 58	NR vs 9.3 (HR 0.28)	82 vs 23	71%

1. Solomon et al., ESMO 2020 2. Camidge et al., JTO 2019 3.Camidge et al., ESMO Asia 2019

Lets discuss the pros and cons of all the available drugs….

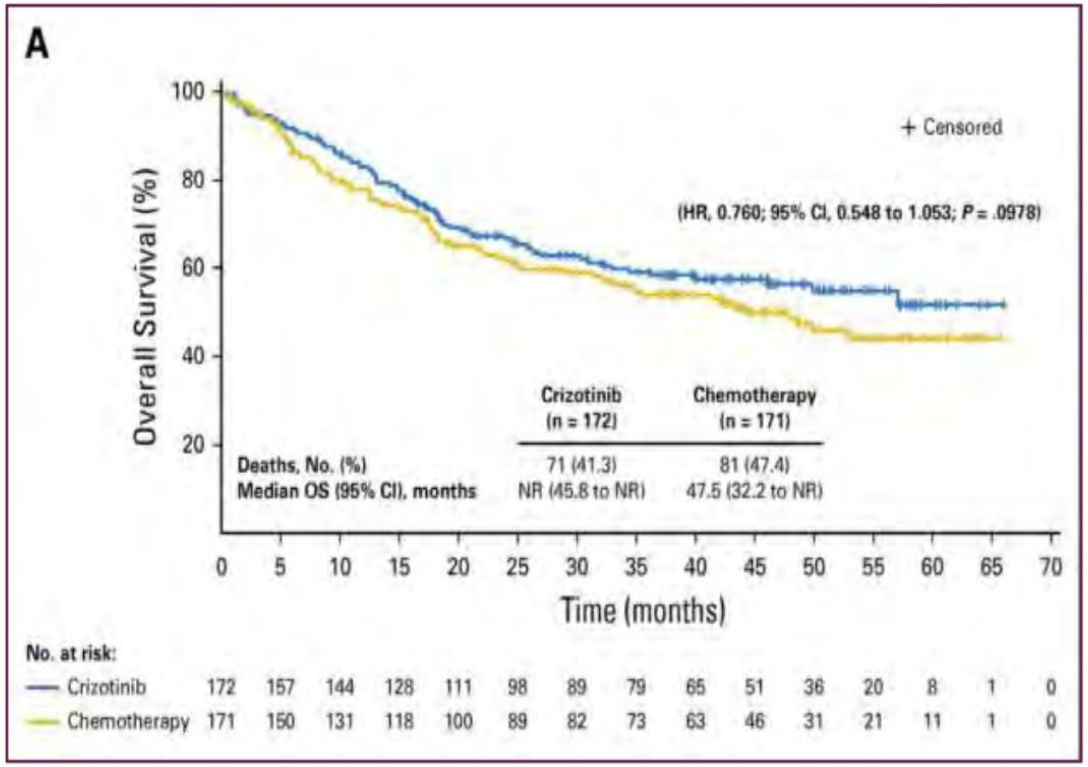
Pros and Cons of Crizotinib

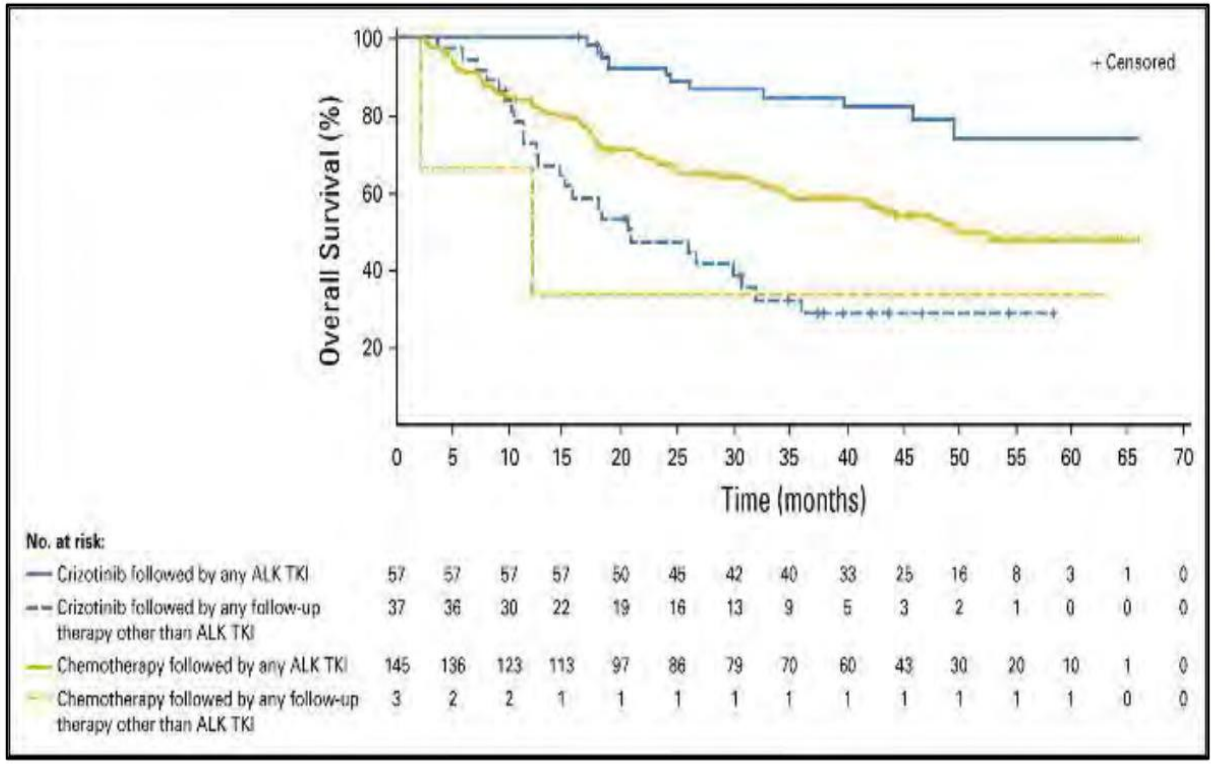
- PROs
- -the first mover advantage
- - relatively cost effective
- Good clinical experience
- -PFS – 10-12 months
- Toxicity profile- easy to manage

- CONS
  - PFS is only 10-12 months
  - Doesn’t cross Blood brain barrier
  - 10 months of crizalk- 6-8 months of 2ng gen TKIs- 6 month of 3rd gen TKIs- overall OS in RWE- 30-32 months
  - Hepatotoxicity could be a concern

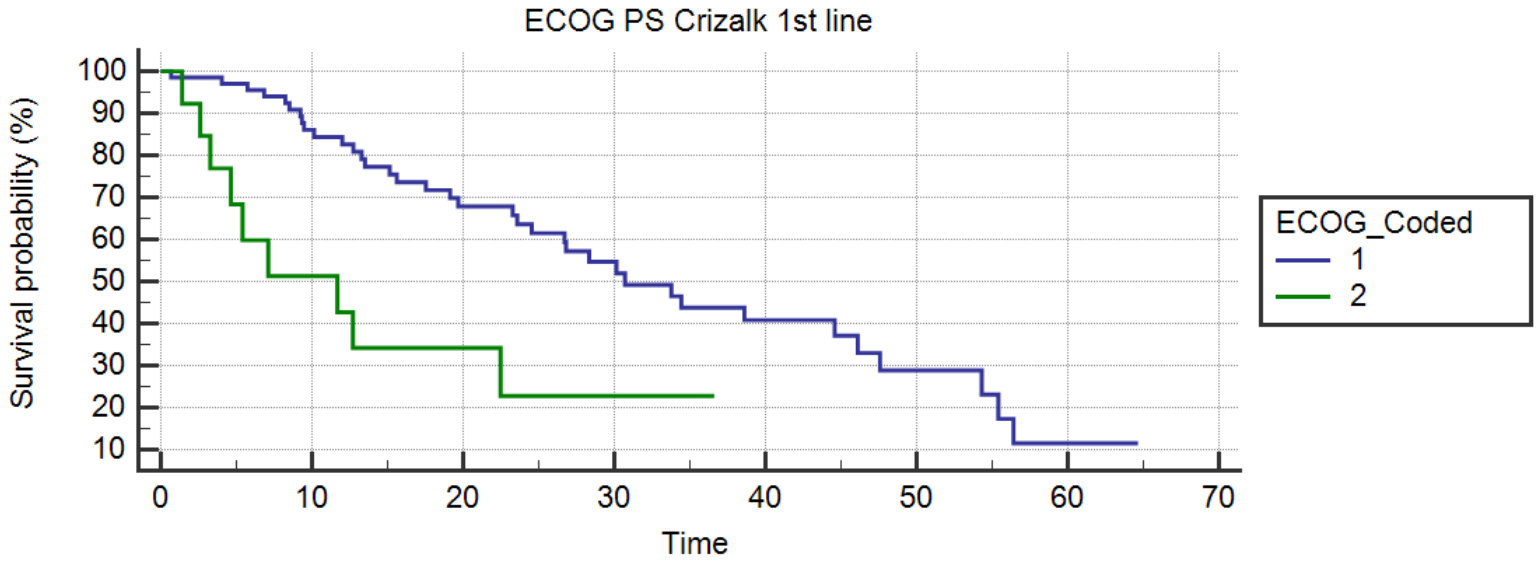
Final Overall Survival Analysis from PROFILE 1014

Solomon et al. JCO 2018





- Survival probability at 4 yrs = 56.6% (95% CI 48.3, 64.1) for crizotinib, median OS NR (45.8,NR)
- Median OS was longest (NR) in 57 patients who received crizotinib then another ALK TKI
- Median OS was 20.8 months in 37 patients who received crizotinib then treatment other than an ALK TKI
- No prospective, randomised data to support sequential crizotinib followed by a next generation ALKi versus a next generation ALKi alone



Median OS for 1st line Crizotinib ECOG PS
ECOG 0-2: 30.8months
ECOG 3-4: 11.8months

P value:0.001

Pros and Cons of Ceretinib

- PROs
  - PFS- 16.6 months
  - Has reasonable BBB activity
  - Cost effective in Indian scenario

- CONS
  - -No head to head data with Crizalk
  - -Toxicity profile
    - Hyperglycemia, nausea, vomiting, Hyperamylasemia
  - What after Ceretinib?

