Final overall survival (OS) and safety analysis of the Phase 3 ALEX study of alectinib vs crizotinib in patients with previously untreated, advanced *ALK*-positive (*ALK*+) non-small cell lung cancer (NSCLC)

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Declaration of interests

Prof. Tony Mok declares the following conflicts:

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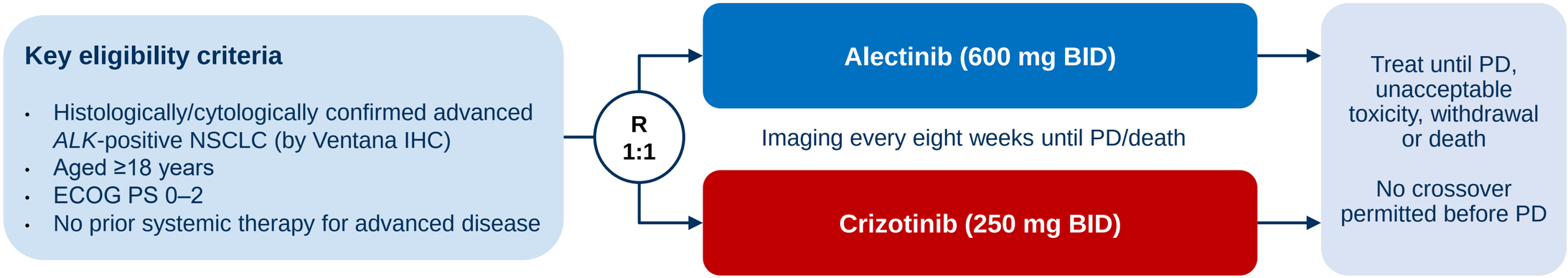
Background

- Results from the randomised, Phase 3 ALEX study (NCT02075840), first published in 2017, led to the global approval of first-line alectinib for the treatment of patients with advanced *ALK*-positive NSCLC[1,2]
- At the **final PFS analysis** (data cut-off: 30 November 2018)[2]
  - investigator-assessed **median PFS** was **significantly prolonged** in the alectinib group compared with the crizotinib group (34.8 vs 10.9 months, respectively; p<0.0001)
  - after a median survival follow-up of 48.2 months, OS data were immature: median OS was not reached with alectinib and 57.4 months with crizotinib (stratified HR 0.67; 95% CI 0.46–0.98)
- Here, we report the final OS analysis from ALEX, as well as updated long-term safety data, after an additional 6 years of follow-up from the previous OS analysis (data cut-off: 28 April 2025)

1. Peters S, et al. N Eng J Med 2017;377:829–838; 2. Mok T, et al. Ann Oncol 2020;31:1056–1064.
ALK, anaplastic lymphoma kinase; CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

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ALEX: randomised, open-label, Phase 3 multicentre study



Stratification factors

- ECOG PS (0 or 1 vs 2)
- Race (Asian vs non-Asian)
- Baseline CNS metastases (yes vs no)

Primary endpoint

- PFS per investigator using RECIST v1.1

Secondary endpoints

- PFS by IRC
- Time to CNS progression
- ORR
- DoR
- OS; safety

NCT02075840.

BID, twice daily; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumours.

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Patient demographics and baseline characteristics

