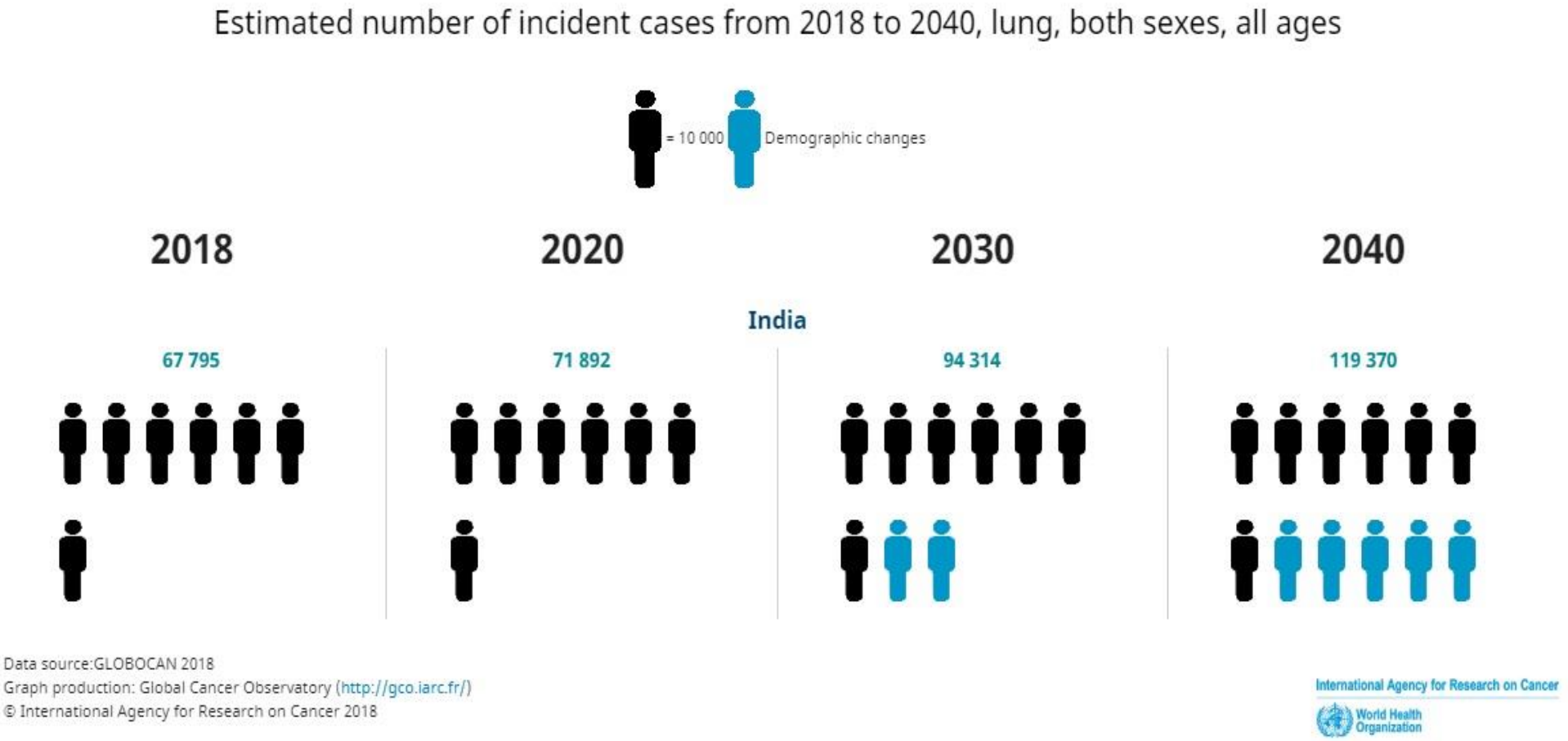
Walk the First Line Management of ALK Positive NSCLC

Lung Cancer Incidence in India



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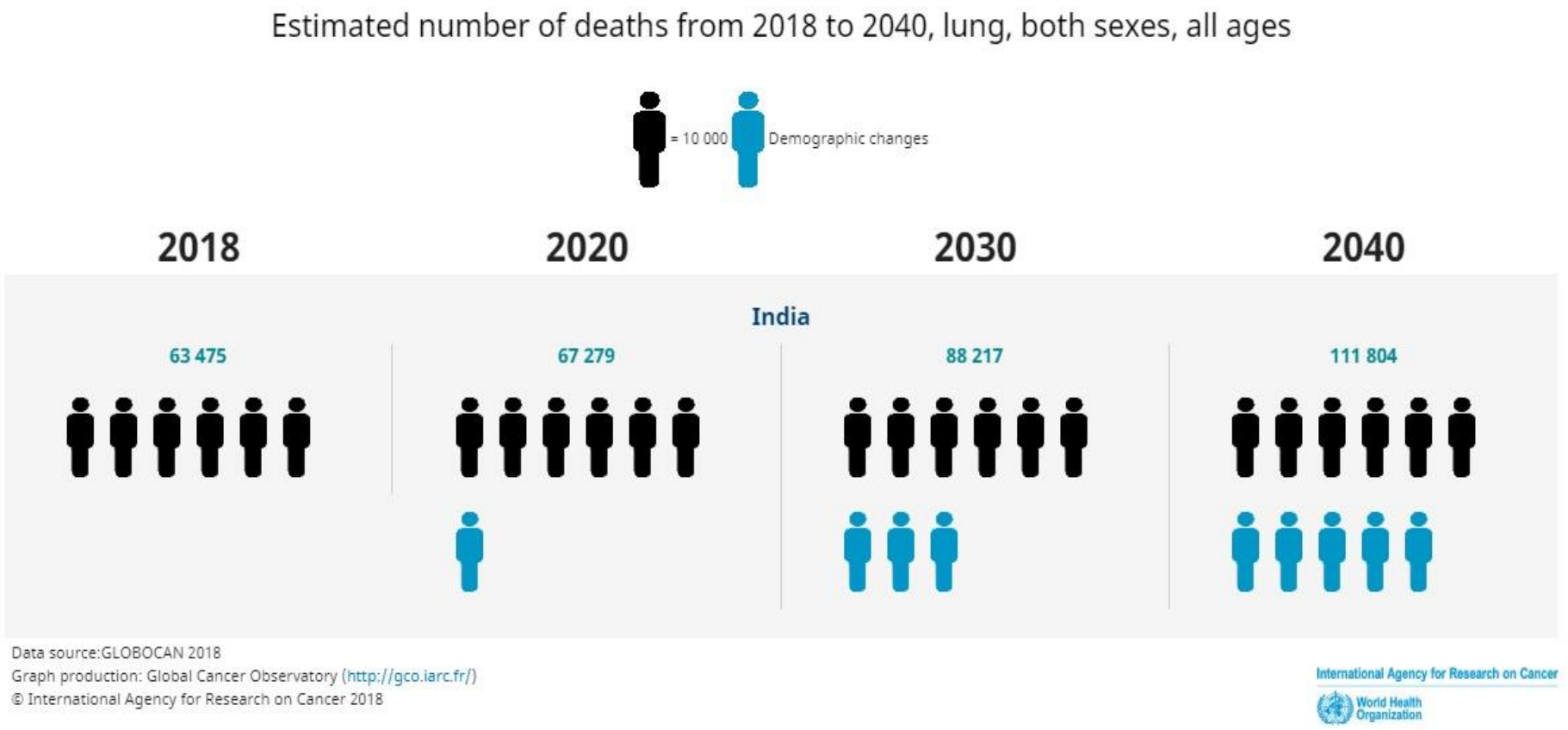
Lung Cancer Mortality in India



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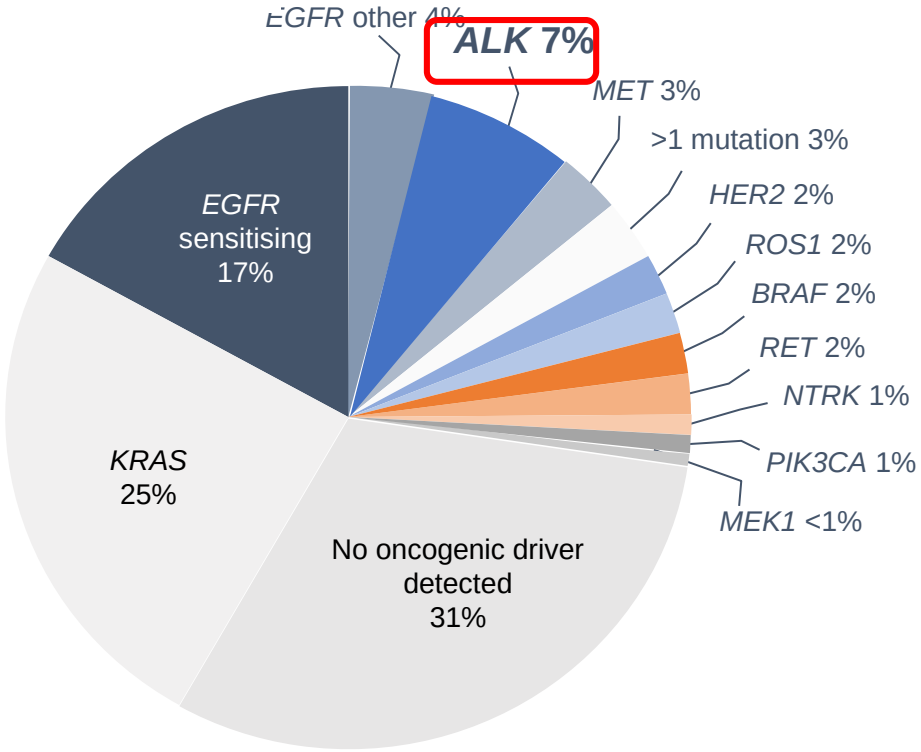
Original Article

ALK gene rearranged lung adenocarcinomas: molecular genetics and morphology in cohort of patients from North India

Amanjit Bal ✉, Navneet Singh, Parimal Agarwal, Ashim Das, Digambar Behera

First published: 08 August 2016 | https://doi.org/10.1111/apm.12581 | Citations: 6

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



Adapted from Tsao, A.S., et al. (2016) *J Thorac Oncol* 11:613-38

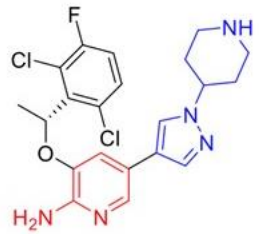
Bal A, Singh N, Agarwal P, Das A, Behera D. ALK gene rearranged lung adenocarcinomas: molecular genetics and morphology in cohort of patients from North India. APMIS. 2016 Oct;124(10):832-8.

ALK-rearranged (ALK+) NSCLC

- ~3-5% of all advanced NSCLC
- More common among patients of younger age, never or light smoking history, adenocarcinoma histology
- 5 ALK-targeted TKIs have been FDA-approved since 2011