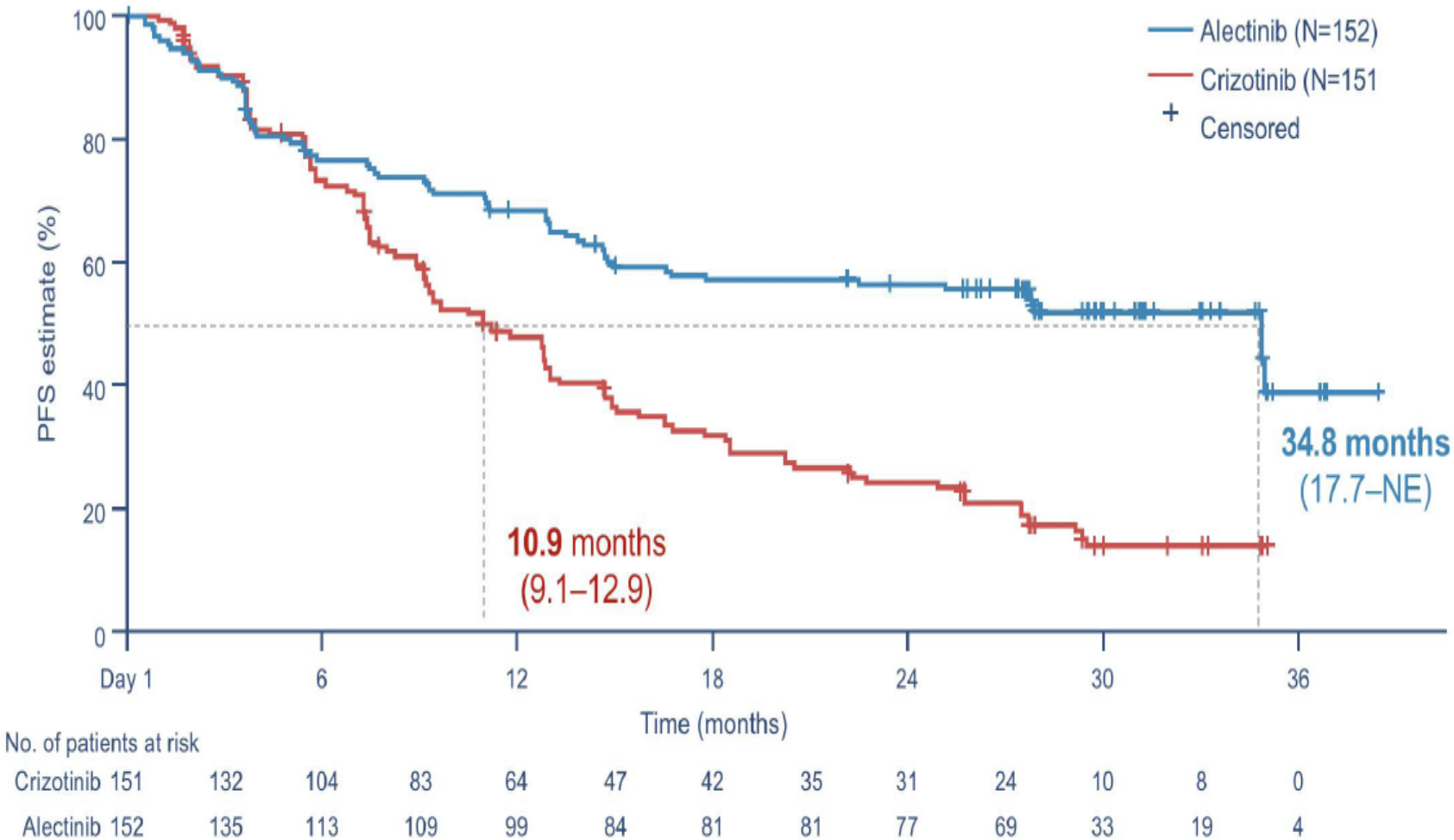
    -3rd Gen TKIs- 6 months- chemo- BSC

Pros and Cons of Alectinib…

- PROS
- Impressive PFS
- Impressive Os
- Favorable toxicity profile
- Crosses BBB

- CONS
  - The ideal dosage
  - J ALEX vs ALEX
  - What if CROWN surpasses ALEX!!!!

Alectinib is Superior to Crizotinib as First-Line Therapy: Updated Results of Global ALEX

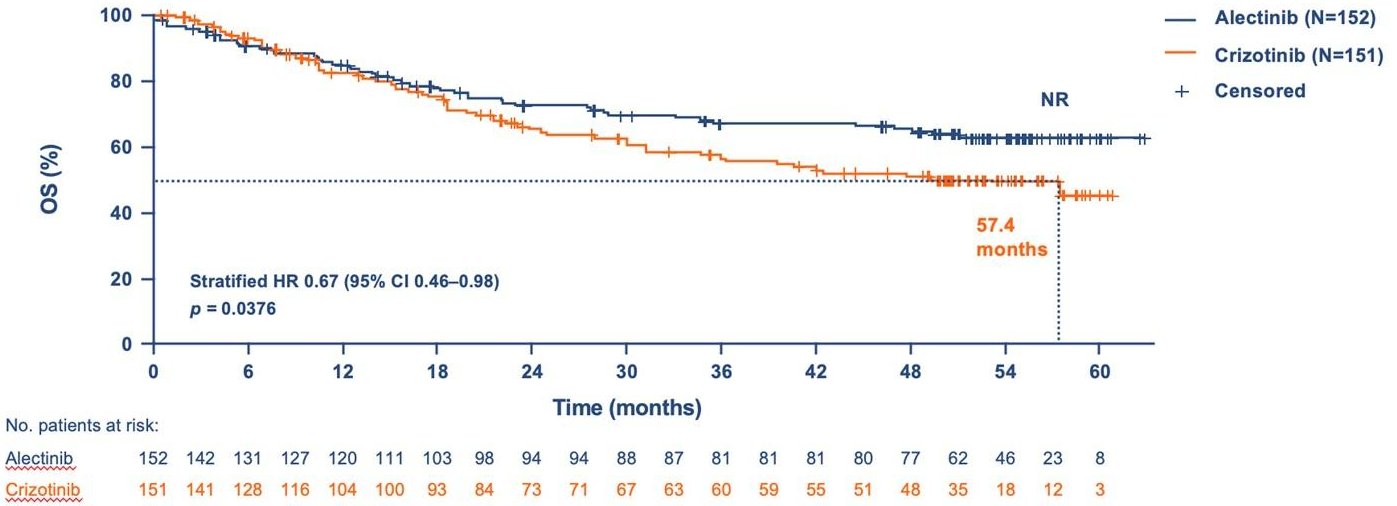


Camidge et al., ASCO 2018

9518

ALEX – updated OS

(median follow-up 48.2 mo)



OS data remain immature, with 37% of events recorded (stratified HR 0.67, 95% CI 0.46–0.98)

Median OS was not reached with alectinib vs 57.4 months with crizotinib (95% CI 34.6–NR)

NR, not reached

Pros and Cons of Lorlatinib

- PROS
- - Impressive HR for PFS
- Impressive HR for OS
- Crosses BBB
- Latest AACR data is mouth watering

- CONS
- Unfavorable toxicity profile
- What after Lorlatinib
- Final Data remains to be seen

AACR 20

Abstract #CT223

Updated Efficacy and Safety From the Phase 3 CROWN Study of First-Line Lorlatinib vs Crizotinib in Advanced Anaplastic Lymphoma Kinase (*ALK*)–Positive Non-Small Cell Lung Cancer (NSCLC)

Benjamin J. Solomon,[1] Todd Bauer,[2] Tony Mok,[3] Geoffrey Liu,[4] Julien Mazieres,[5] Filippo de Marinis,[6] Yasushi Goto,[7] Dong-Wan Kim,[8] Yi-Long Wu,[9] Mikhail Dvorkin,[10] Jacek Jassem,[11] Froylán López-López,[12] Ross Soo,[13] Anna Polli,[14] Elisa Dall'O',[14] Laura Iadeluca,[15] Francesca Toffalorio,[14] Enriqueta Felip[16]

Conclusions

- With approximately 18 months of additional follow-up since the interim analysis of the phase 3 CROWN study, lorlatinib continued to show superior overall and intracranial (IC) efficacy compared with crizotinib in patients with *ALK*-positive NSCLC
  - Progression-free survival (PFS) by blinded independent central review (BICR) remained longer with lorlatinib than crizotinib; 3-year PFS was 63.5% with lorlatinib and 18.9% with crizotinib
  - Time to IC progression was longer with lorlatinib than crizotinib
- These efficacy benefits with lorlatinib compared with crizotinib were observed not only in patients with baseline brain metastases but also in patients without baseline brain metastases
  - In patients without baseline brain metastases, only 1 of 112 patients had evidence of IC progression, suggesting a protective effect against development of brain metastases on lorlatinib treatment
- No new safety signals were observed with longer follow-up
- These updated long-term data from CROWN confirm the efficacy of lorlatinib over crizotinib in patients with treatment-naive *ALK*-positive NSCLC and support the use of lorlatinib in these patients with and without baseline brain metastases

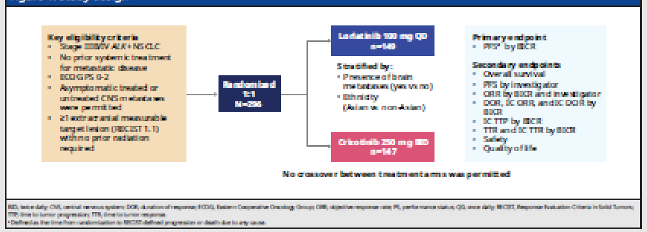
Background

- Lorlatinib, a third-generation ALK inhibitor designed to cross the blood-brain barrier, offers higher potency and greater coverage of *ALK* resistance mutations than second-generation ALK inhibitors[1]
- In the planned interim analysis of the phase 3 CROWN study (NCT03052608), lorlatinib improved PFS and demonstrated IC activity in patients with untreated *ALK*-positive NSCLC[2]
  - At 18.3 months of median follow-up in the lorlatinib arm, median PFS was not reached (NR; 95% CI, NR-NR) with lorlatinib and was 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (hazard ratio [HR], 0.28; 95% CI, 0.19-0.41; *P*<.001)
  - In patients with measurable baseline brain metastases, the frequency of confirmed IC response was greater with lorlatinib (82%) than crizotinib (23%)
- Based on the results of this study, the US Food and Drug Administration and regulatory authorities in Japan and Europe expanded lorlatinib approval to include first-line treatment in patients with metastatic NSCLC whose tumors are ALK positive[3-6]
- We report updated efficacy and safety data from the CROWN study after approximately 3 years of follow-up

Methods

- The CROWN study is an ongoing, international, randomized phase 3 trial comparing lorlatinib with crizotinib in patients with previously untreated *ALK*-positive NSCLC (**Figure 1**)

Figure 1. Study design



Results (Data Cutoff: September 20, 2021)