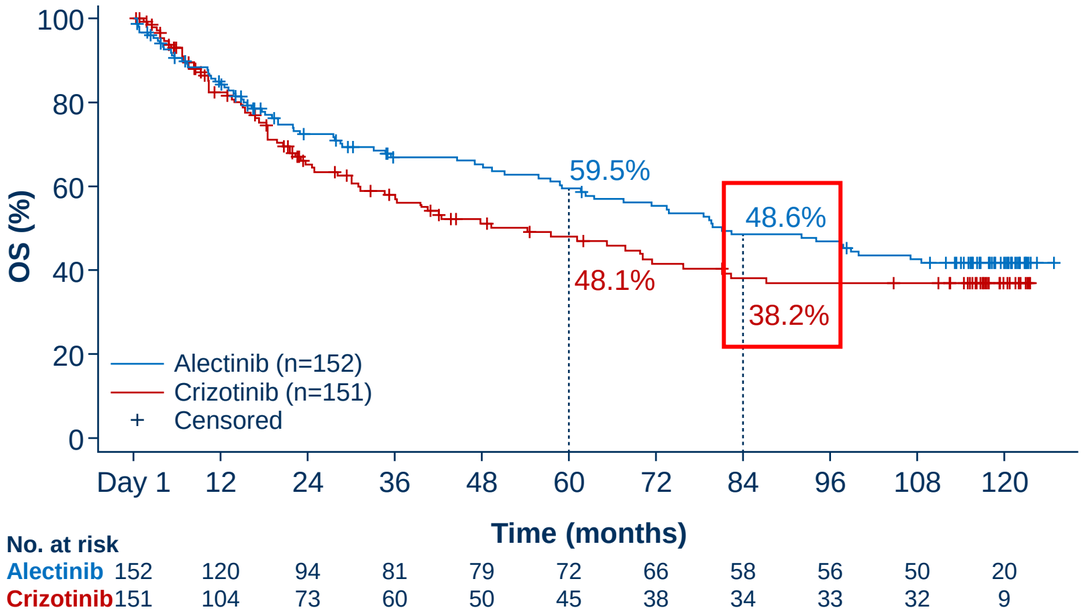
Characteristic	Alectinib (n=152)	Crizotinib (n=151)
Median age, years (range)	**58.0** (25-88)	**54.0** (18-91)
Sex, n (%) Male Female	 68 (**44.7**) 84 (**55.3**)	 64 (**42.4**) 87 (**57.6**)
Race, n (%) Asian Non-Asian	 69 (**45.4**) 83 (**54.6**)	 69 (**45.7**) 82 (**54.3**)
ECOG PS, n (%) 0 or 1 2	 142 (**93.4**) 10 (**6.6**)	 141 (**93.4**) 10 (**6.6**)
Disease stage, n (%) IIIB IV	 4 (**2.6**) 148 (**97.4**)	 6 (**4.0**) 145 (**96.0**)
CNS metastases (by IRC), n (%) Yes No	 64 (**42.1**) 88 (**57.9**)	 58 (**38.4**) 93 (**61.6**)
Prior brain radiation, n (%) Yes No	 26 (**17.1**) 126 (**82.9**)	 21 (**13.9**) 130 (**86.1**)

NCT02075840. Data cut-off date: 28 April 2025.

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OS in the ITT population

- Median follow-up was 53.5 months with alectinib and 23.3 months with crizotinib
- 7-year OS rate: 48.6% with alectinib vs 38.2% with crizotinib



No. at risk

Alectinib	152	120	94	81	79	72	66	58	56	50	20
Crizotinib	151	104	73	60	50	45	38	34	33	32	9

	Alectinib (n=152)	Crizotinib (n=151)
Patients with event, n (%)	76 (**50.0**)	73 (**48.3**)
Median, months (95% CI)	**81.1** (62.3–NE)	**54.2** (34.6–75.6)
Stratified HR (95% CI)	**0.78** (0.56–1.08)	
p-value (stratified log-rank)	0.1320	

Alectinib induced a clinically meaningful **OS benefit** compared with **crizotinib**

NCT02075840. Data cut-off date: 28 April 2025.

The study was not powered for OS. Median follow-up was shorter than the additional 6-year follow-up time in this analysis due to patients who died, withdrew consent or were lost to follow-up. ITT, intent to treat; NE, not estimable.

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OS in pre-specified patient subgroups

Baseline risk factors	Total n	Alectinib (n=152) n	Alectinib (n=152) Events	Alectinib (n=152) Median (months)	Crizotinib (n=151) n	Crizotinib (n=151) Events	Crizotinib (n=151) Median (months)	HR	95% CI
All patients	303	152	76	81.1	151	73	54.2	0.82	(0.59, 1.13)
Age group (years)									
<65	233	115	61	79.7	118	53	61.1	0.92	(0.63, 1.33)
≥65	70	37	15	NE	33	20	35.9	0.58	(0.30, 1.14)
Sex									
Female	171	84	39	94.0	87	35	75.6	0.88	(0.55, 1.38)
Male	132	68	37	67.4	64	38	35.9	0.77	(0.49, 1.22)
Race									
Asian	138	69	30	97.4	69	25	70.1	0.89	(0.52, 1.52)
Non-Asian	165	83	46	73.7	82	48	42.4	0.79	(0.53, 1.19)
Smoking status									
Active smoker	17	12	6	28.5	5	2	57.4	1.75	(0.35, 8.79)
Non-smoker	188	91	43	97.4	97	42	61.1	0.81	(0.53, 1.24)
Past smoker	98	49	27	73.7	49	29	40.6	0.78	(0.46, 1.31)
ECOG PS									
0	97	43	18	NE	54	21	81.2	0.76	(0.40, 1.43)
1	186	99	50	79.6	87	46	39.5	0.78	(0.52, 1.16)
2	20	10	8	27.5	10	6	10.4	1.47	(0.51, 4.29)
CNS metastases (by investigator)									
No	191	93	45	94.0	98	46	69.8	0.87	(0.58, 1.32)
Yes, no radiation	69	34	20	46.9	35	19	23.7	0.73	(0.38, 1.38)
Yes, with radiation	43	25	11	92.0	18	8	39.5	0.62	(0.24, 1.60)