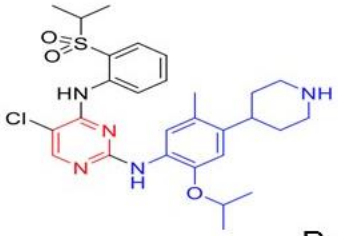
First-Generation

Crizotinib

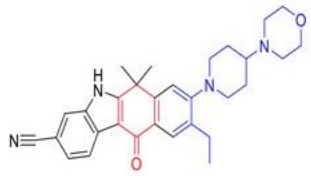


Second-Generation

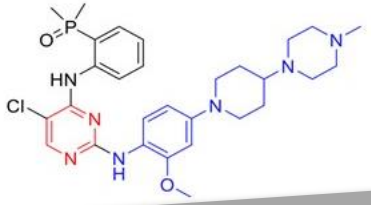
Ceritinib



Alectinib

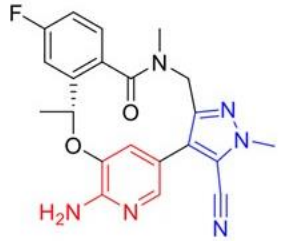


Brigatinib



Third-Generation

Lorlatinib



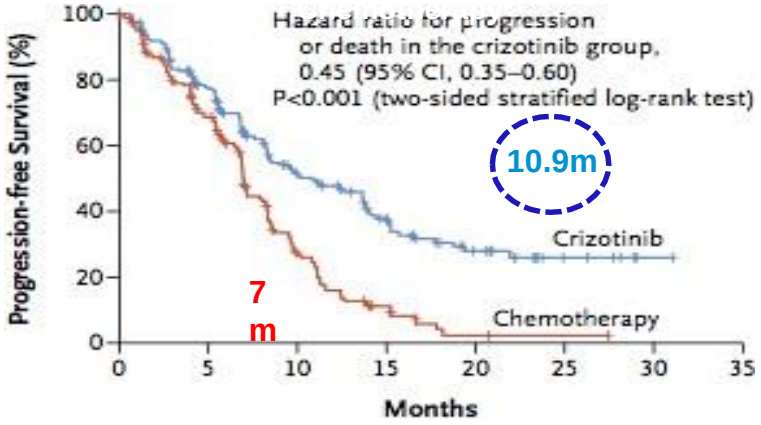
Potency against ALK

Activity against *ALK* mutations

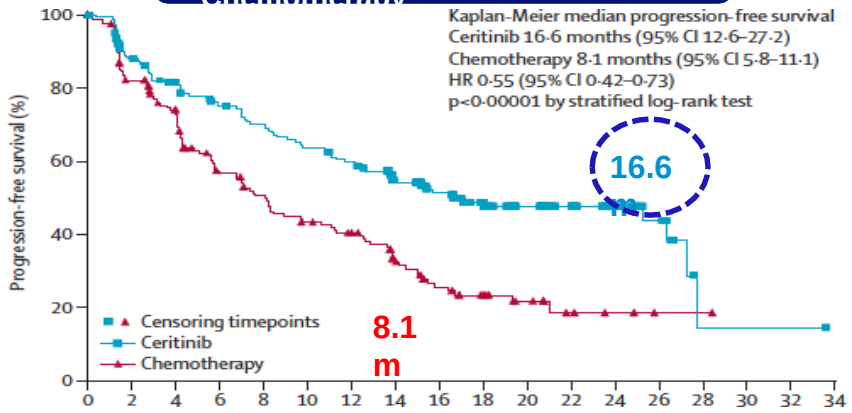
CNS activity

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

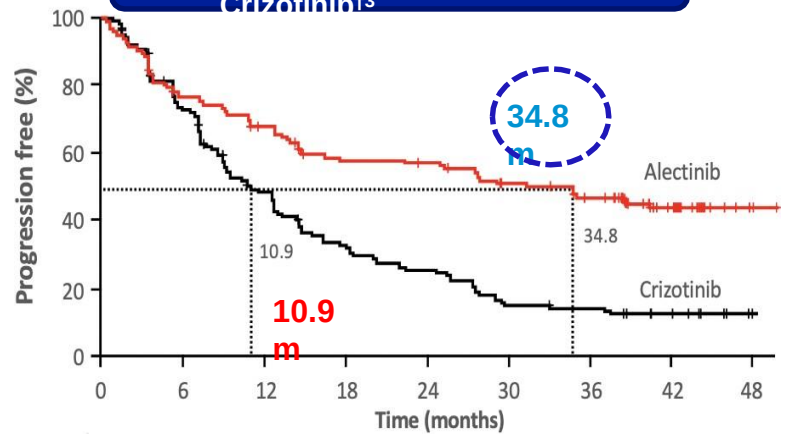
PROFILE 1014: Crizotinib vs



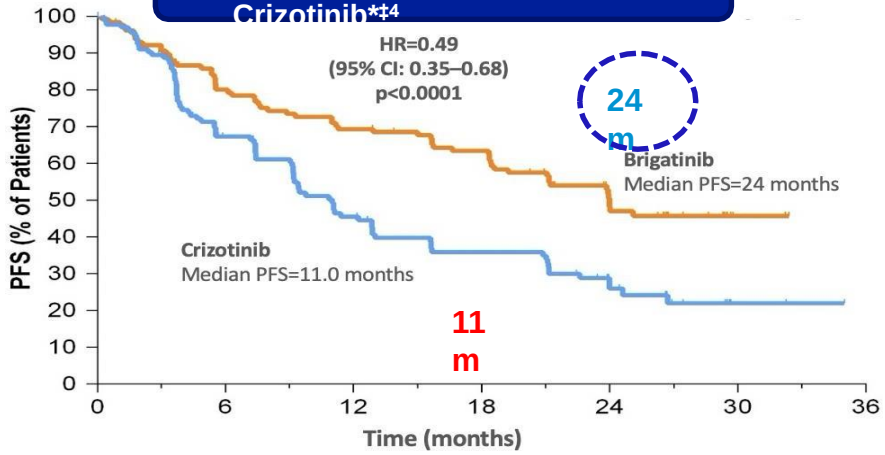
ASCEND 4: Ceritinib vs Chemotherapy*2



ALEX: Alectinib vs Crizotinib†3



ALTA 1L: Brigatinib vs Crizotinib*‡4

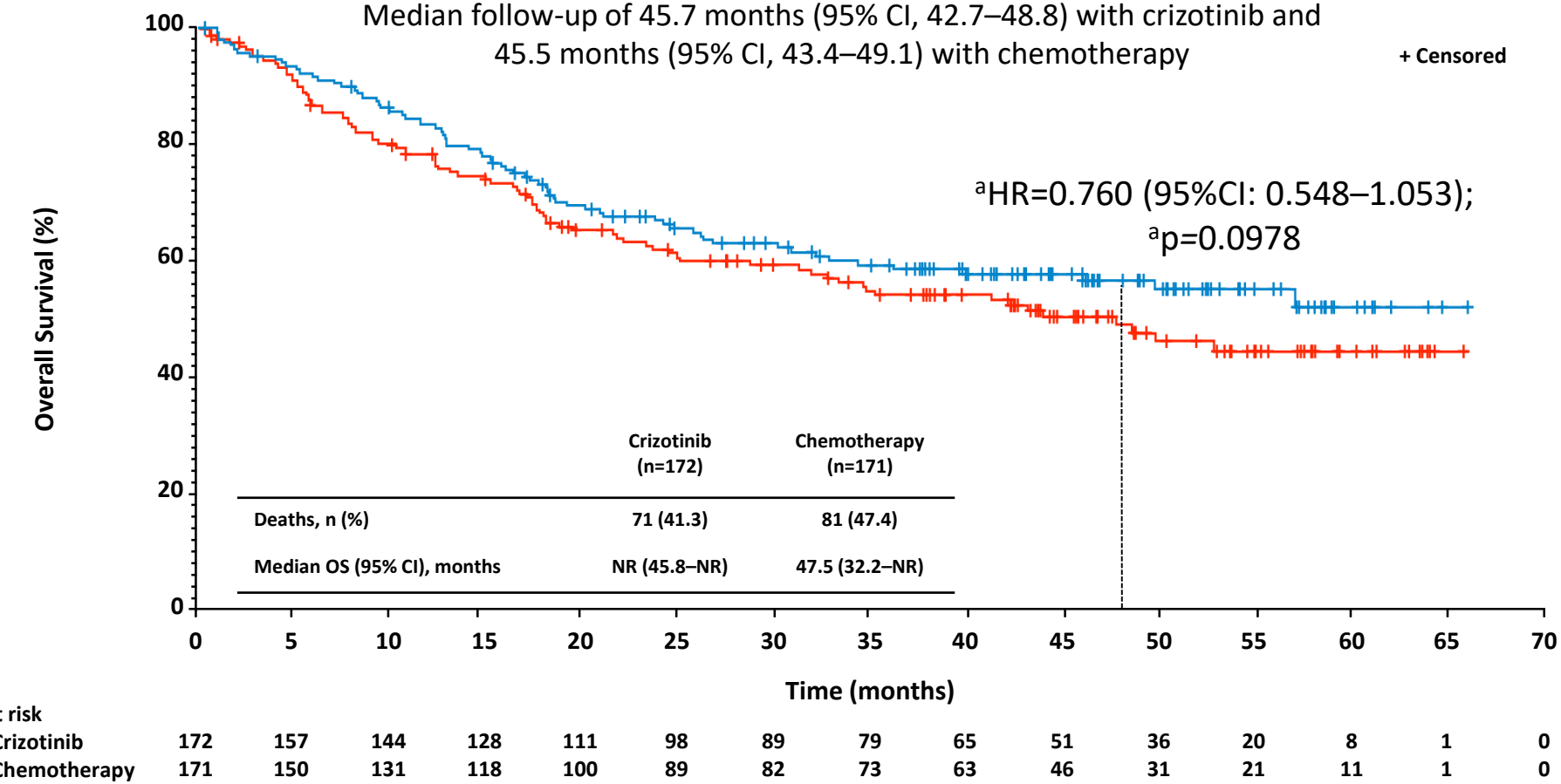


*PFS assessed by independent review committee; †PFS assessed by investigator.
‡Brigatinib is currently not approved for use as a first line treatment option for ALK+ NSCLC in India.
CI, confidence interval; HR, hazard ratio; m, months; PFS, progression-free survival.

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.

PROFILE 1014 Updated OS: Final OS Analysis (ITT Population)

Median follow-up of 45.7 months (95% CI, 42.7–48.8) with crizotinib and 45.5 months (95% CI, 43.4–49.1) with chemotherapy



Adapted from J Clin Oncol. 2018 Aug 1;36(22):2251-2258

[a]Estimated by Cox proportional hazards regression analysis with adjustment for ECOG PS, race, brain metastases;

[b]2-sided p-value from the log-rank test stratified by ECOG PS, race, brain metastases.

Solomon BJ, et al. J Clin Oncol. 2018 Aug 1;36(22):2251-2258

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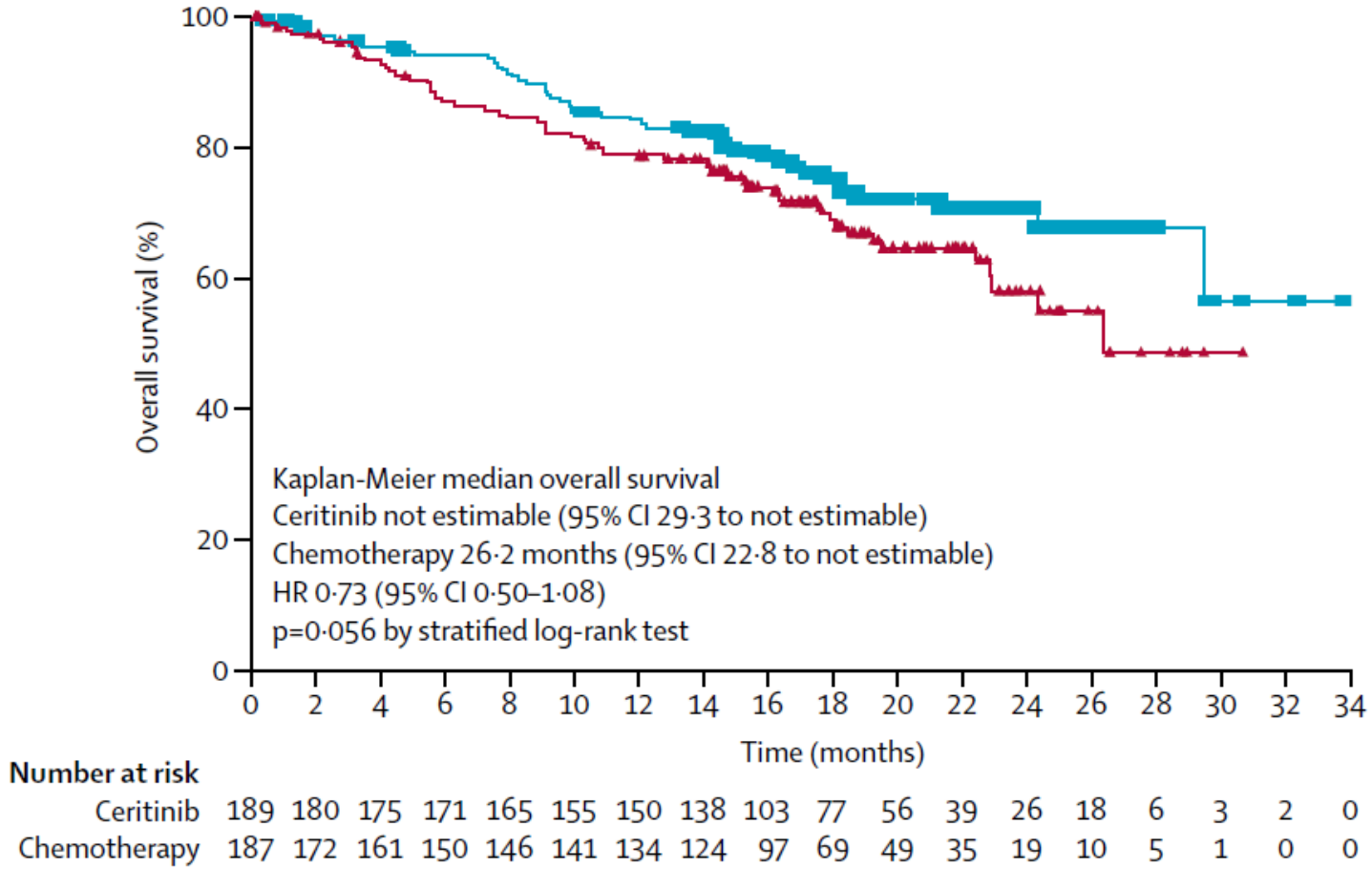
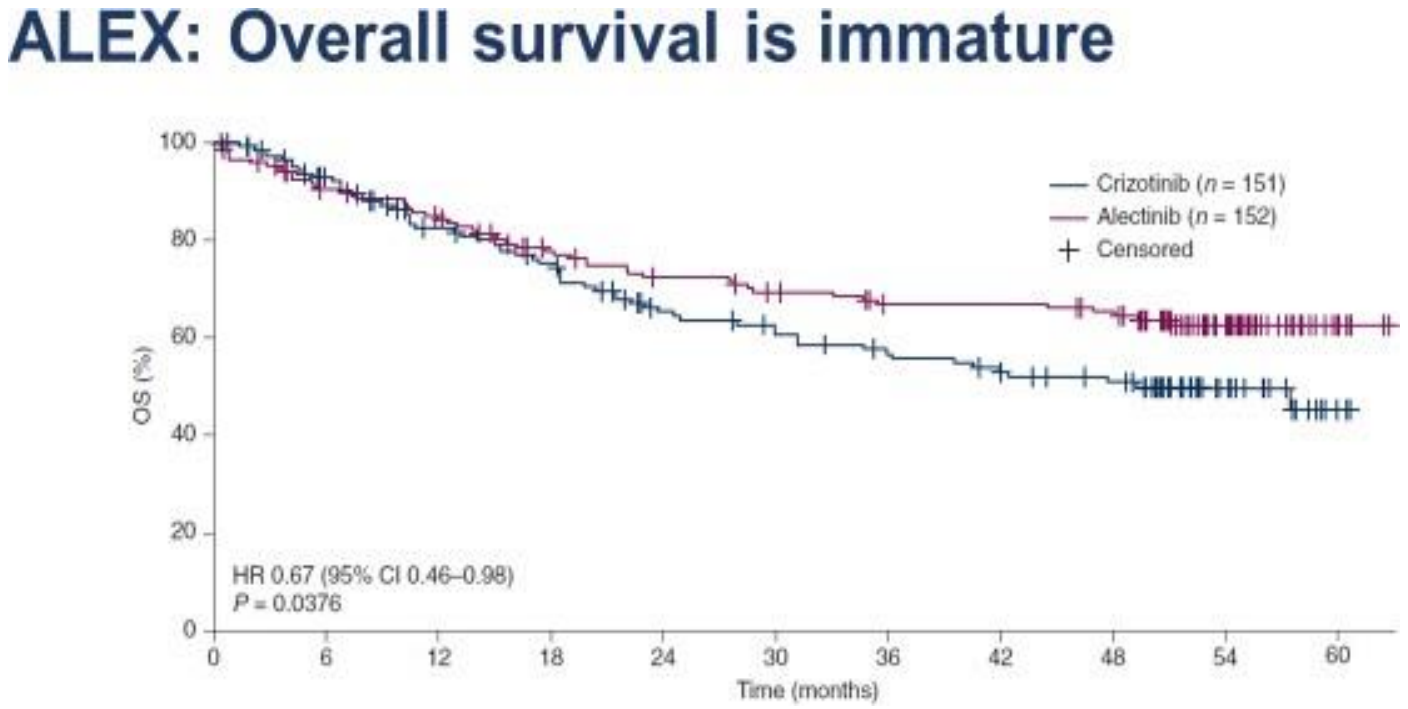
ASCEND-4 : OS Data