- Between May 2017 and February 2019, a total of 296 patients were randomly assigned to receive lorlatinib (n=149) or crizotinib (n=147)
- Median duration of treatment was 33.3 months with lorlatinib and 9.6 months with crizotinib
- Median duration of follow-up for PFS by BICR was 36.7 months with lorlatinib and 29.3 months with crizotinib
- Median PFS by BICR was NR (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (HR, 0.27; 95% CI, 0.184-0.388; **Figure 2A**)
- PFS as assessed by the investigators was also longer with lorlatinib than crizotinib
  - Median PFS was NR (95% CI, NR-NR) with lorlatinib and 9.1 months (95% CI, 7.4-10.9 months) with crizotinib (HR, 0.19; 95% CI, 0.131-0.274)
- PFS benefit with lorlatinib compared with crizotinib was also observed in patients with (**Figure 2B**) and without baseline brain metastases (**Figure 2C**)
- Time to IC progression by BICR was longer with lorlatinib than crizotinib in the intention-to-treat (ITT) population (**Figure 3A**) as well as in patients with (**Figure 3B**) and without baseline brain metastases (**Figure 3C**)
  - 8 of 37 patients with baseline brain metastases and only 1 of 112 patients without baseline brain metastases had IC progression with lorlatinib treatment
- In patients with measurable baseline brain metastases, confirmed IC ORR by BICR was 83.3% with lorlatinib and 23.1% with crizotinib (**Table 1**)
  - 72.2% and 7.7%, respectively, had a complete IC response
- With longer follow-up, no new safety signals have emerged
- Grade 3/4 all-causality adverse events (AEs) occurred in 75.8% of patients in the lorlatinib arm and 57.0% in the crizotinib arm (**Table 2**)
  - The incidence of grade 3/4 AEs in the lorlatinib arm was largely due to frequent occurrence of altered lipid levels such as hypercholesterolemia and hypertriglyceridemia (**Figure 4**)
- Cognitive effects occurred in 20.8% of patients in the lorlatinib arm; however, most (27 of 31) cognitive effects were grade 1/2 and no grade 4 event was observed
- AEs leading to permanent treatment discontinuation were reported in 7.4% of patients in the lorlatinib arm and 9.9% in the crizotinib arm

Figure 2: PFS by BICR

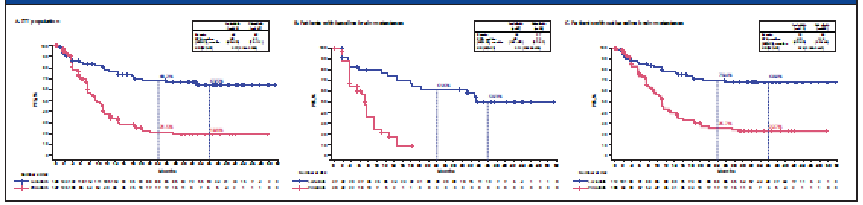


Figure 3: Time to IC progression by BICR

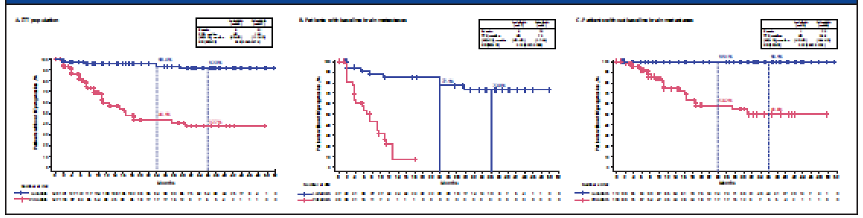


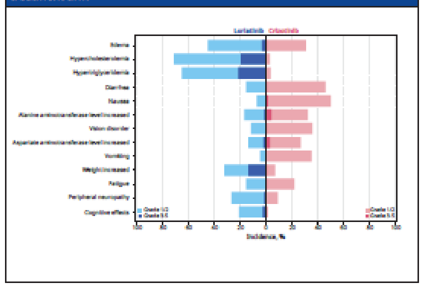
Table 1: Summary of overall and IC response by BICR

	Lorlatinib	Crizotinib
ITT population, n	**149**	**147**
Confirmed ORR by BICR, n (%)	115 (77.2)	86 (58.5)
Complete response	4 (2.7)	0
DOR, median (95% CI), months	NR (NR-NR)	9.6 (9.0-12.9)
Patients with any brain metastases at baseline, n	**37**	**39**
Confirmed IC ORR by BICR, n (%)	24 (64.9)	7 (17.9)
Complete IC response	22 (59.5)	5 (12.8)
IC DOR, median (95% CI), months	NR (NR-NR)	9.4 (6.0-11.1)
Patients with ≥1 measurable brain metastasis at baseline, n	**18**	**13**
Confirmed IC ORR by BICR, n (%)	15 (83.3)	3 (23.1)
Complete IC response	13 (72.2)	1 (7.7)
IC DOR, median (95% CI), months	NR (NR-NR)	10.2 (9.4-11.1)

Table 2: Summary of AEs

	n (%)	
	Lorlatinib (n=149)	Crizotinib (n=142)
Any-grade AE	149 (100.0)	140 (98.6)
Treatment related	145 (97.3)	133 (93.7)
Grade 3/4 AE	113 (75.8)	81 (57.0)
Treatment related	94 (63.1)	54 (38.0)
Death	10 (6.7)	7 (4.9)
Treatment related	2 (1.3)	0
Any serious AE	57 (38.3)	44 (31.0)
Treatment related	13 (8.7)	9 (6.3)
AEs leading to dose reduction	32 (21.5)	21 (14.8)
AEs leading to temporary discontinuations	84 (56.4)	69 (48.6)
AEs leading to permanent treatment discontinuation	11 (7.4)	14 (9.9)

Figure 4: Any-grade treatment-related AEs in ≥20% of patients within either treatment arm



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Correspondence: Todd Bauer, tbauer@tnonc.com

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Presented at the AACR Annual Meeting 2022, April 8-13, 2022; New Orleans, Louisiana, USA.

At 36.7 months of median follow-up in the lorlatinib arm, BICR assessed PFS remained longer with lorlatinib than with crizotinib

Intention-to-treat population (ITT)

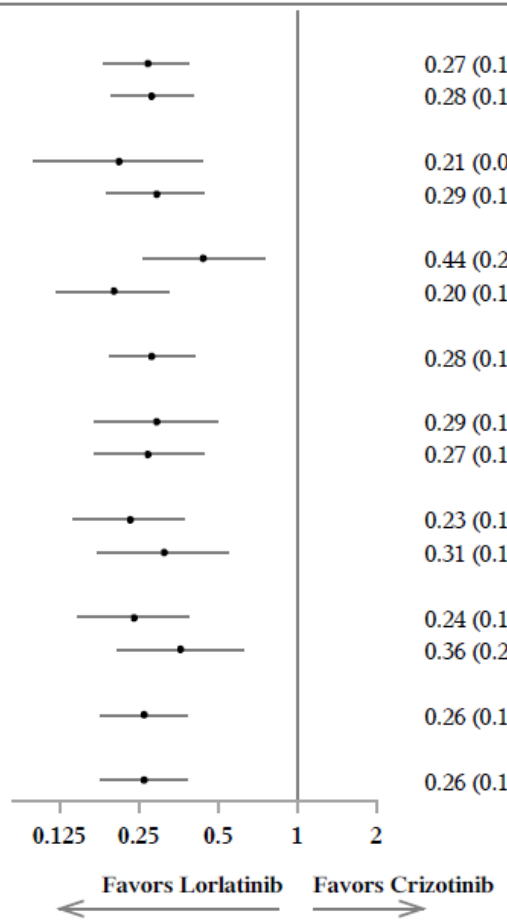
	ITT	
	Lorlatinib (n=149)	Crizotinib (n=147)
Events	49	92
PFS, median (95% CI), months	NR (NR–NR)	9.3 (7.6–11.1)
% CI)	0.27 (0.184–0.388)	

- Confirmed ORR by BICR
  - 77.2% (lorlatinib) vs 58.5% (crizotinib)
- Median DOR, months
  - NR (lorlatinib) vs 9.6 months (crizotinib)

21

CROWN: Subgroup analysis of PFS by BICR

Subgroup	Number of Patients, n (%) Lorlatinib	Number of Patients, n (%) Crizotinib	Number of Events/ Number of Patients (N) Lorlatinib	Number of Events/ Number of Patients (N) Crizotinib	Hazard Ratio (95% CI)	1-sided p-value	2-sided p-value
All patients (stratified)	149 (100.0)	147 (100.0)	49/149	92/147	0.27 (0.184, 0.388)	<.0001	<.0001
All patients (unstratified)	149 (100.0)	147 (100.0)	49/149	92/147	0.28 (0.195, 0.401)	<.0001	<.0001
Presence of Brain Metastases							
Yes	37 (24.8)	39 (26.5)	16/37	27/39	0.21 (0.099, 0.436)	<.0001	<.0001
No	112 (75.2)	108 (73.5)	33/112	65/108	0.29 (0.188, 0.442)	<.0001	<.0001
Ethnic Origin							
Asian	66 (44.3)	65 (44.2)	25/66	33/65	0.44 (0.259, 0.754)	0.0011	0.0022
Non-Asian	83 (55.7)	82 (55.8)	24/83	59/82	0.20 (0.121, 0.324)	<.0001	<.0001
ECOG Performance Status							
0/1	146 (98.0)	138 (93.9)	47/146	84/138	0.28 (0.194, 0.407)	<.0001	<.0001
Gender							
Male	65 (43.6)	56 (38.1)	23/65	37/56	0.29 (0.169, 0.498)	<.0001	<.0001
Female	84 (56.4)	91 (61.9)	26/84	55/91	0.27 (0.169, 0.441)	<.0001	<.0001
Age							
< 65 Years	90 (60.4)	103 (70.1)	24/90	63/103	0.23 (0.141, 0.371)	<.0001	<.0001
≥ 65 Years	59 (39.6)	44 (29.9)	25/59	29/44	0.31 (0.174, 0.545)	<.0001	<.0001
Smoking Status							
Never	81 (54.4)	94 (63.9)	25/81	60/94	0.24 (0.146, 0.385)	<.0001	<.0001
Current/Former	68 (45.6)	52 (35.4)	24/68	31/52	0.36 (0.207, 0.621)	<.0001	0.0001
Extent of Disease							
Metastatic	135 (90.6)	139 (94.6)	44/135	89/139	0.26 (0.179, 0.379)	<.0001	<.0001
Histology							
Adenocarcinoma	140 (94.0)	140 (95.2)	43/140	87/140	0.26 (0.178, 0.379)	<.0001	<.0001



Pfizer data on file.

BICR, blinded independent central review; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival.