Longer OS with **alectinib** versus **crizotinib** was consistently observed across many patient subgroups

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Follow-up ALK TKI anticancer therapy

n (%)	Alectinib (n=152)	Crizotinib (n=151)
≥1 subsequent therapy	57 (**37.5**)	72 (**47.7**)
Lorlatinib	28 (**18.4**)	18 (**11.9**)
Brigatinib	16 (**10.5**)	16 (**10.6**)
Crizotinib	14 (**9.2**)	10 (**6.6**)
Alectinib	13 (**8.6**)	38 (**25.2**)
Ceritinib	10 (**6.6**)	29 (**19.2**)
Ensartinib	1 (**0.7**)	0
NVL 655	1 (**0.7**)	0
APG 2449	0	1 (**0.7**)

OS results were not statistically significant; this may be due to data being confounded by the **cross-over** of **crizotinib-treated** patients to the **alectinib** arm

NCT02075840. Data cut-off date: 28 April 2025.
TKI, tyrosine kinase inhibitor.

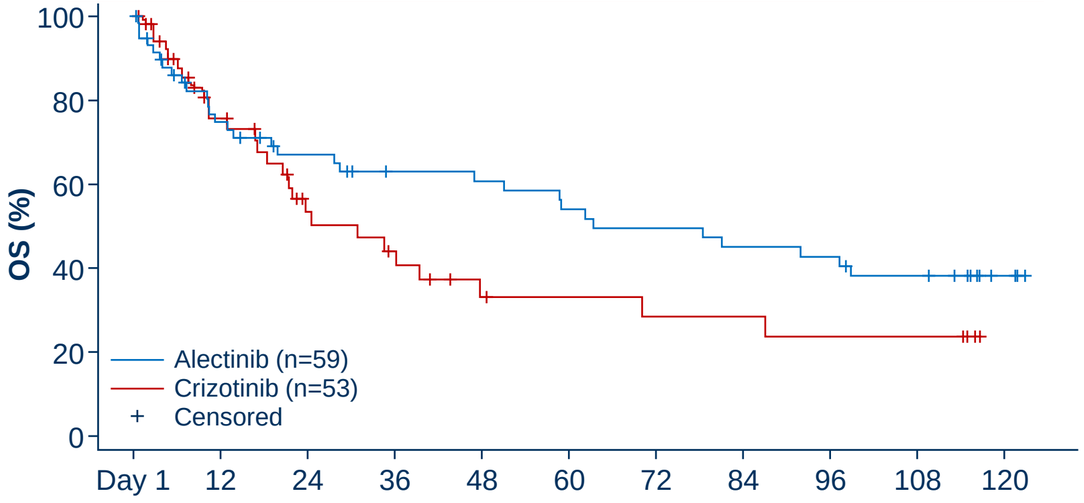
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OS by CNS metastases* at baseline

Patients with CNS metastases at baseline

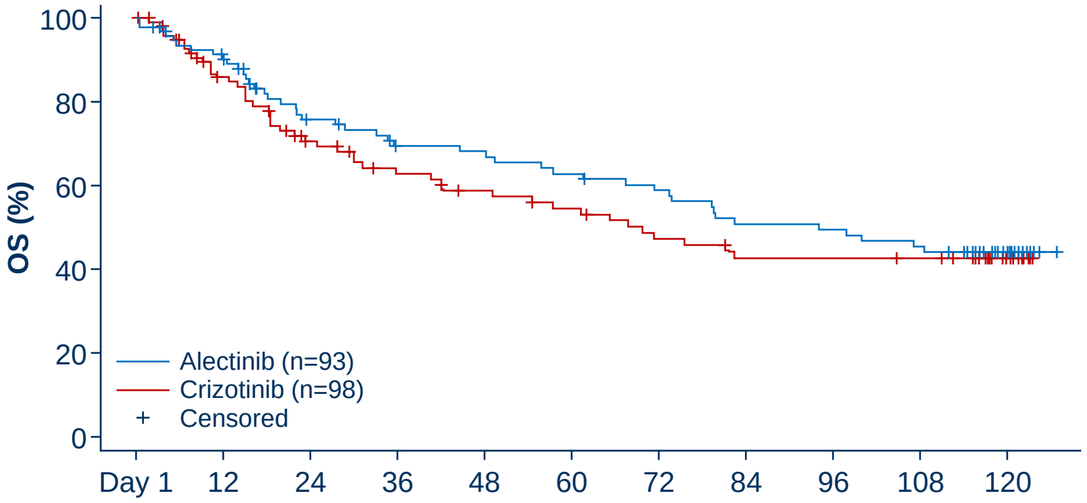
- Median OS: 63.4 months with alectinib vs 30.9 months with crizotinib (HR 0.68; 95% CI 0.40–1.15)