Overall survival in ALEX



Alectinib vs. Crizotinib HR 0.67[1]

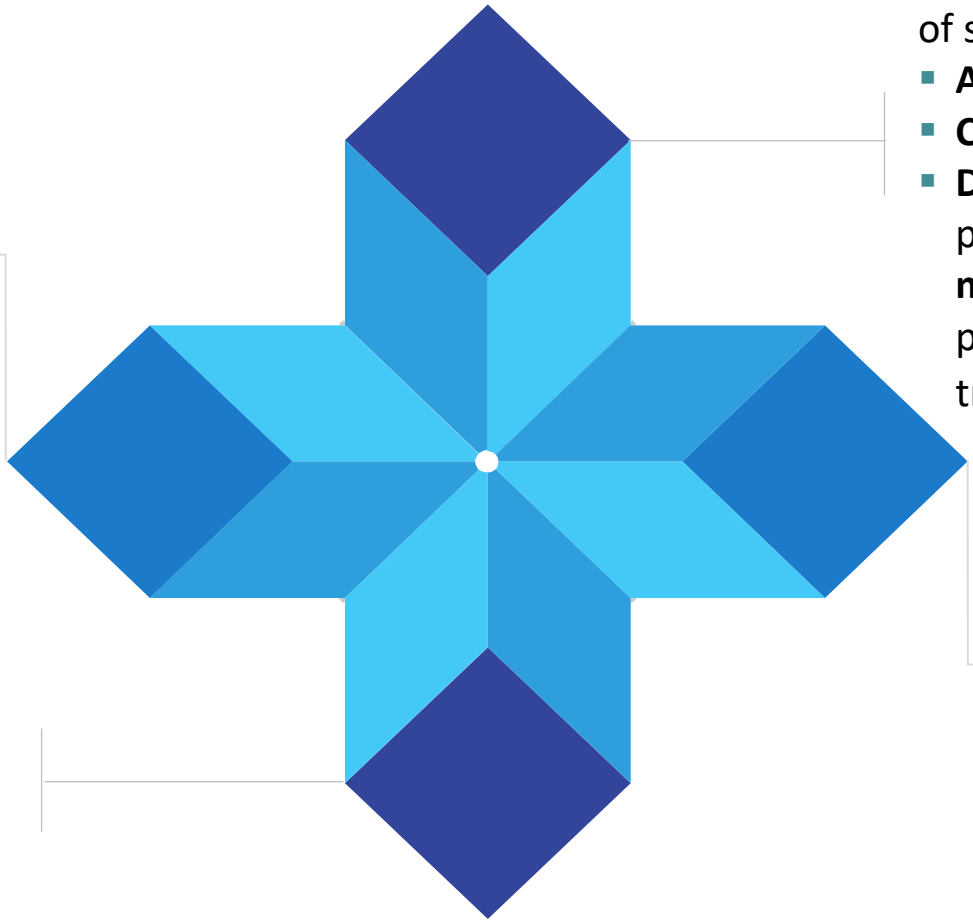
1. Peters S, et al. 9518. Presented at ASCO 2020, Virtual, 8–10 August 2020; 2. Camidge DR, et al. *J Clin Oncol* 2020;38:3592–603; 3. Shaw A, et. al. *N Engl J Med.* 2020;383:2018-29

HR, hazard ratio; OS, overall survival.

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.

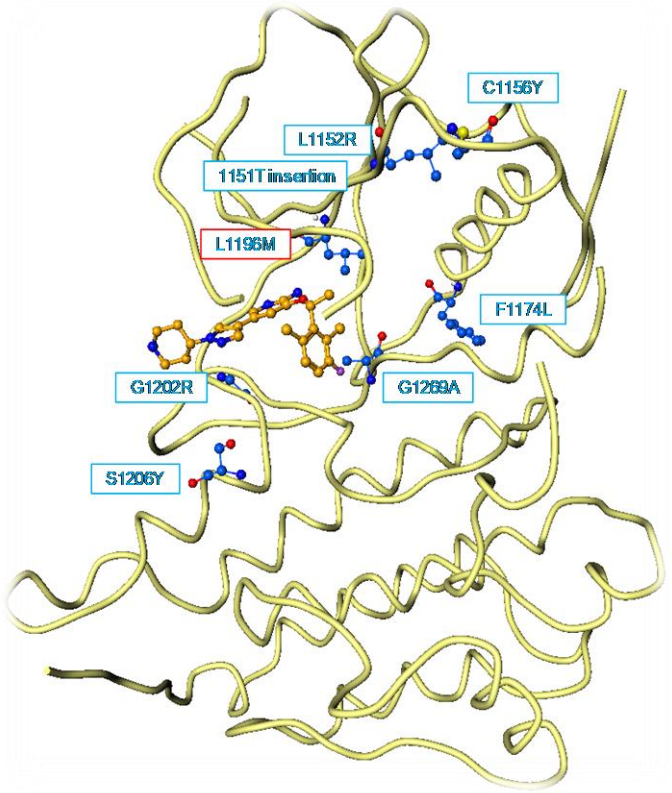
There is a need for additional *ALK-TKI*s that prevent the emergence of resistant subclones in untreated patients.[8]

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.

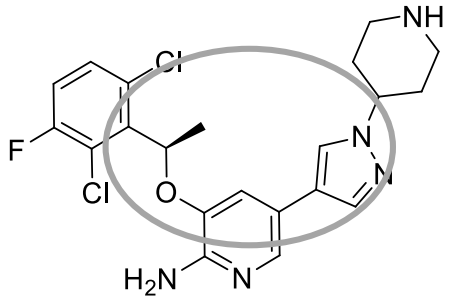
ALK: Anaplastic lymphoma kinase; BM: Brain metastases; CNS: Central nervous system; NSCLC: Non-small cell lung cancer; TKI: Tyrosine kinase inhibitor.

Lorlatinib design and mechanism of action

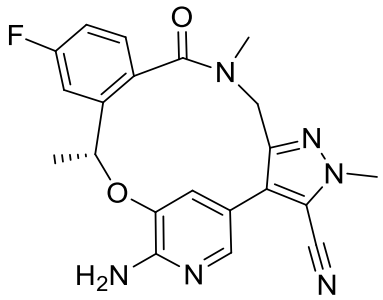
- Lorlatinib (PF-06463922) was rationally designed to address unmet needs in ALK+ NSCLC[1]
  - Metastatic brain disease
  - Acquired resistance to ALK TKIs



Adapted from: Lovly CM, et al. *Sci Transl Med* 2012;4:120ps2



Crizotinib



Lorlatinib

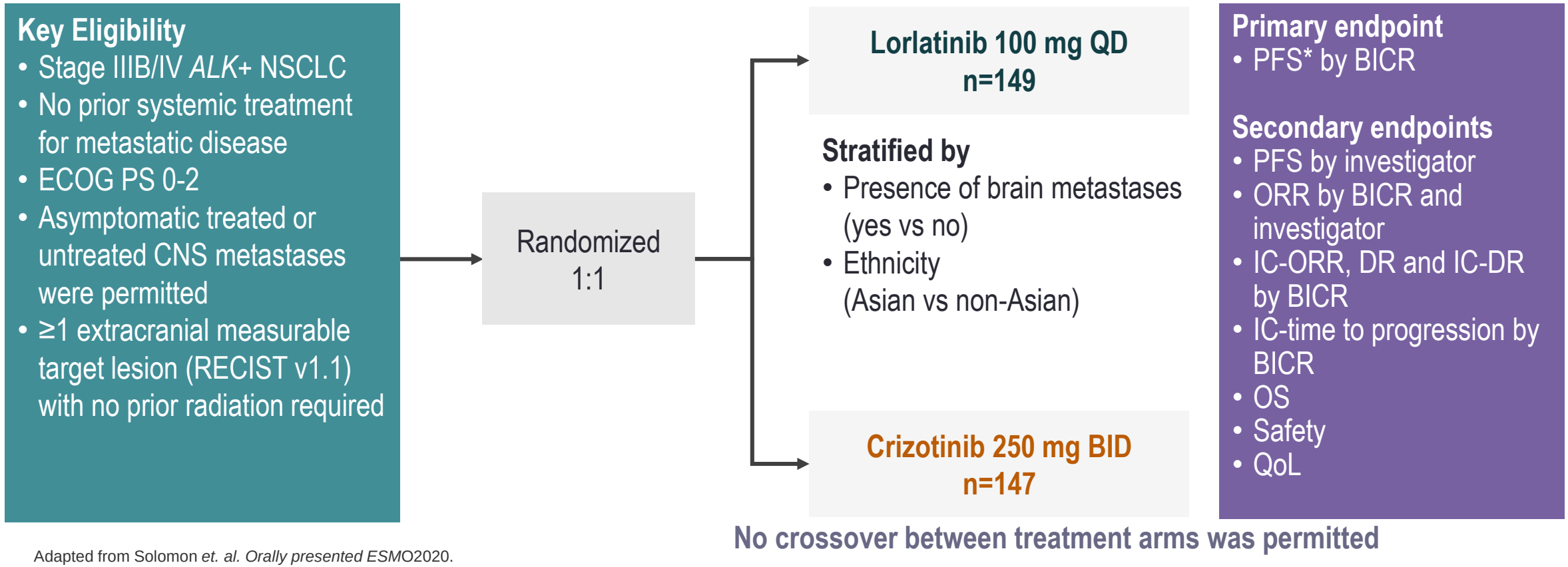
Adapted from Johnson TW, et al. *J Med Chem* 2014;57:4720−44

Effective CNS penetration and retention

Binds with high affinity to most ALK resistance mutations

1. Johnson TW, et al. *J Med Chem* 2014;57:4720−44;

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.

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Baseline Characteristics

Characteristic		Lorlatinib (n=149)	Crizotinib (n=147)
Age, years, median (IQR)		61 (51–69)	56 (45–66)
Sex, %	Female	56	62
	Male	44	38
Race, %	White	48	49
	Asian	44	44
	Black or African American	0	1
	Missing*	8	6
ECOG PS, %	0	45	39
	1	53	55
	2	2	6
Smoking status, %	Never smoked	54	64
	Previous smoker	37	29
	Current smoker	9	6
Current stage of disease, %	Stage IV	91	95
Brain metastases at baseline, %**	Yes	26	27
Prior brain radiotherapy, %	Yes	6	7

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

*Includes patients with race not reported for local regulations; **based on BICR assessment
ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range.