Primary end points in bold

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:

18.3 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)**	

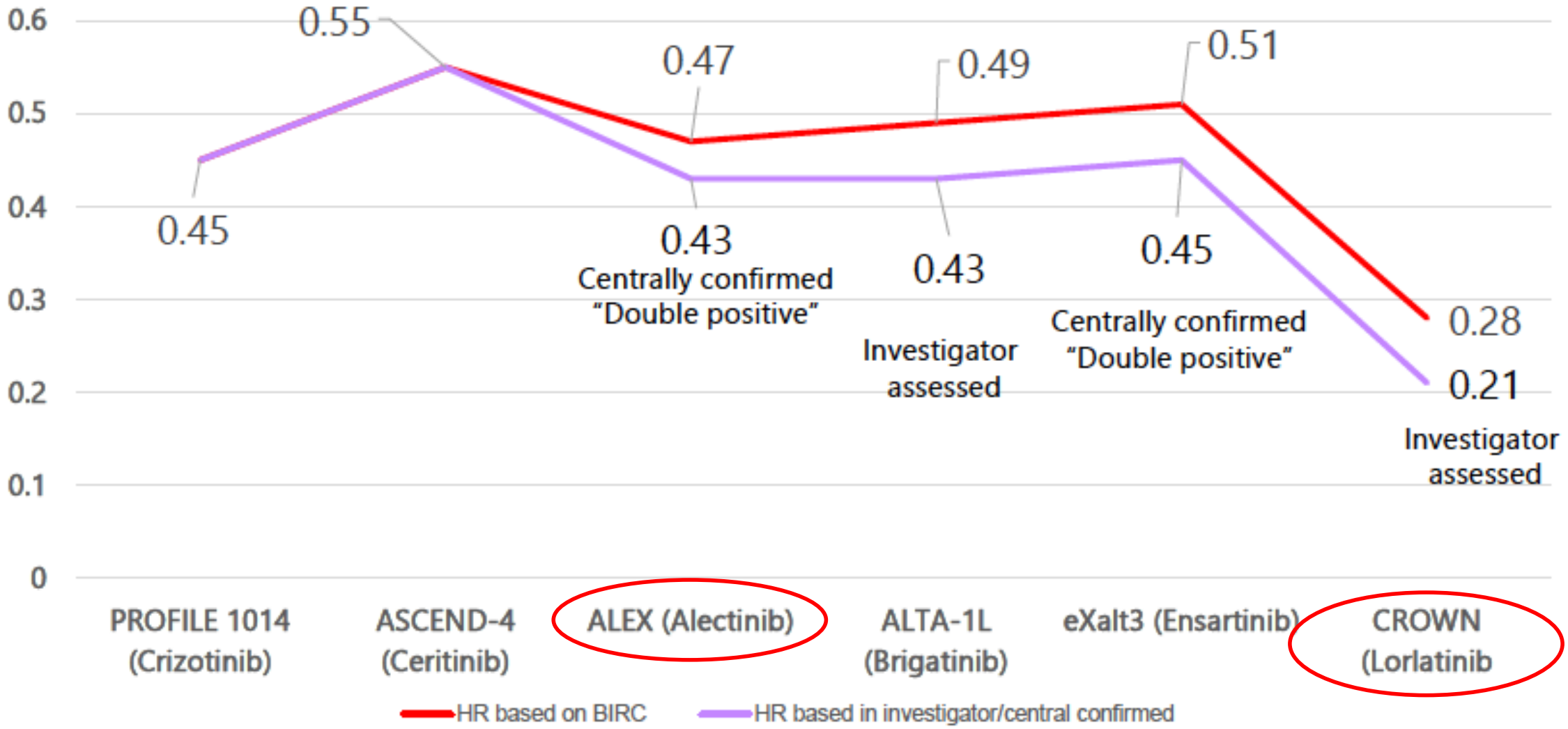
36 mo

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*

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

Hazard Ratio (BIRC and investigator-assessed/double positive)



Ou SH S04.02, Presented at IASLC TTLC 2021

KEY Assessed by BICR Assessed by Investigator

CROWN, ALTA–1L & ALEX: Summary of overall and intracranial response

	CROWN		ALEX	
	Lorlatinib[1]	Crizotinib[1]	Alectinib[3]	Crizotinib[3]
ITT population, n	**149**	**147**	**152**	**151**
Confirmed ORR, % patients	77.2	58.5	82.9	75.5
Complete response, % patients	2.7	0.0	4	1
Median DoR (95% CI), months	NR (NR–NR)	9.6 (9.0–12.9)	NE	11.1 (7.9–13.0)
Patients with any brain metastases at baseline, n	**37**	**39**	**64**	**58**
Confirmed IC-ORR, % patients	64.9	17.9	59	26
Complete IC response, % patients	59.5	12.8	45	9
Median IC-DoR (95% CI), months	NR (NR–NR)	9.4 (6.0–11.1)	NE (17.3–NE)	3.7 (3.2–6.8)
Patients with at least 1 measurable brain metastases at baseline, n	**18**	**13**	**22**	**21**
Confirmed IC-ORR, % patients	83.3	23.1	81	50
Complete IC response, % patients	72.2	7.7	38	5
Median DoR (95% CI), months	NR (NR–NR)	10.2 (9.4–11.1)	5.5 (2.1–17.3)	17.3 (14.8–NE)

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

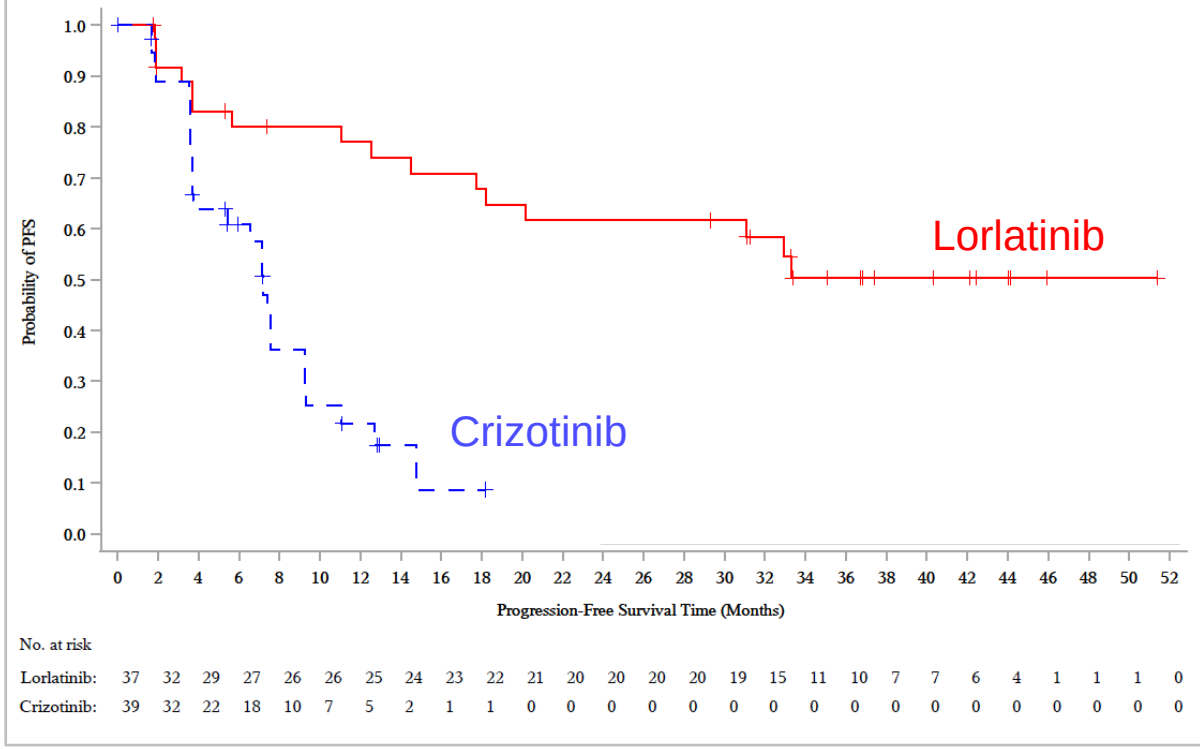
1. Pfizer data on file; 2. Camidge DR et al. *J Thor Onc* 2021;16: 2091–2108; 3. Peters S et al. *N Engl J Med* 2017;377:829–838; 4. Camidge DR et al. *J Thor Onc* 2021;16: 2091–2108 Supplementary Data

BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; IC, intracranial; IC-DoR, intracranial duration of response; IC-ORR, intracranial objective response rate; ITT, intention-to-treat; NE, not estimable; NR, not reached; ORR, objective response rate.

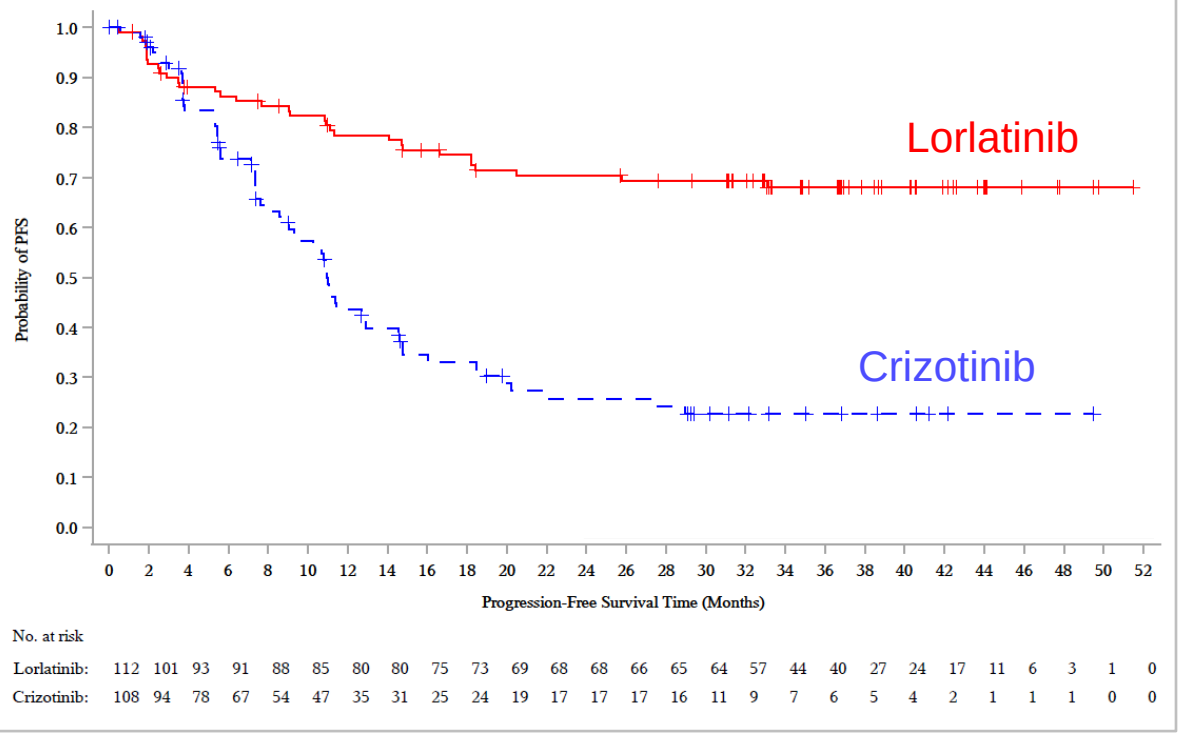
CROWN: BICR-assessed PFS in patients with and without brain metastases

	With brain metastases		Without brain metastases	
	Lorlatinib (n=37)	Crizotinib (n=39)	Lorlatinib (n=112)	Crizotinib (n=108)
Events	16	27	33	65
Median PFS (95% CI), months	NR (18.2–NR)	7.2 (3.7–9.2)	NR (NR–NR)	11.0 (9.0–14.6)
HR (95% CI)	0.21 (0.10–0.44)		0.29 (0.19–0.44)	

Patients with baseline brain metastases



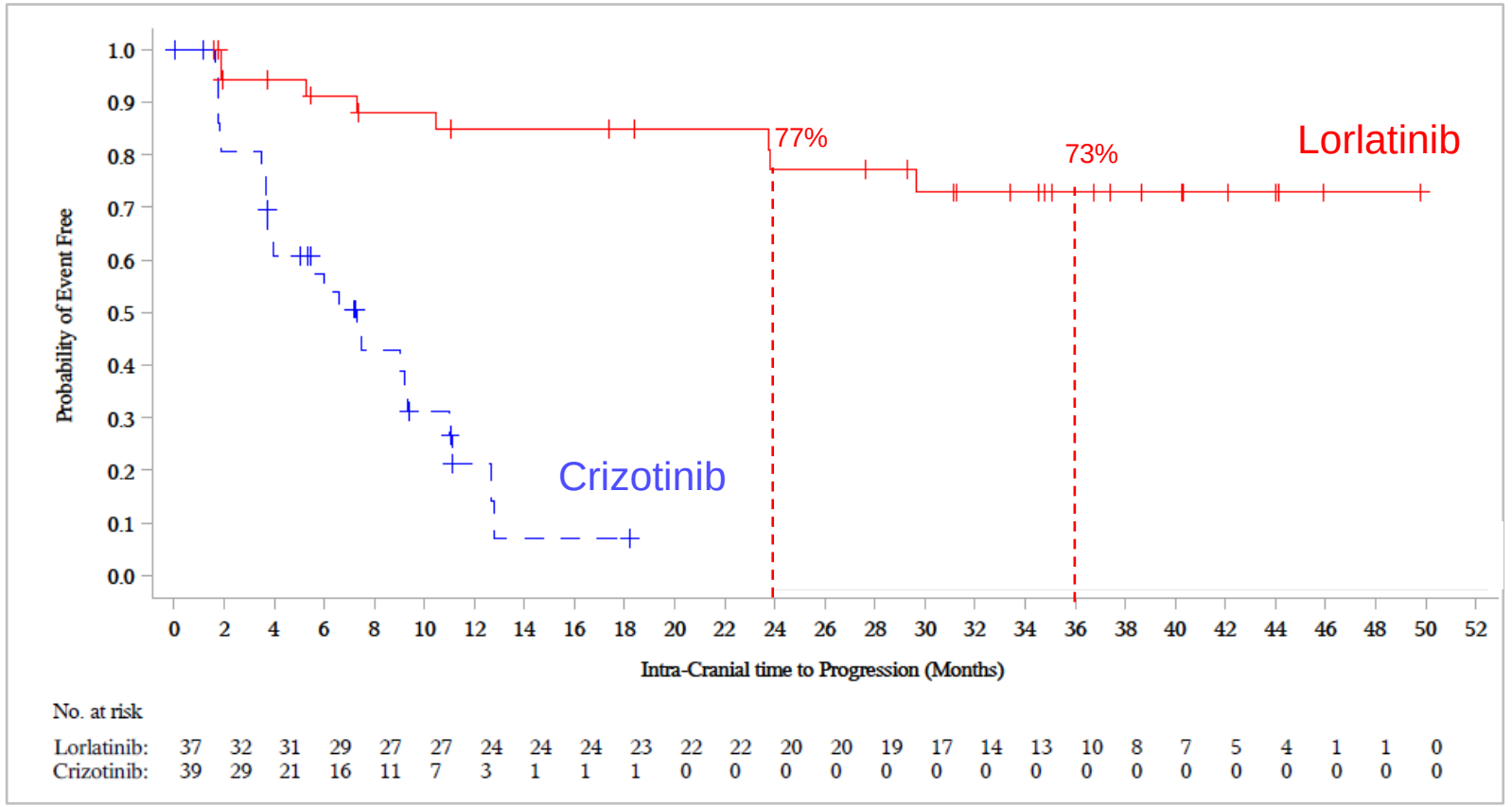
Patients without baseline brain metastases



Pfizer data on file.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

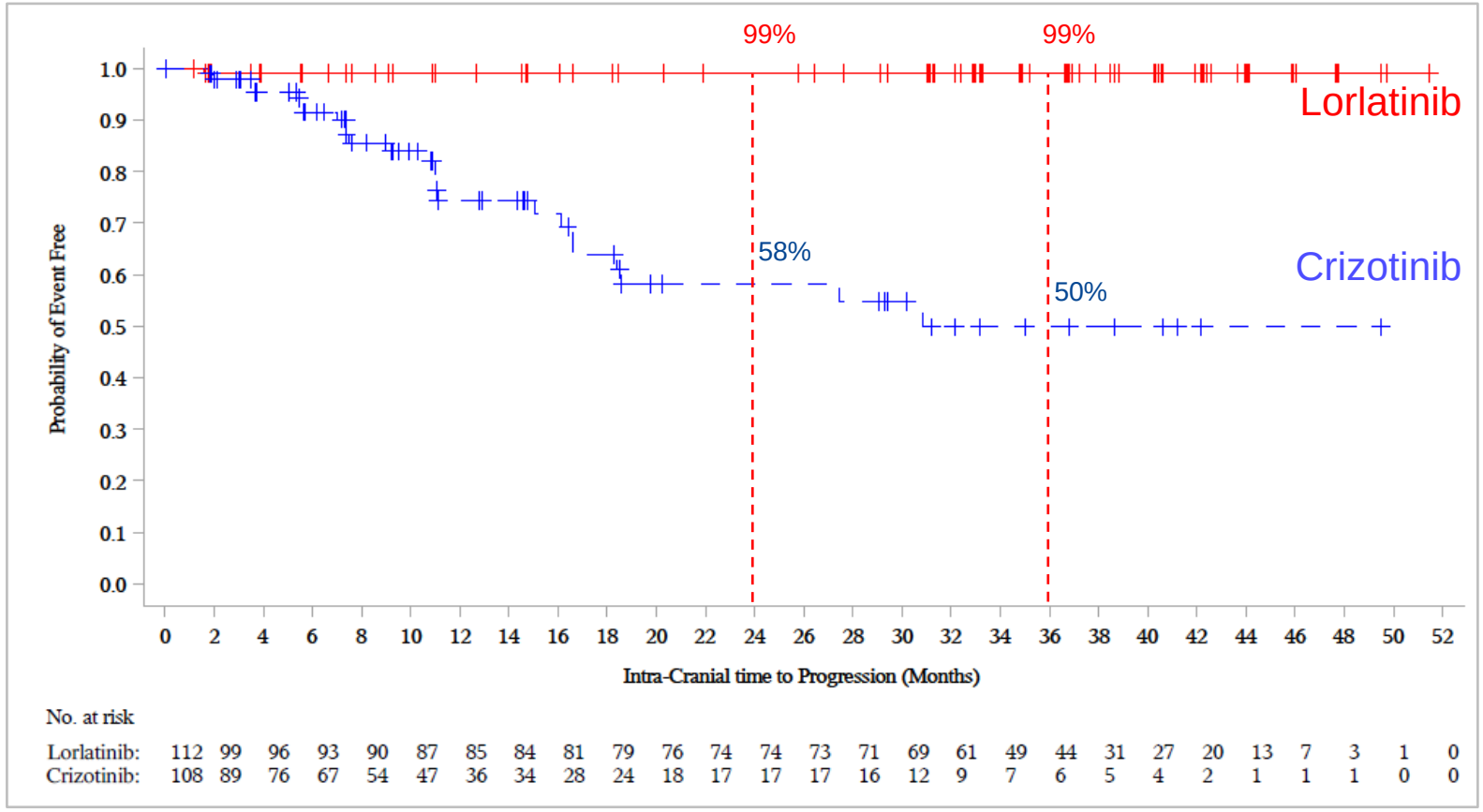
CROWN: BICR-assessed intracranial time to progression in patients with baseline brain metastases



	With brain metastases	
	Lorlatinib (n=37)	**Crizotinib (n=39)**
Events	8	26
Median PFS (95% CI), months	NR (NR–NR)	7.3 (3.7–9.3)
HR (95% CI)	0.10 (0.04–0.27)	

Pfizer data on file.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

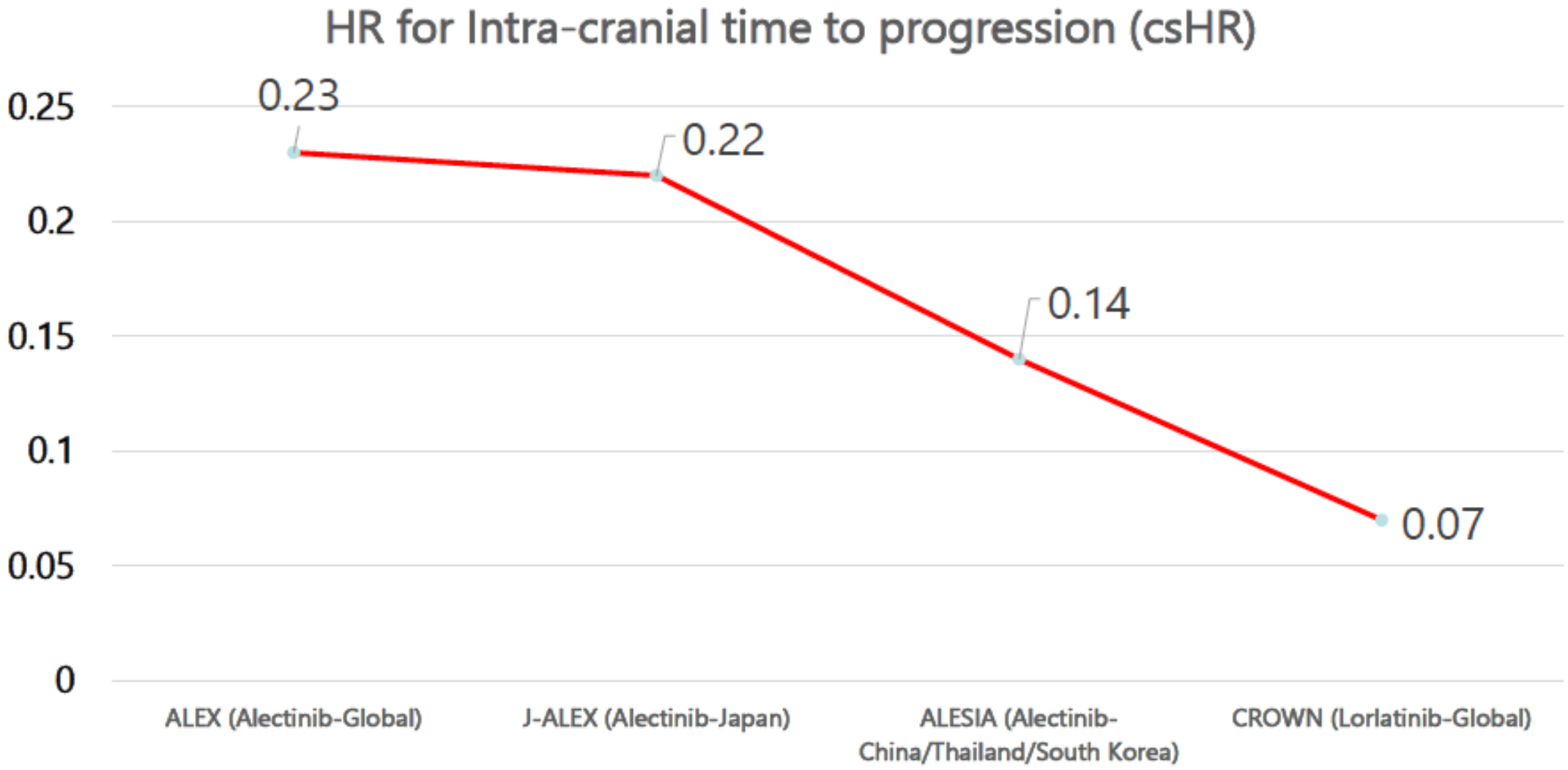
CROWN: BICR-assessed intracranial time to progression in patients without baseline brain metastases



	Without brain metastases	
	Lorlatinib (n=112)	**Crizotinib (n=108)**
Events	1	25
Median PFS (95% CI), months	NR (NR–NR)	30.8 (18.4–NR)
HR (95% CI)	0.02 (0.002–0.14)	

Pfizer data on file.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

Who wins in the CNS, wins the game! Or ??