AACR 2022

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]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; [3]State Key Laboratory of South China, Chinese University of Hong Kong, Hong Kong; [4]University Health Network, Toronto, ON, Canada; [5]Toulouse University Hospital, Toulouse, France; [6]European Institute of Oncology, IRCCS, Milan, Italy; [7]National Cancer Center Hospital, Tokyo, Japan; [8]Seoul National University Hospital, Seoul, South Korea; [9]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; [10]Budget Healthcare Institution of Omsk Region, Omsk, Russian Federation; [11]Medical University of Gdańsk, Gdańsk, Poland; [12]San Peregrino Cancer Center, Aguascalientes, Mexico; [13]National University Cancer Institute, Singapore, Singapore; [14]Pfizer, Milan, Italy; [15]Pfizer, New York, NY; [16]Vall d'Hebron University Hospital, Barcelona, Spain

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

Plain Language Summary
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Correspondence: Todd Bauer, tbauer@tnonc.com

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References: 1. Johnson TW, et al. *J Med Chem.* 2014;57:4720-4744. 2. Shaw AT, et al. *N Engl J Med.* 2020;383:2018-2029. 3. US Food and Drug Administration. Accessed February 28, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lorlatinib-metastatic-alk-positive-nsclc 4. Lorbrena (lorlatinib). Prescribing information. Pfizer Inc; 2021. Accessed March 3, 2022. https://labeling.pfizer.com/ShowLabeling.aspx?id=11140 5. Lorbrena (lorlatinib). Japanese prescribing information. Pfizer Japan Inc; 2021. Accessed March 3, 2022. 6. European Medicines Agency. Accessed March 3, 2022. https://www.ema.europa.eu/en/documents/overview/lorviqua-epar-medicine-overview_en.pdf

Acknowledgements: This study was sponsored by Pfizer Inc. Medical writing support was provided by Kakoli Parai, PhD, of ClinicalThinking, Inc, and funded by Pfizer.

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

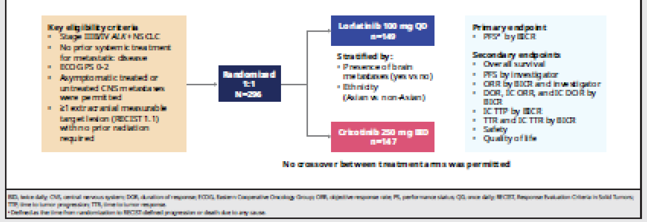
Background

- 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

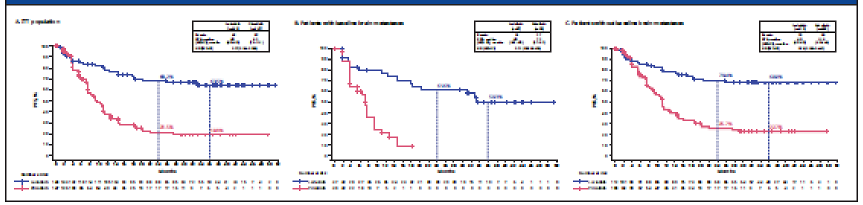


Figure 3: Time to IC progression by BICR

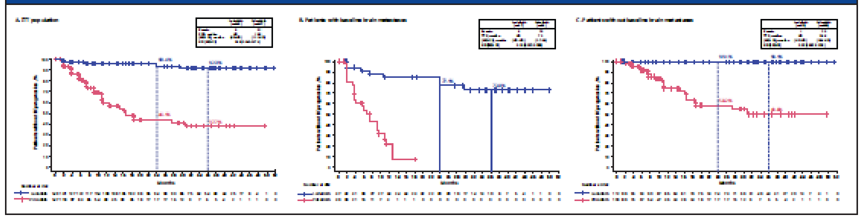


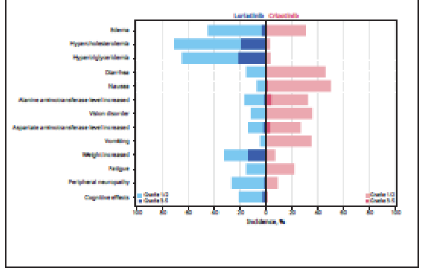
Table 1: Summary of overall and IC response by BICR

	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

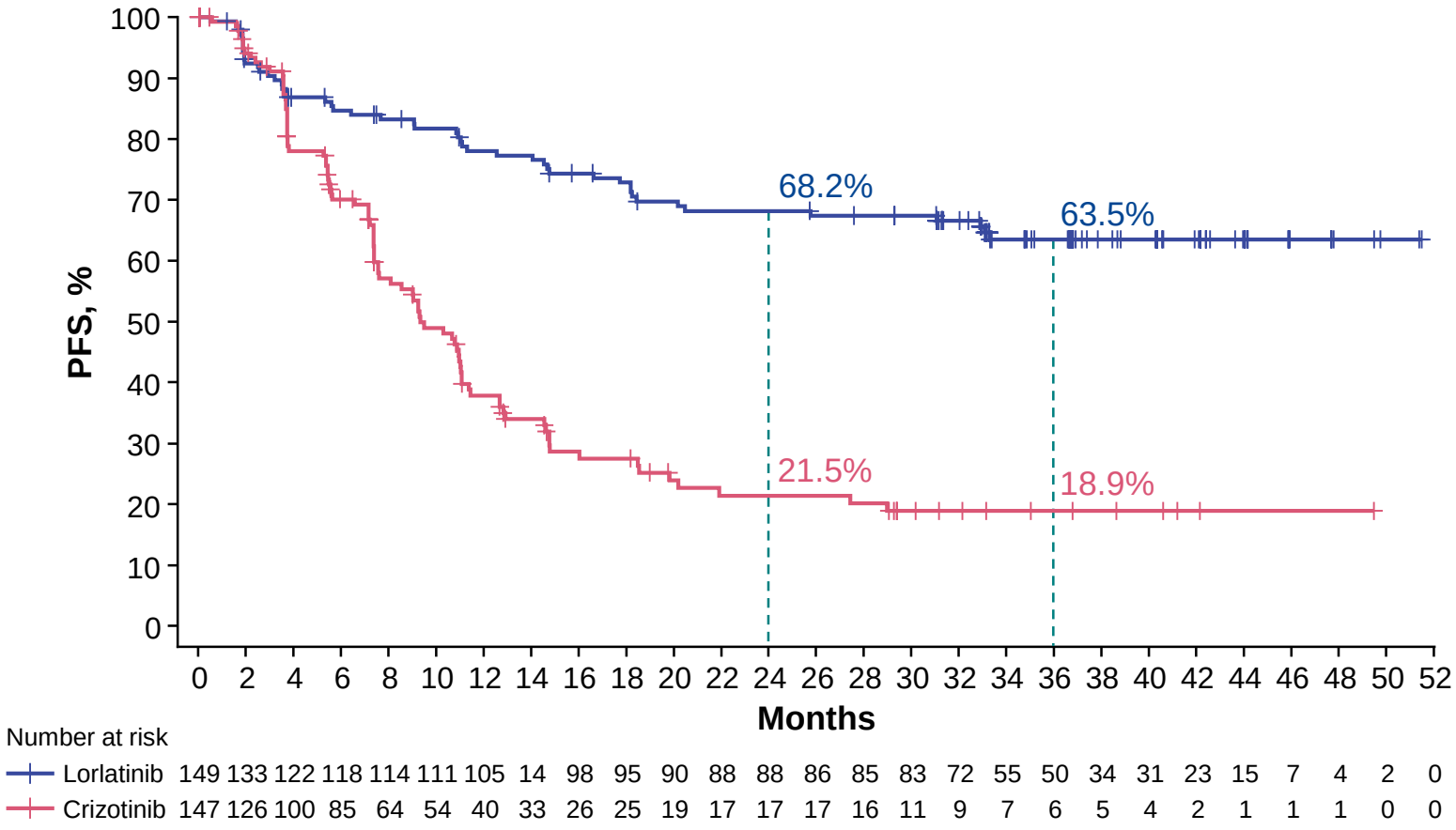
	n (%)	
	Lorlatinib (n=149)	Crizotinib (n=142)
Any-grade AE	149 (100.0)	140 (98.6)
Treatment related	145 (97.3)	133 (93.7)
Grade 3/4 AE	113 (75.8)	81 (57.0)
Treatment related	94 (63.1)	54 (38.0)
Death	10 (6.7)	7 (4.9)
Treatment related	2 (1.3)	0
Any serious AE	57 (38.3)	44 (31.0)
Treatment related	13 (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



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)



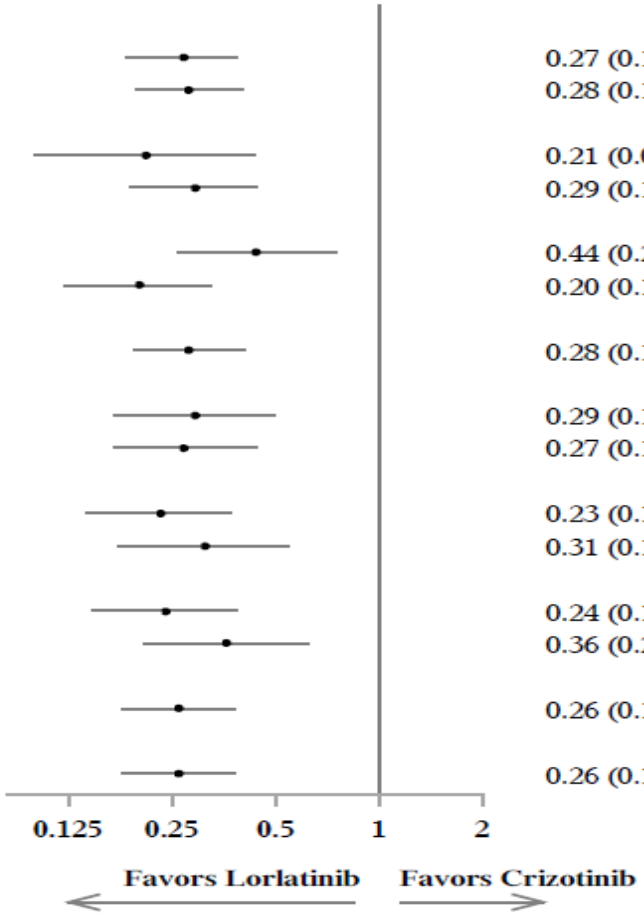
	ITT	
	Lorlatinib (n=149)	**Crizotinib (n=147)**
Events	49	92
PFS, median (95% CI), months	NR (NR–NR)	9.3 (7.6–11.1)
HR (95% CI)	0.27 (0.184–0.388)	

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

Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

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, 0.32		1
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



Please see summary of prescribing information on last slide

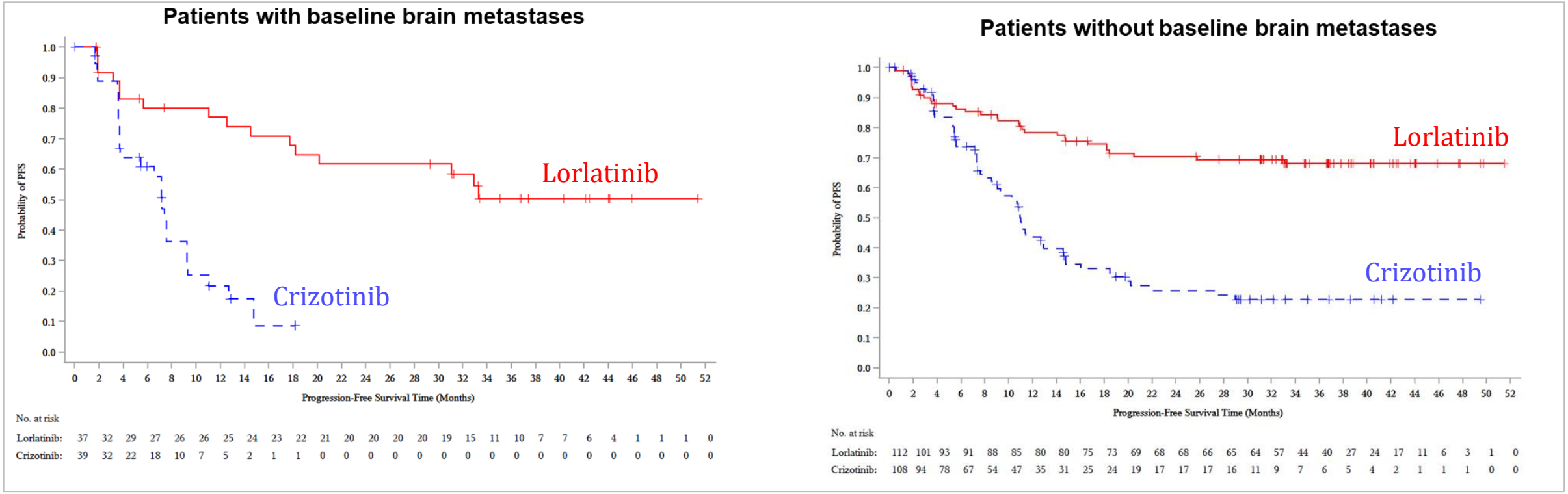
BICR, blinded independent central review; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival.

Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

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)	

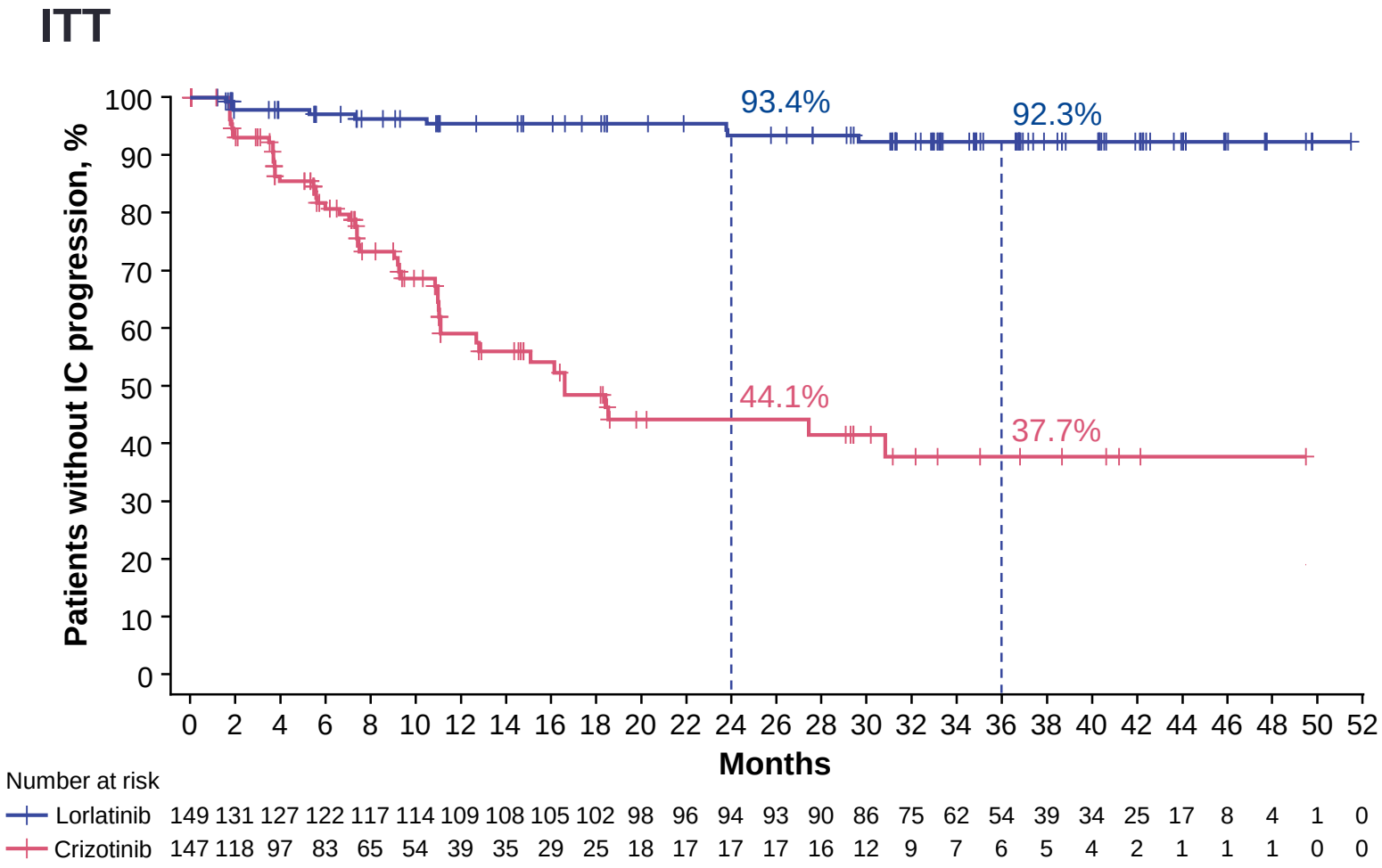
36-Month Data



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

Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

Time to IC progression was longer with lorlatinib than with crizotinib



	ITT	
	Lorlatinib (n=149)	Crizotinib (n=147)
Events	9	51
TTP, median (95% CI), months	NR (NR–NR)	16.6 (11.1–NR)
HR (95% CI)	0.08 (0.040–0.174)	

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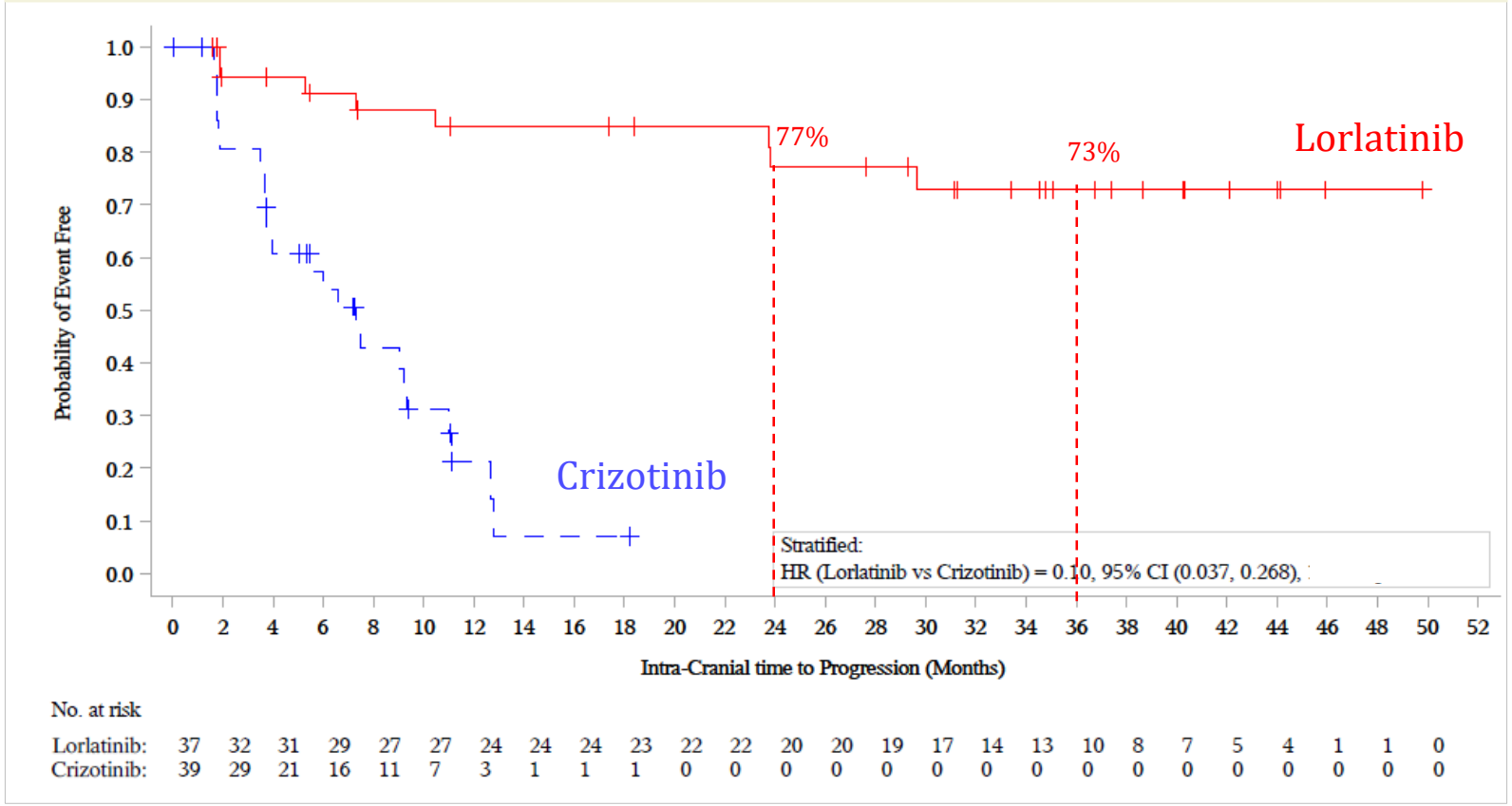
CROWN: BICR-assessed intracranial time to progression in patients with baseline brain metastases

36-Month Data

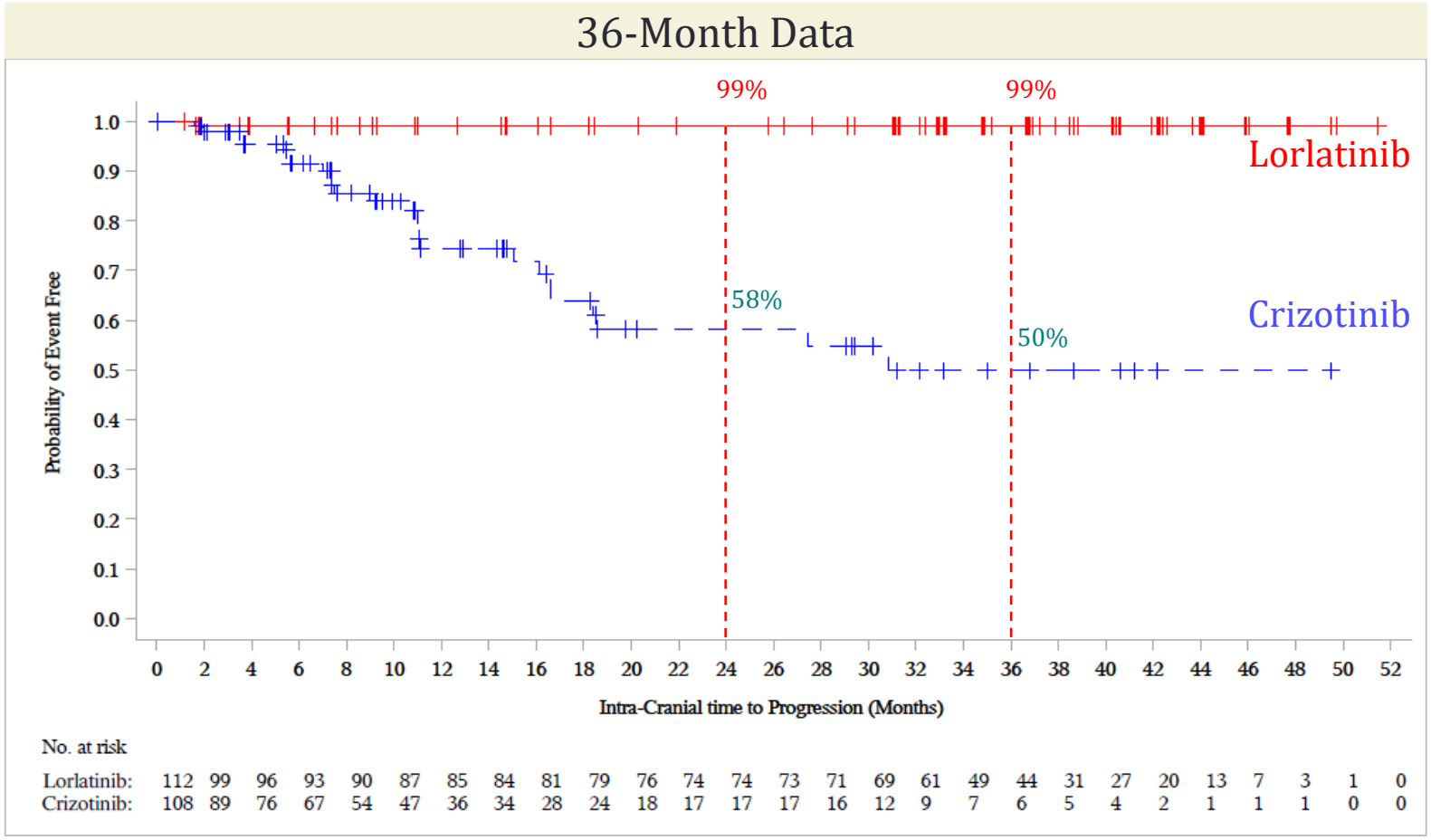


	With brain metastases	
	Lorlatinib (n=37)	Crizotinib (n=39)
Events	8	26
Median PFS (95% CI), months	NR (NR–NR)	7.3 (3.7–9.3)
HR (95% CI)	0.10 (0.04–0.27)	

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

Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

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)	

Only 1 out of 112 patients without baseline brain metastases had intracranial progression on lorlatinib

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

Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: Summary of overall and intracranial response

	Lorlatinib	Crizotinib
ITT population, n	**149**	**147**
Confirmed ORR by BICR, n (%)	115 (77.2)	86 (58.5)
Complete response, n (%)	4 (2.7)	0 (0)
Median DoR (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, n (%)	22 (59.5)	5 (12.8)
Median IC-DoR (95% CI), months	NR (NR–NR)	9.4 (6.0–11.1)
Patients with at least 1 measurable brain metastasis at baseline, n	**18**	**13**
Confirmed IC-ORR by BICR, n (%)	15 (83.3)	3 (23.1)
Complete IC response, n (%)	13 (72.2)	1 (7.7)
Median DoR (95% CI), months	NR (NR–NR)	10.2 (9.4–11.1)

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; NR, not reached; ORR, objective response rate.

Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: Summary of adverse events

	36-Month Data	
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)
Grade 5 AE	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)

AE, adverse event

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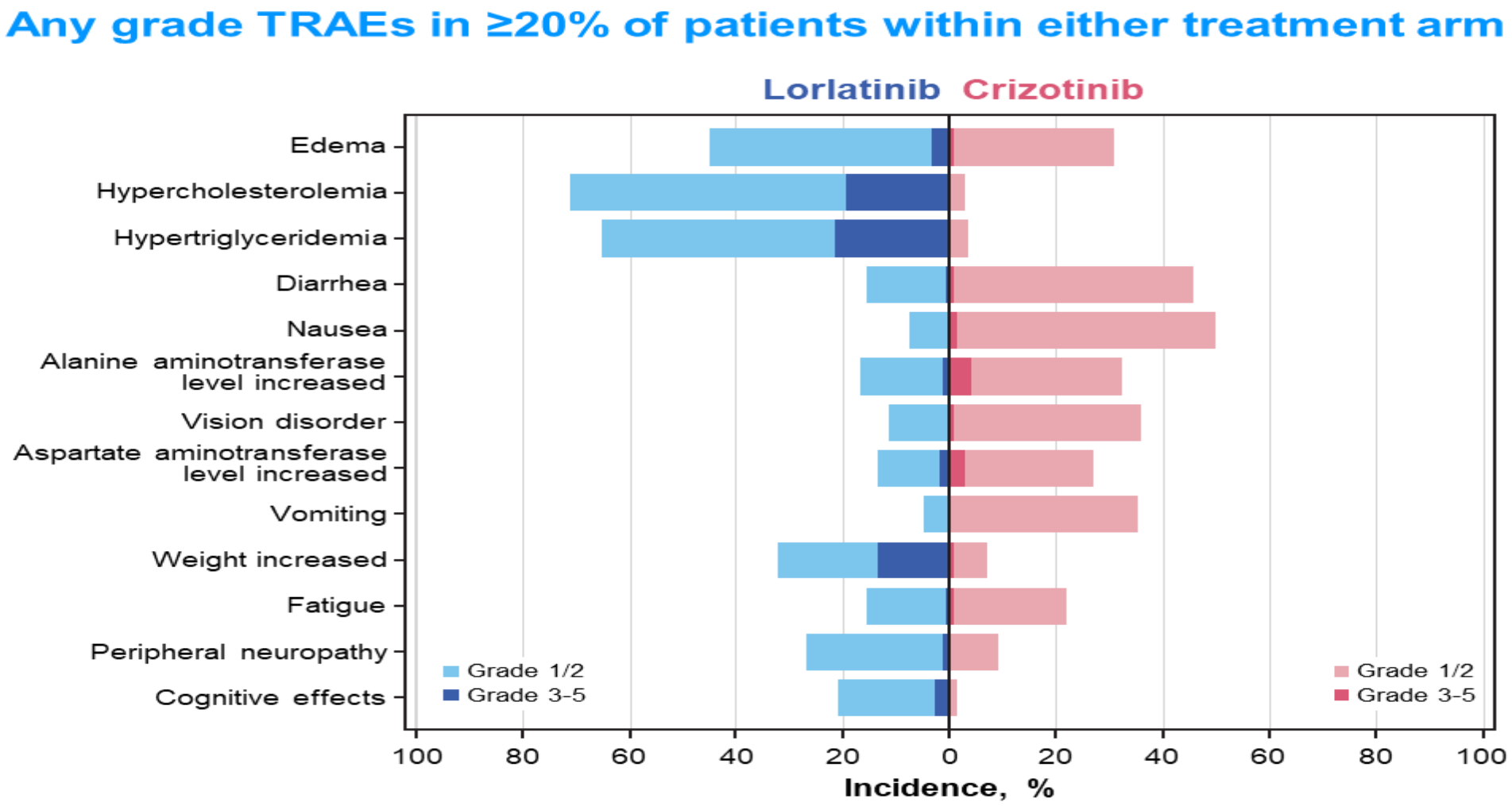
Safety profile of lorlatinib was similar to that reported in the interim analysis



AE, adverse event; TRAE, treatment-related AE.

Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

Summary of CROWN Trial for Lorlatinib Arm at 18 and 36 months respectively

Parameters	18 month Follow up	36 month follow up
PFS (HR) (BICR)	0.28	0.27
ORR (%)	76	77.2
Time to intra-cranial progression (HR)	0.07	0.08
Complete IC response, n (%) (any brain metastases at baseline)	23 (61)	22 (59.5)
Complete IC response, n (%) (at least 1 measurable brain metastasis at baseline)	12 (71)	13 (72.2)
AEs leading to permanent treatment discontinuation (%)	7	7.4

The Efficacy and Safety of Lorlatinib is maintained after 36 months of follow up

1. Solomon et al. Orally presented at European Society of Medical Oncology (ESMO) Virtual Congress; Sep19-21,2020.
2. Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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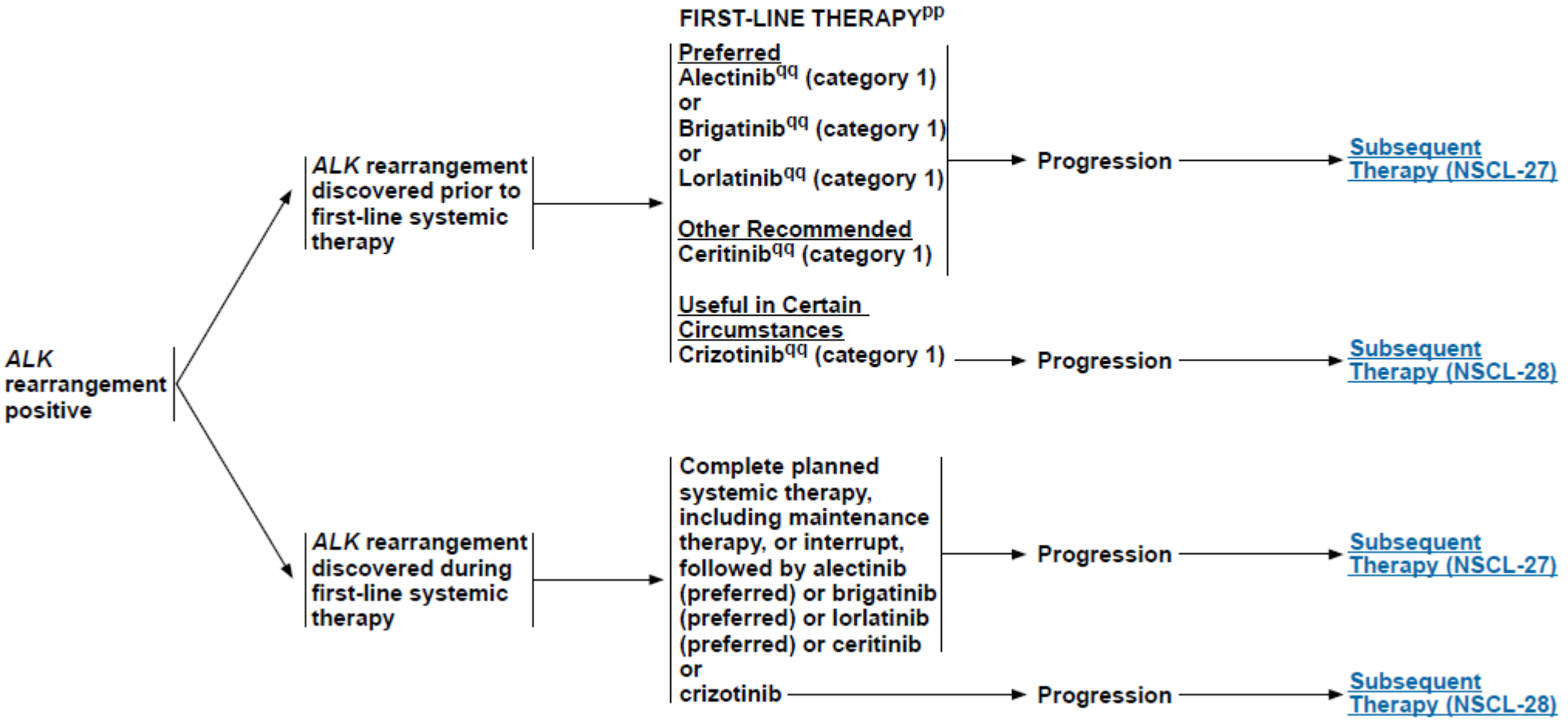
Discussion

ALK REARRANGEMENT POSITIVE[mm]



Adapted from NCCN guidelines version 3.2022 accessed on 18th May 2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf .

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Lorlatinib in 1L Treatment of Patients with ALK+ Non-Small–Cell Lung Cancer: A Network Meta-analysis

Joanne Gregory[1], Hannah Kilvert[1], Troy Williams[2], Miranda Cooper[1], Anna Polli[3], Laura Iadeluca[4], Sai-Hong Ignatius Ou[5]

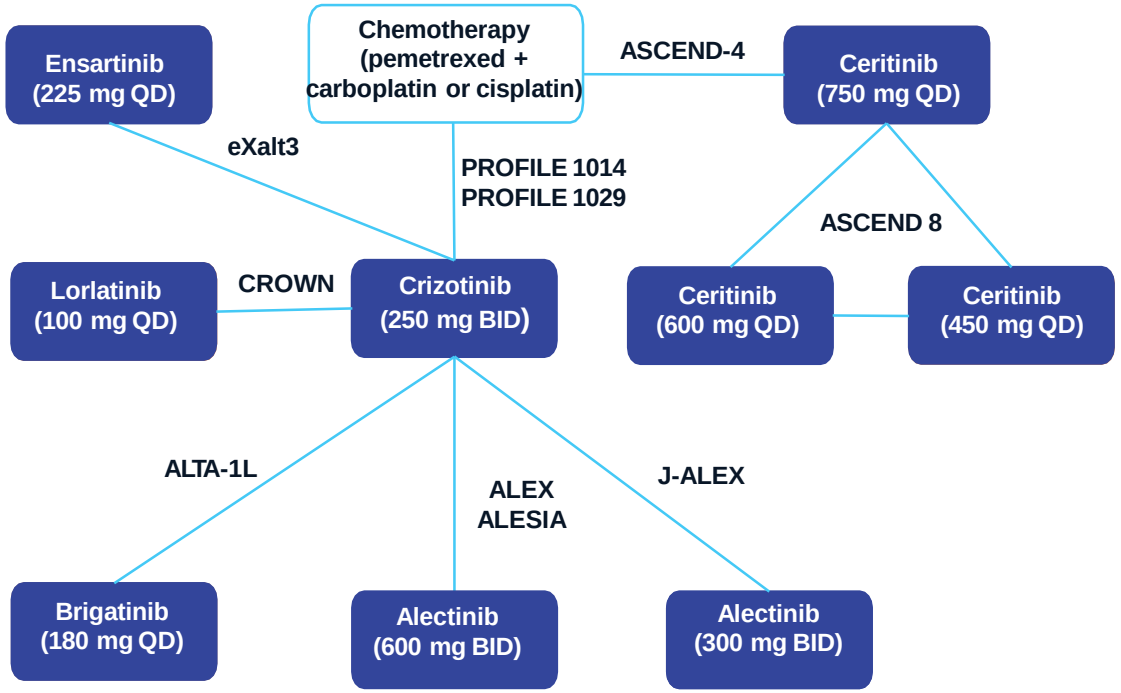
[1]BresMed Health Solutions, Sheffield, UK, [2]BresMed Health Solutions, Las Vegas, US, [3]Pfizer Inc, Milan, Italy, [4]Pfizer Inc, New York, US, [5]UCI School of Medicine, University of California, Irvine, California

IASLC 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

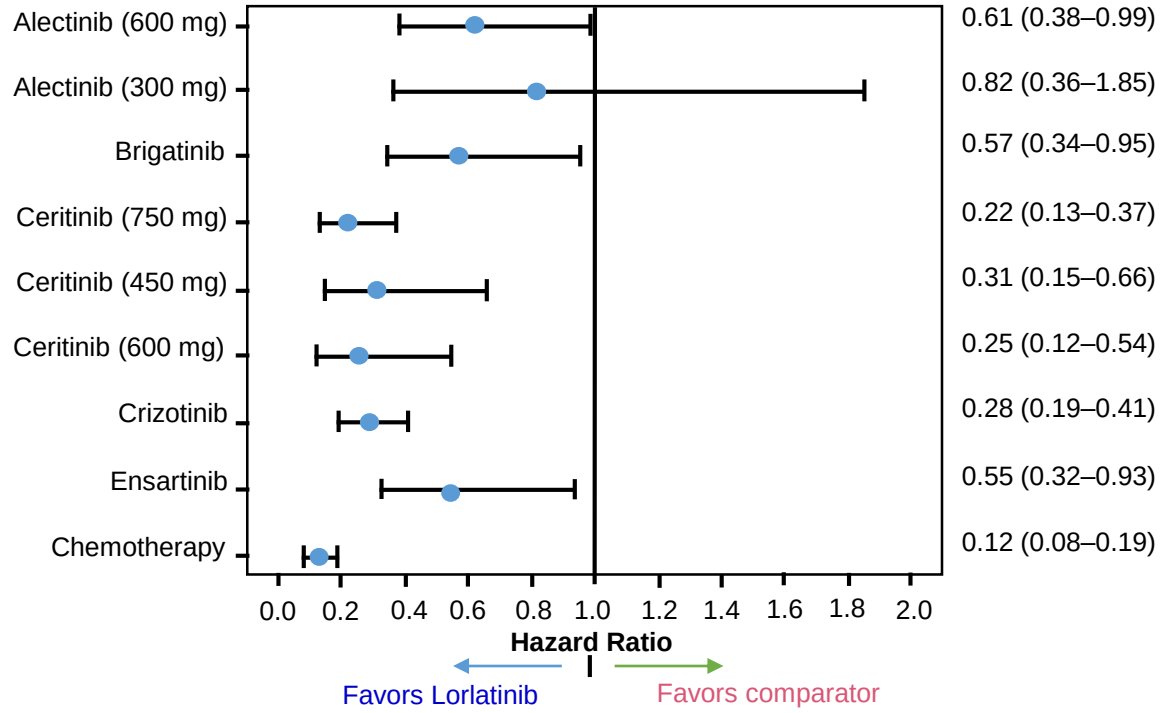
1L: First line; ALK: Anaplastic lymphoma kinase.