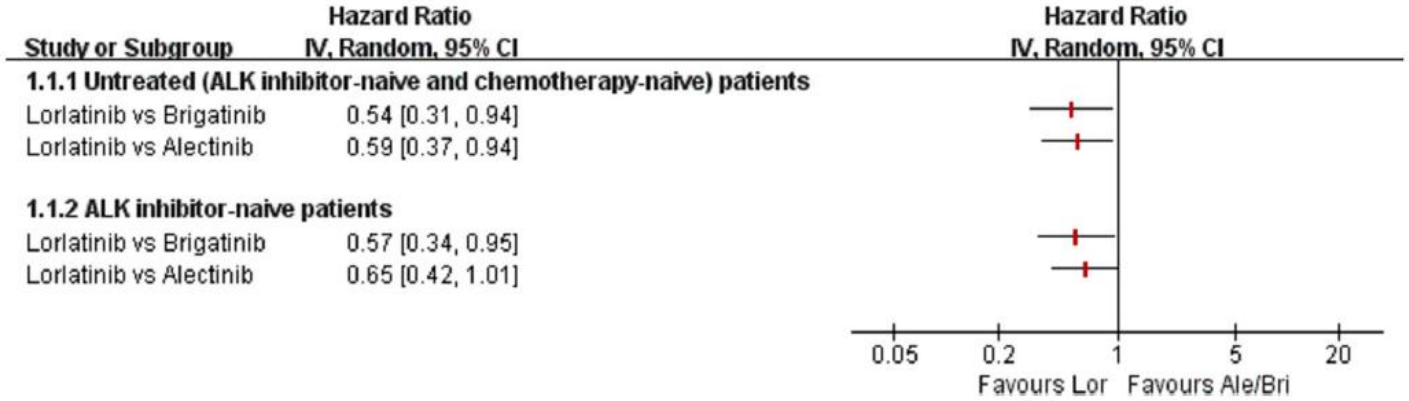
Comparison of lorlatinib, alectinib and brigatinib in ALK inhibitor–naive/untreated ALK-positive advanced non-small-cell lung cancer: a systematic review and network meta-analysis

Table 1. The characteristics of included RCTs.

Study		N	Regimen	Cohort	Primary endpoint
ALTA-1L	E	58	Brigatinib	ALK inhibitor (-): Untreated (74%)	PFS
	C	60	Crizotinib	ALK inhibitor (-): Untreated (73%)	
ALEX	E	152	Alectinib	Untreated	PFS
	C	151	Crizotinib		
CROWN	E	149	Lorlatinib	Untreated	PFS
	C	147	Crizotinib		
ALESIA	E	125	Alectinib	Untreated	PFS
	C	62	Crizotinib		
J-ALEX	E	103	Alectinib	ALK inhibitor (-): Untreated (64%)	PFS
	C	104	Crizotinib	ALK inhibitor (-): Untreated (63%)	

Abbreviation: E, experiment arm; C, control arm; PFS, progression free survival.

PFS



In conclusion, in terms of **PFS**, our results indicated that **lorlatinib was the best treatment choice for patients with ALK inhibitor-naive or untreated** (ALK inhibitor-naive and chemotherapy-naive) ALK-positive advanced NSCLC.

Lida Wang et al. (2021): 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, Journal of Chemotherapy, DOI: 10.1080/1120009X.2021.1937782

ESMO Clinical Practice Guidelines Stage IV ALK + NSCLC

Factors affecting drug choice

Disease

- Line of therapy/disease pattern
- CNS metastases
- Molecular profile if available

Patient

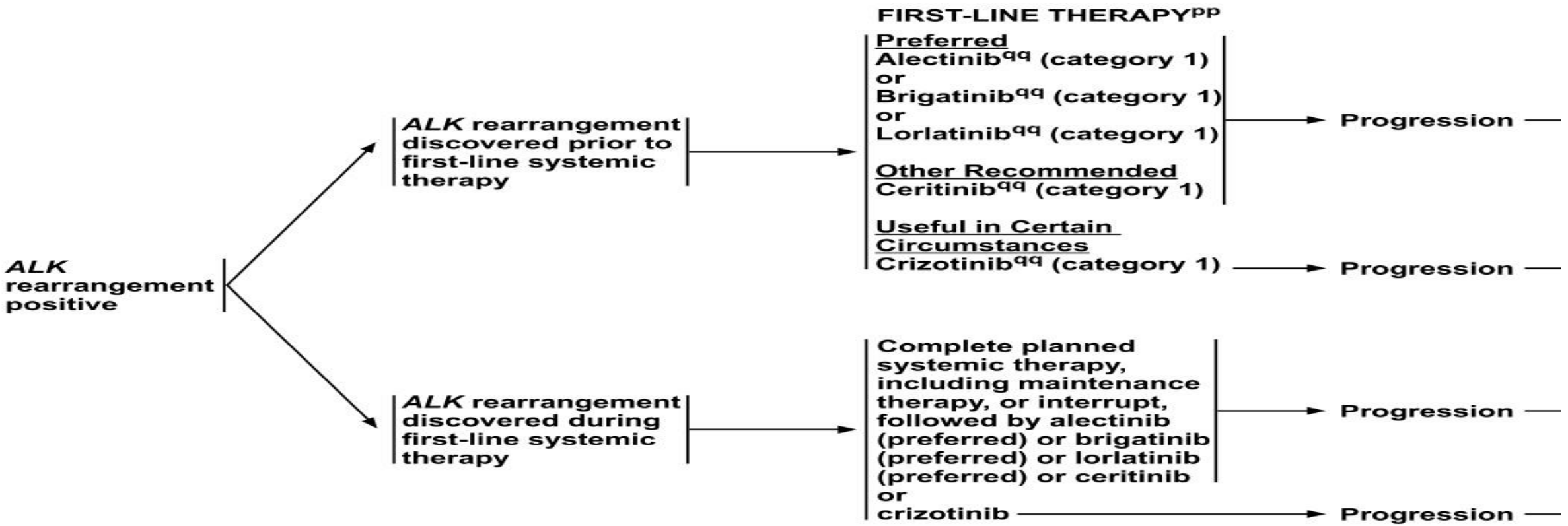
- Tolerance/toxicity including financial
- Co-morbidity and concomitant meds
- Pill burden preferences

[a]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee; [b]Preferred option; [c]Not EMA-approved.
ChT, chemotherapy; CNS, central nervous system; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; MCBS, ESMO-Magnitude of Clinical Benefit Scale; RT, radiotherapy.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

ALK REARRANGEMENT POSITIVE[mm]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially enco

Summary of principal AEs observed during phase III trials in the first-line ALK-positive NSCLC setting

- With increasing ALK TKIs available, each with their own individual tolerability profiles, there is a need to optimise and understand therapy management to ensure time on treatment is maximised for patients[1]

	ALEX[2,3] Alectinib (n=152)	ALTA-1L†[4] Brigatinib (n=136)	Exalt3‡§[5] Ensartinib (n=143)	CROWN¶[6,7] Lorlatinib (n=149)
Most common all Grade AEs in each treatment arm (%)	Constipation (36)*	Diarrhoea (52)	Rash (68)	Hypercholesterolaemia† (70)
	Anaemia (22)*	Increased blood CPK (46)	ALT increased (51)	Hypertriglyceridaemia† (64)
	Fatigue (20)*	Cough (35)	AST increased (37)	Oedema† (55)
	Blood bilirubin increased (19)*	Hypertension (32)	Constipation (32)	Weight increased (38)
	Peripheral oedema (18)*	Nausea (30)	Cough (31)	Peripheral neuropathy† (34)
	ALT increased (17)*	AST level increased (26)	Pruritus (29)	Cognitive effects†‡ (21)
	Myalgia (16)*	Increased lipase (23)	Nausea (27)	Diarrhoea (21)
	AST increased (16)*	ALT level increased (21)	Oedema (25)	Dyspnoea (20)
Dose reduction due to AEs, n (%)	29 (19)**	52 (38)	34 (24)	31 (21)
Dose interruption due to AEs, n (%)	38 (25)**	90 (66)	Not reported	73 (49)
Discontinuation due to AEs, n (%)	21 (14)**	17 (13)	13(9)	10 (7)

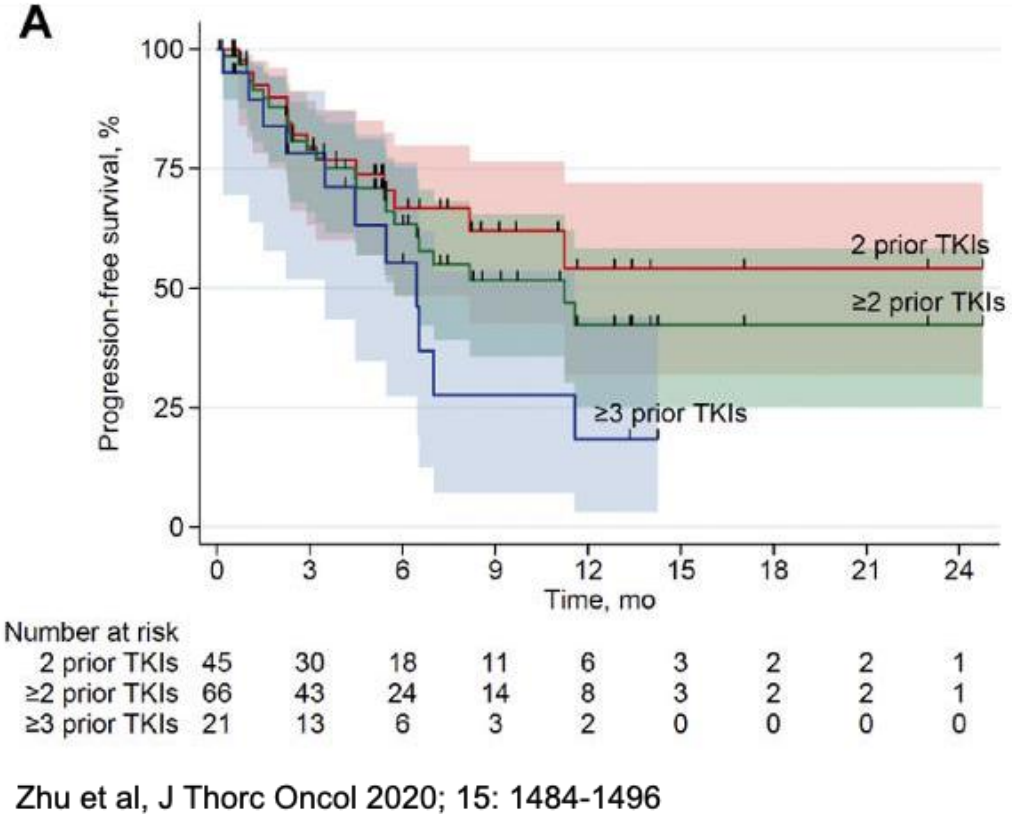
Please note, data are from unrelated studies, with different study designs and inclusion criteria. Therefore, cross trial comparisons should not be made.