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)

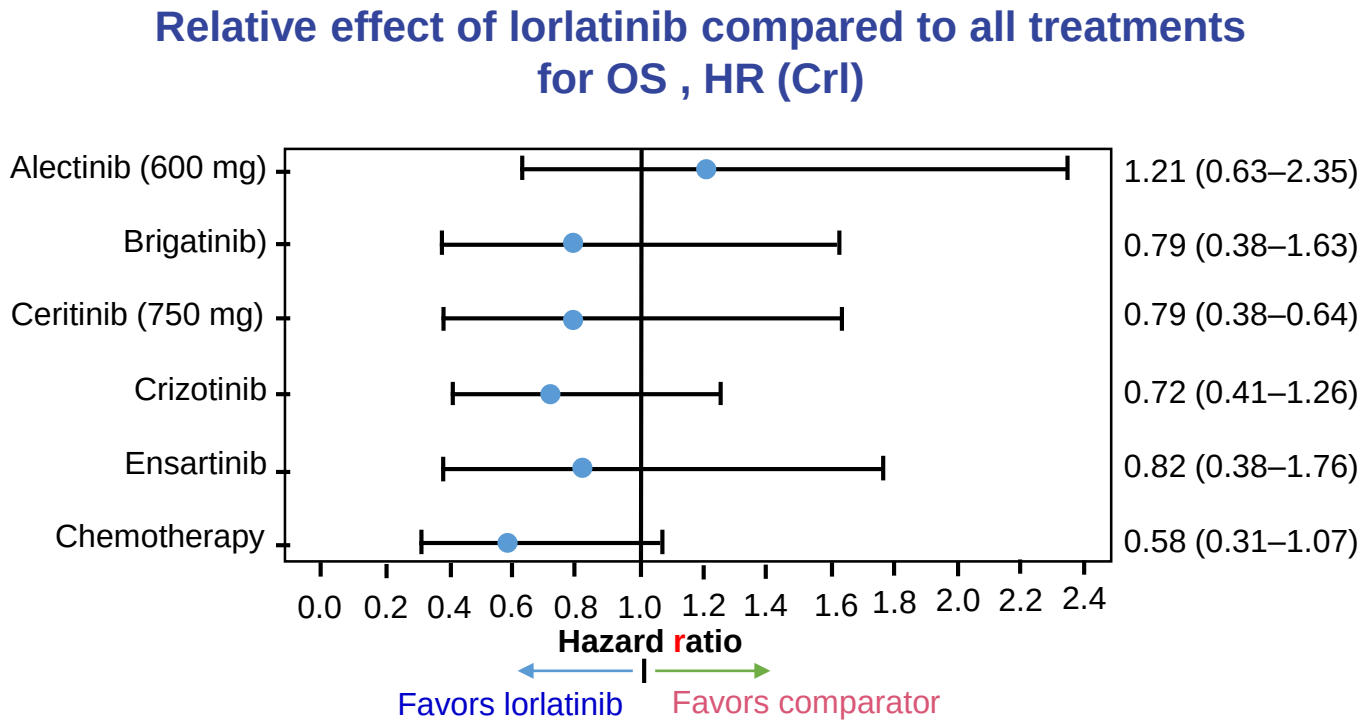


Lorlatinib is an effective first-line treatment for ALK+ NSCLC when compared to crizotinib and other next-generation ALK-TKIs.

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

ALK: Anaplastic 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.

Immature Overall Survival Data for Most Included Studies in Network Meta-analysis



No statistical difference between lorlatinib and the other treatments for OS. However, OS was immature for many of the included studies.

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

CrI: Credible interval; HR: Hazard ratio; OS: Overall survival.

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]

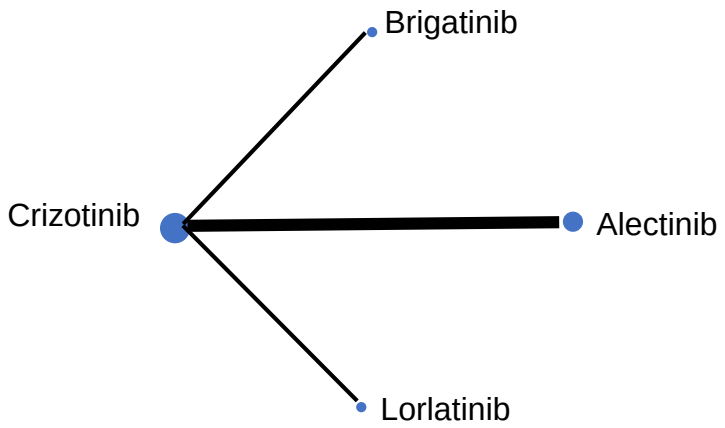
[a]Department of E.N.T, Weifang People's Hospital, Weifang, China; [b]Department of Hematology, Weifang People's Hospital, Weifang, China; [c]Department of Stomatology, Weifang People's Hospital, Weifang, China; [d]Infection Department, Weifang People's Hospital, Weifang, China; [e]Department of Respiration, 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: Anaplastic lymphoma kinase; NSCLC: Non-small–cell lung cancer; PFS: Progression-free survival.

Lorlatinib PFS Advantage Over Alectinib and Brigatinib in NMA

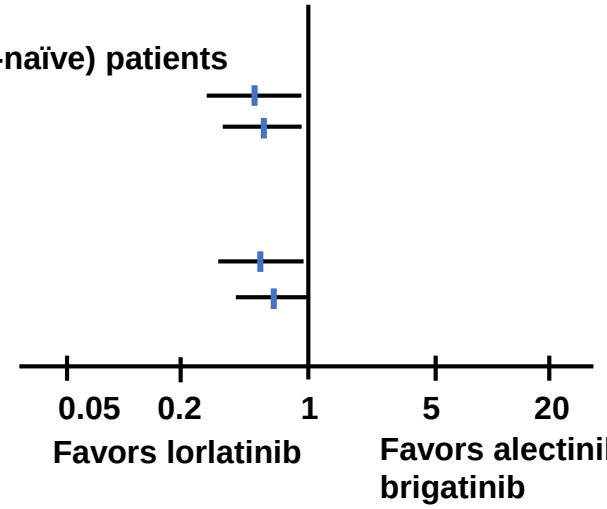
Network plot of different comparisons



ALK inhibitor-naive or untreated (ALK inhibitor-naive and chemotherapy-naive), *ALK*-positive, advanced NSCLC. NMA of three 5-phase RCTs with lorlatinib, alectinib, brigatinib, and crizotinib, involving 1111 subjects.

Network comparison of lorlatinib, alectinib, and brigatinib for ALK inhibitor-naïve and previously untreated, *ALK*+, advanced NSCLC in PFS analysis

Study or subgroup	Hazard ratio IV. Random. 95% CI
Untreated (ALK inhibitor-naïve and chemotherapy-naïve) patients	
Lorlatinib vs. brigatinib	0.54 [0.31, 0.94]
Lorlatinib vs. alectinib	0.59 [0.37, 0.94]
ALK inhibitor-naïve patients	
Lorlatinib vs. brigatinib	0.57 [0.34, 0.95]
Lorlatinib vs. alectinib	0.65 [0.42, 1.01]



Results from a meta-analysis including only RCTs of ALK-TKIs with head-to–head comparison with crizotinib indicate that first-line lorlatinib is the best treatment choice for PFS.

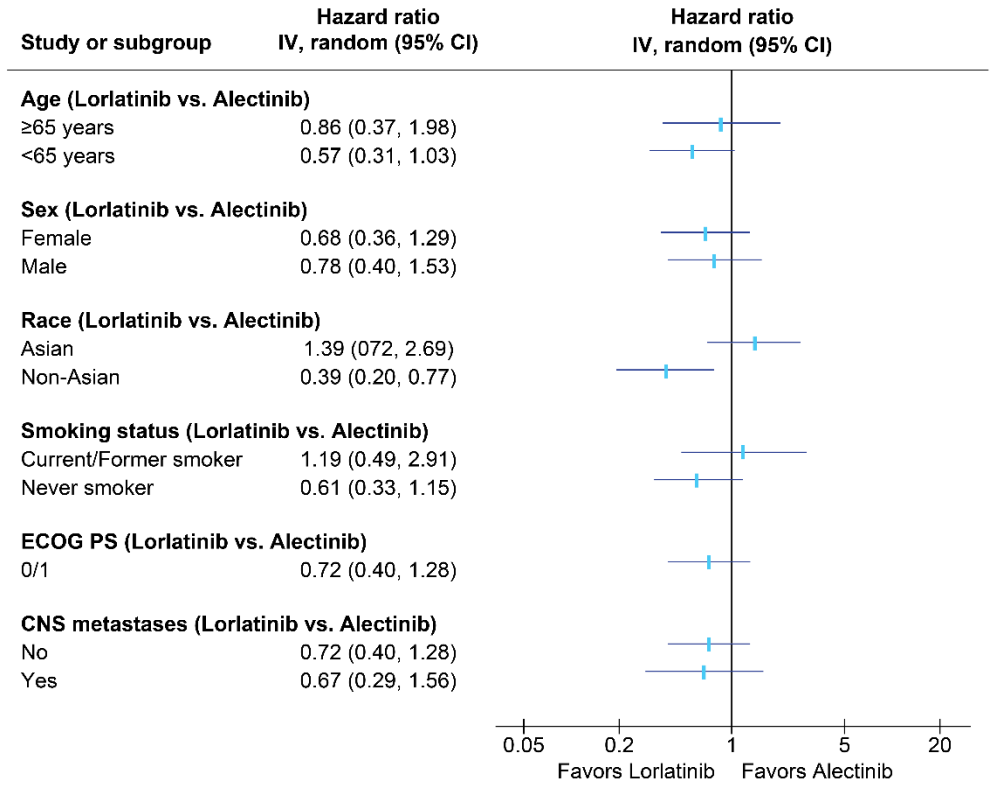
- **Lorlatinib shows a significant PFS advantage vs. brigatinib and alectinib with a probability to reach the best PFS of 97.5% in previously untreated patients with ALK+, advanced NSCLC.**
- **Lorlatinib prolongs PFS vs. brigatinib and alectinib with a probability to reach the best PFS of 96.4% in ALK inhibitor–naive patients.**

Wang L, *et al*. *J Chemother*. 2022;34(2):87–96.

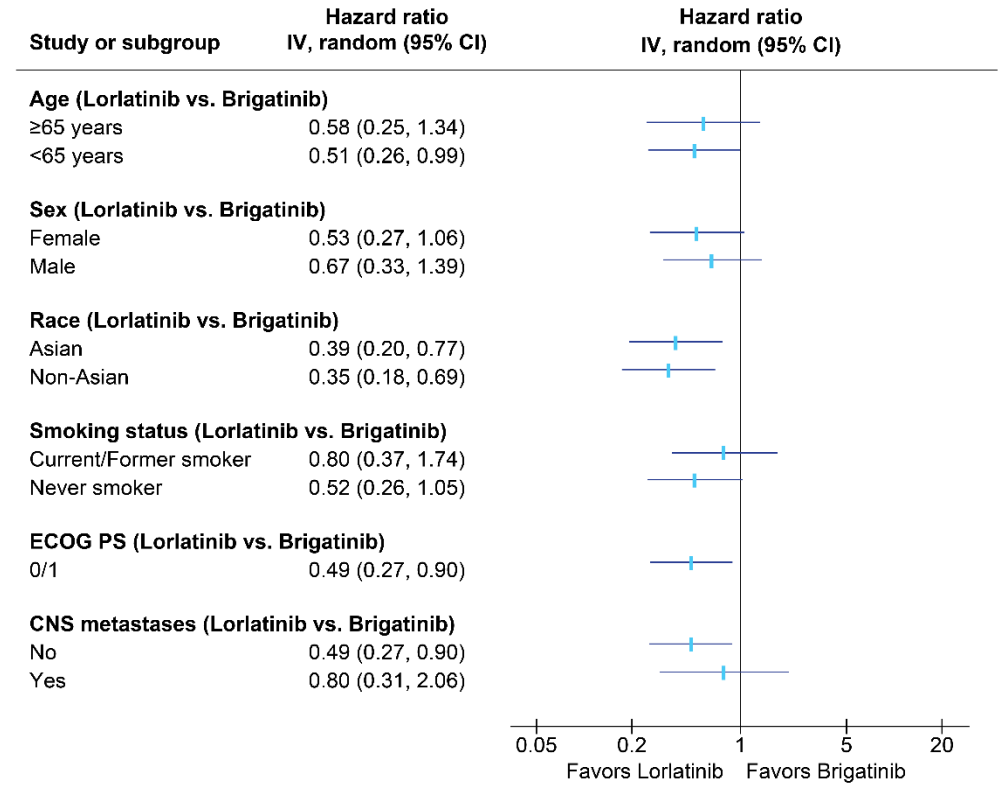
ALK: Anaplastic lymphoma kinase; CI: Confidence interval; CNS: Central nervous system; HR: Hazard ratio; NMA: Network meta-analysis; NSCLC: Non-small–cell lung cancer; PFS: Progression-free survival; RCT: Randomised clinical trials; TKI: Tyrosine kinase inhibitors.