*Based on a data cut-off of 1 December 2017; **Based on data cut-off of 30 November 2018; †Based on a data cut-off of 28 June 2019 (second interim analysis); ‡Exact data were not reported; §Based on a data cut-off of 01 July 2020; ¶Based on cut-off of 20 March 2020 (planned interim analysis).
AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate amino transferase; CPK, creatine phosphokinase; NSCLC, non-small cell lung carcinoma; TKI, tyrosine kinase inhibitor.

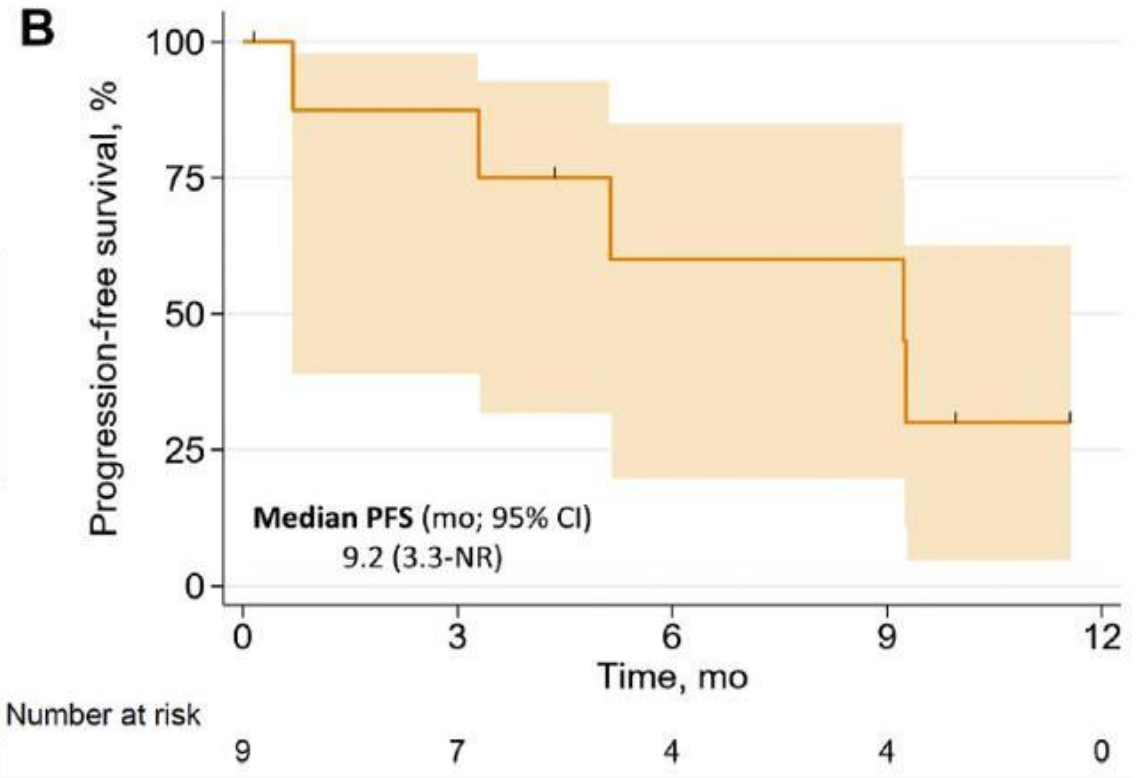
1. Blackhall F, et al. Presented at ESMO Lung Preceptorship 2020, 19–21 October 2020; 2. Camidge DR, et al. J Thorac Oncol. 2019;14(7):1233–43. Supplementary appendix; 3. Mok T, et al. 1484PD. Presented at ESMO Virtual Congress 2020, 19–21 September 2020; 4. EMA Assessment Report: Alunbrig® (brigatinib). www.ema.europa.eu/en/documents/variation- report/alunbrig-h-c-4248-ii-0003-epar-assessment-report-variation_en.pdf (Accessed 03 November 2020); 5. Horn L, et al. Presented at WCLC 2020 Presidential Symposium 2020, 08 August 2020 at 8 Eng A, Med. 2020;383:2018–20. Supplementary 7. Shaw appendix.

Diminishing PFS with more prior lines of ALK TKIs

Lorlatinib PFS in by lines of prior ALK TKIs



	Median PFS (mo; 95% CI)
2 prior TKIs	NR (4.5-NR)
≥2 prior TKIs	11.2 (4.5-NR)
≥3 prior TKIs	6.5 (3.5-11.6)

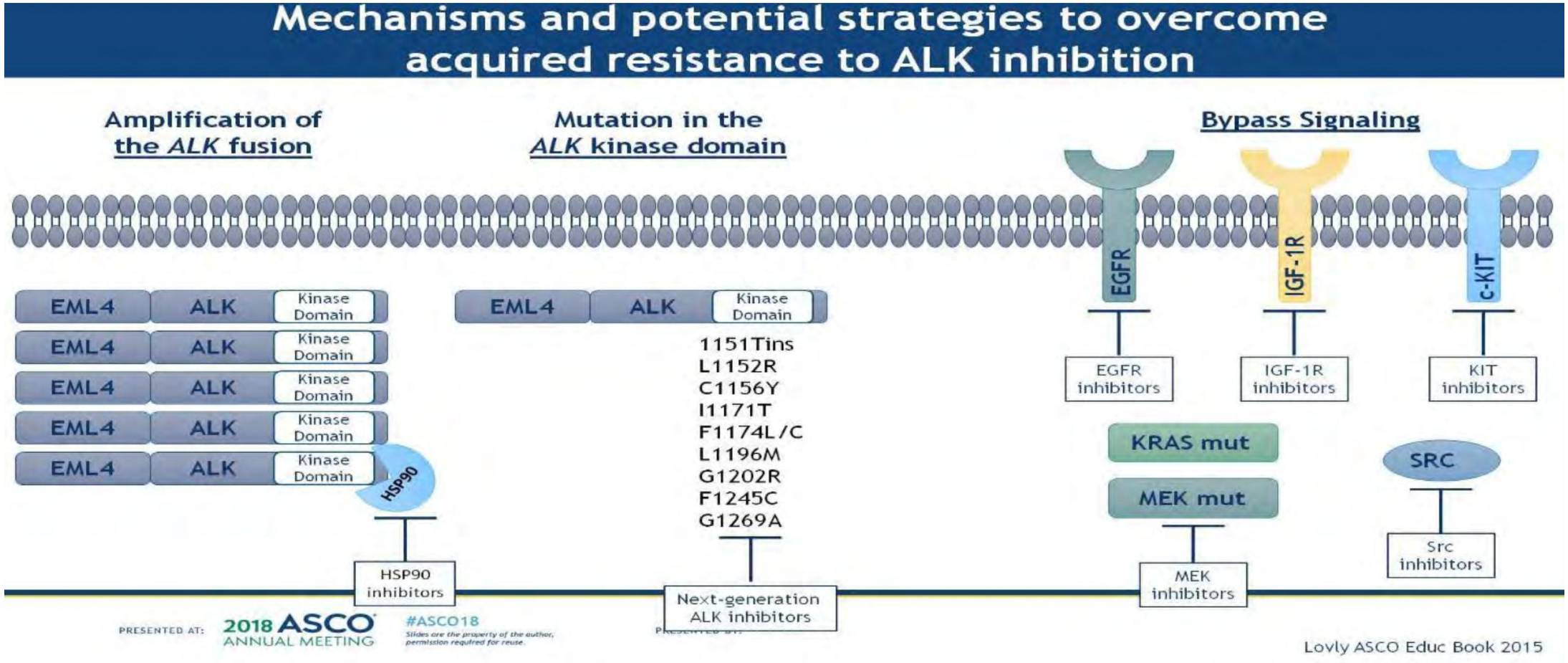


Zhu et al, J Thorc Oncol 2020; 15: 1484-1496

Ou SH S04.02, Presented at IASLC TTLC 2021

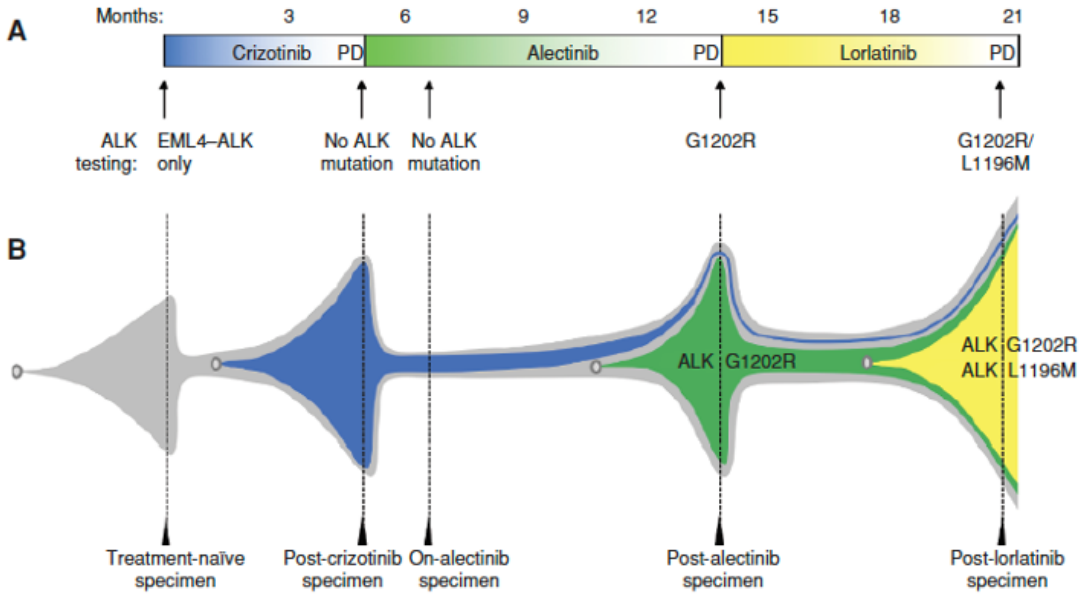
What after Lorlatinib- is it a concern??