Subgroup Analysis of ALK-TKIs for ALK Inhibitor-Naïve, *ALK*-positive, Advanced NSCLC

Subgroup analysis of different ALK-TKIs (lorlatinib, alectinib, and brigatinib) for ALK inhibitor-naïve, *ALK*-positive, advanced NSCLC in PFS analysis.



Vs. Alectinib



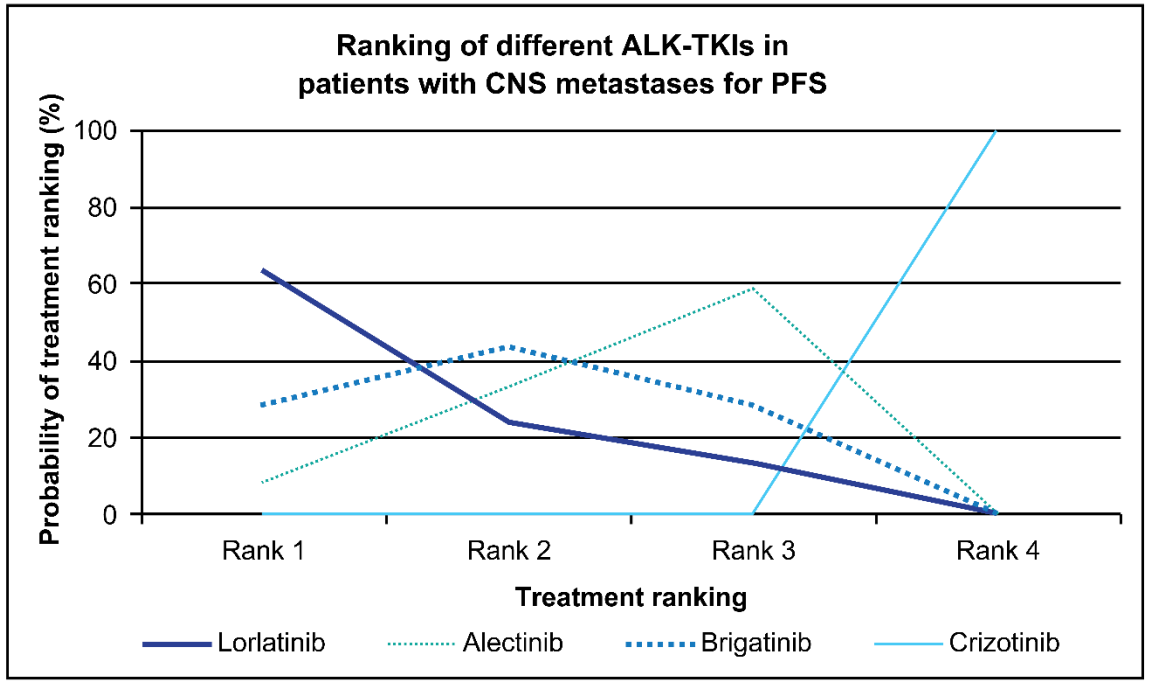
Vs. Brigatinib

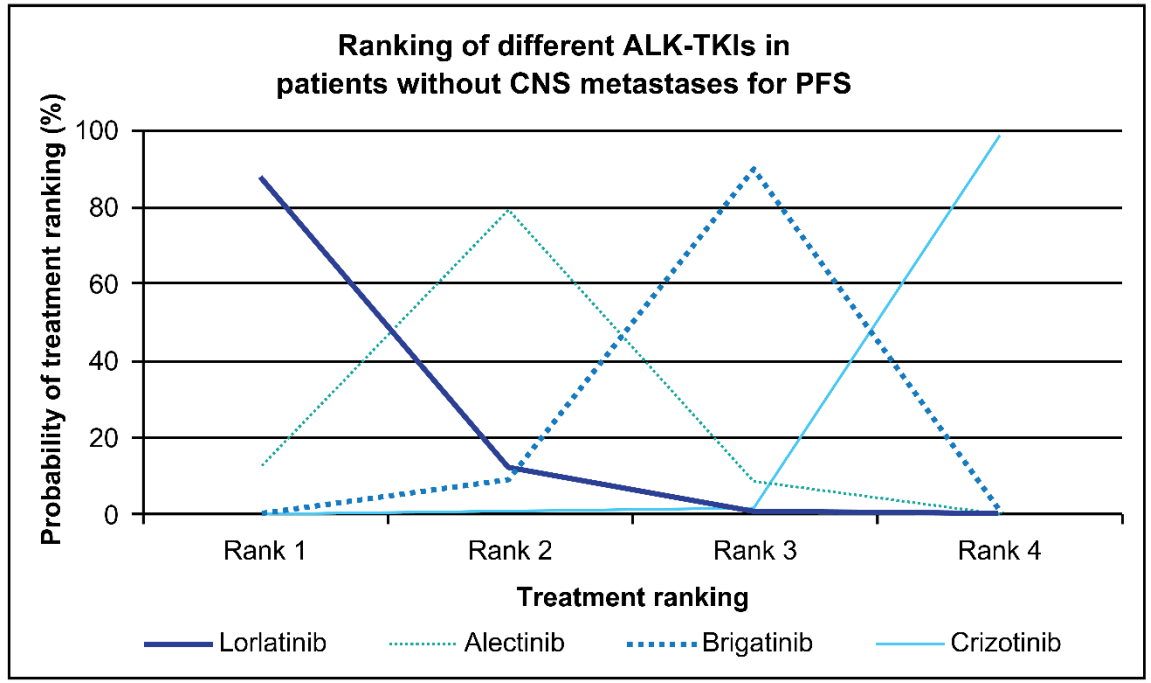
Wang L, *et al*. *J Chemother*. 2022;34(2):87–96.

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

Ranking of ALK-TKIs in PFS Analysis

Ranking of different ALK-TKIs (lorlatinib, alectinib, brigatinib, and crizotinib) in PFS analysis for ALK inhibitor-naïve patients with advanced NSCLC.



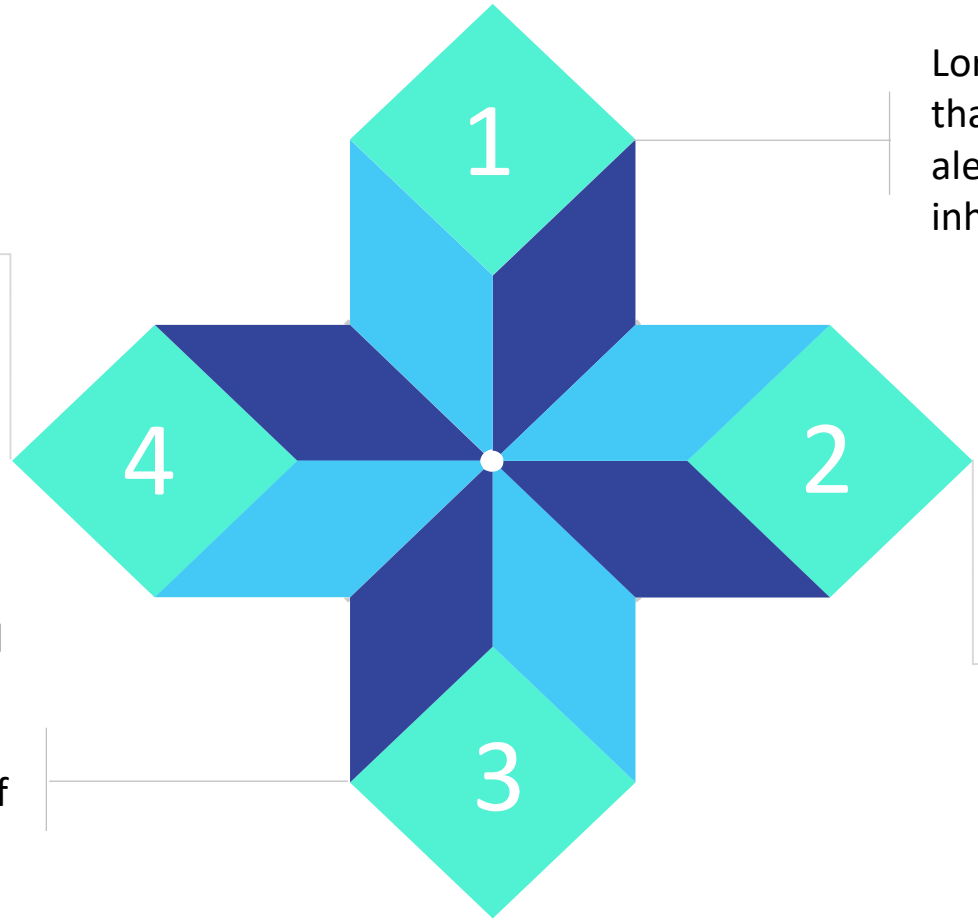


Wang L, *et al*. *J Chemother*. 2022;34(2):87–96.

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

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.

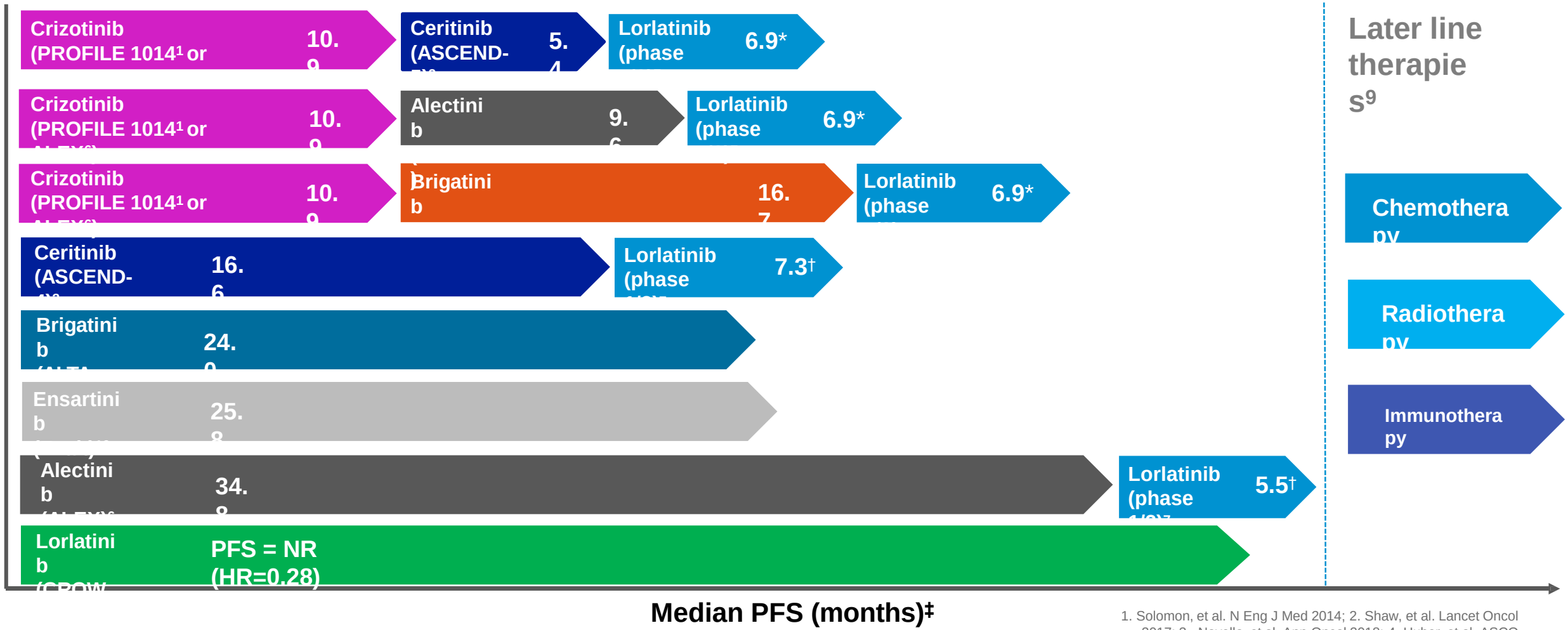
No significant difference was found among them in OS and AE analysis.

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%)

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

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. **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, 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

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 IC efficacy compared with crizotinib in patients with ALK-positive NSCLC
    - PFS by BICR remained longer with lorlatinib than crizotinib; the 3-year rate 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 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 brain metastases

BICR, blinded independent central review; IC, intracranial; NSCLC, non-small cell lung cancer; PFS, progression free survival


Thank
you