CAUTION ! WE KNOW VERY LITTLE OF RESISTANCE MECHANISMS TO LORLATINIB !



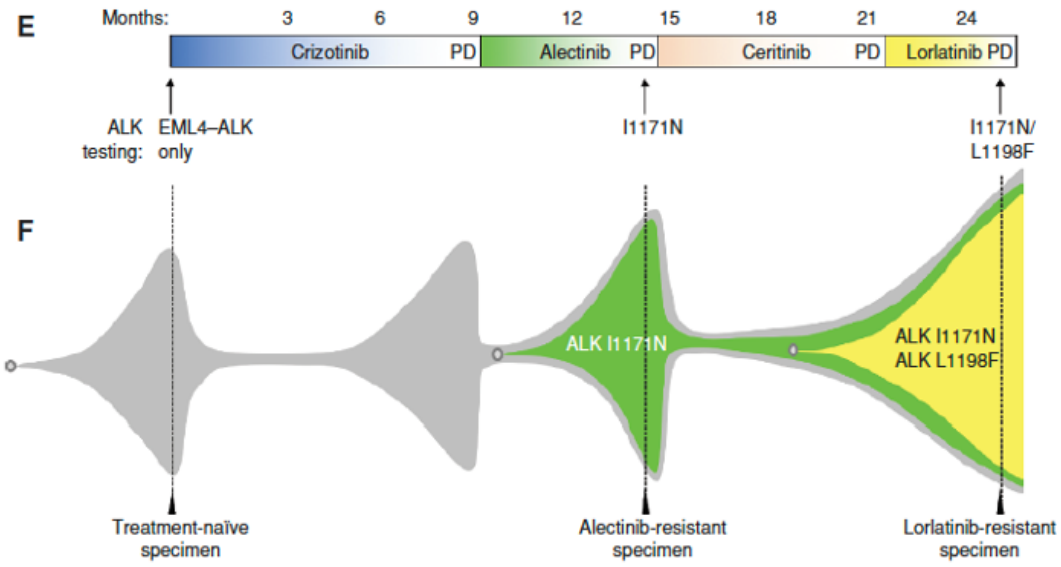
The more generations of ALK TKI are sequenced the more "monster" ALK resistance mutations appeared

Sequential 3 generations of ALK TKI



Double mutations
G1202R
L1196M

Sequential 3 generations with "in-generation" sequencing

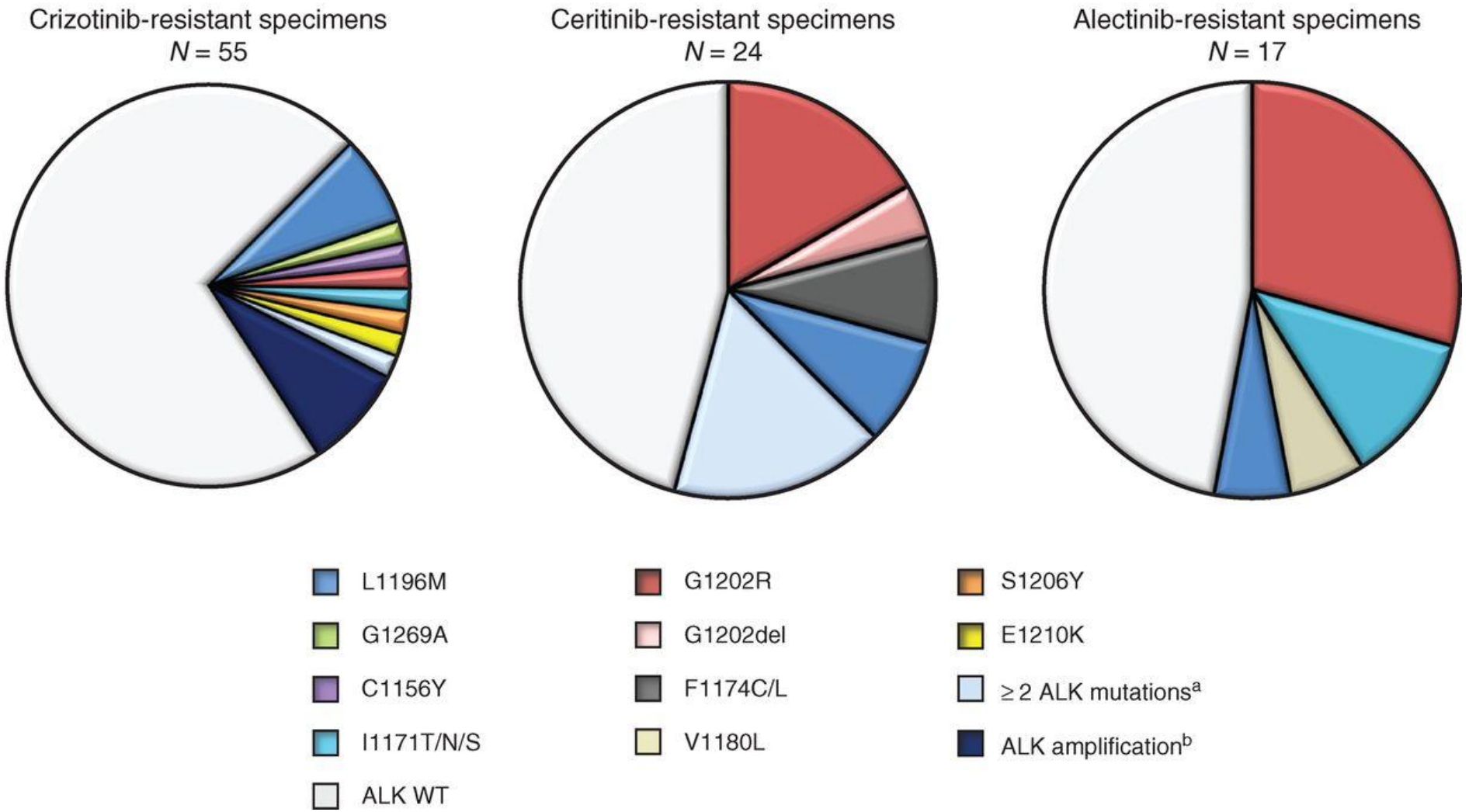


Double mutations
I1171N
L1198F

Yoda et al, *Cancer Discov* 2018; 8: 714-729

Ou SH S04.02, Presented at IASLC TTLC 2021

Resistance to 2nd-Gen ALK TKIs is Largely Driven by Secondary ALK Kinase Domain Mutations, Particularly G1202R



Gainor Cancer Discovery 2016

Lorlatinib is a potent 3rd-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-gen ALK TKIs

ALK G1202R confers resistance to the available first- and second-gen ALK TKIs

Lorlatinib has 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

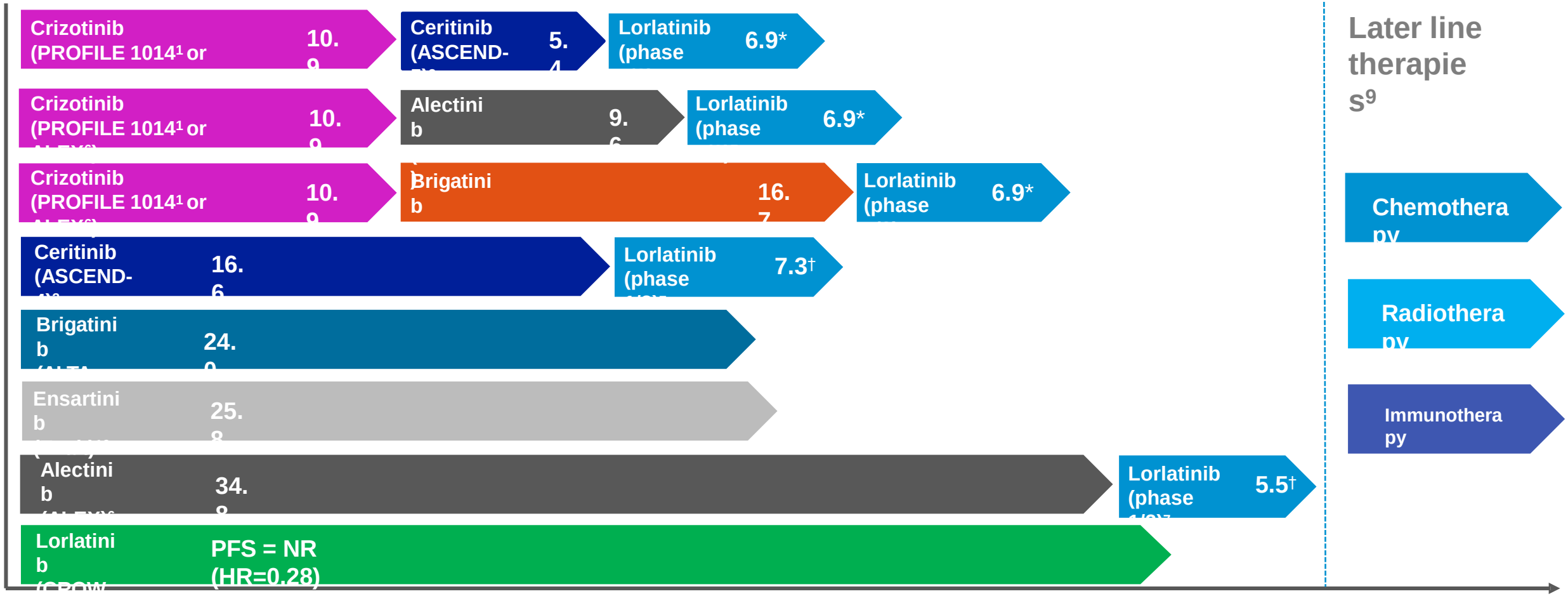
Cellular ALK Phosphorylation Mean IC_{50} (nM)

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

ALK, anaplastic lymphoma kinase; IC_{50}, half-maximal inhibitory concentration; ND, not done; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.

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

The rapidly evolving ALK+ NSCLC landscape and growing body of clinical evidence is defining a 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. . 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

Data not drawn to scale

1. Solomon, et al. N Eng J Med 2014; 2. Shaw, et al. Lancet Oncol 2017; 3. Novello, et al. Ann Oncol 2018; 4. Huber, et al. ASCO 2018; 5. Soria, et al. Lancet Oncol 2017; 6. Camidge, et al. J Thorac Oncol 2019; 7. Besse, et al. ASCO 2018; 8. Camidge, et al. N Engl J Med 2018; 9. Ferrara, et al. J Thorac Oncol 2018; 10. Horn L. WCLC2020 Presidential session

Summary

- There are now multiple 1L treatment options in advanced ALK+ lung cancer.

- Next-generation ALK TKIs(alectinib/lorlatinib) are the standard-of-care for frontline management of advanced ALK+ lung cancer.

KISS

- Every Time When I Make PPTs,
  I get this message from my wife
  But she actually means

- Keep … It…Short…Stupid

THANKS