No. at risk											
Alectinib	59	40	33	28	27	24	22	20	19	16	5
Crizotinib	53	30	17	13	8	7	6	6	5	5	0

Patients without CNS metastases at baseline

- Median OS: 94.0 months with alectinib vs 69.8 months with crizotinib (HR 0.87; 95% CI 0.58–1.32)



No. at risk											
Alectinib	93	80	61	53	52	48	44	38	37	34	15
Crizotinib	98	74	56	47	42	38	32	28	28	27	9

Alectinib induced a clinically meaningful **OS benefit** compared with **crizotinib** in patients both **with** and **without CNS metastases**

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*Assessed by investigator.

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OS by CNS metastases* at baseline

Patients with CNS metastases at baseline

- Median OS: 63.4 months with alectinib vs 30.9 months with crizotinib (HR 0.68; 95% CI 0.40–1.15)

In patients **with prior brain radiation**

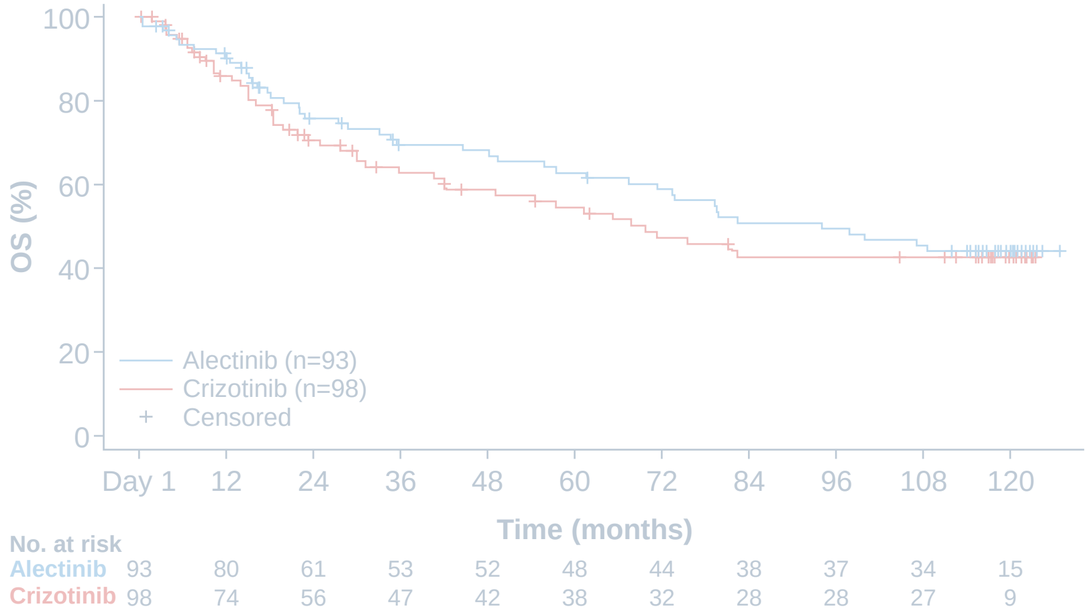
- Median OS: **92.0** months with **alectinib** (n=25) vs **39.5** months with **crizotinib** (n=18)
  HR **0.62**; 95% CI 0.24–1.60

In patients **without prior radiation**

- Median OS: **46.9** months with **alectinib** (n=34) vs **23.7** months with **crizotinib** (n=35)
  HR **0.73**; 95% CI 0.38–1.38

Patients without CNS metastases at baseline

- Median OS: 94.0 months with alectinib vs 69.8 months with crizotinib (HR 0.87; 95% CI 0.58–1.32)

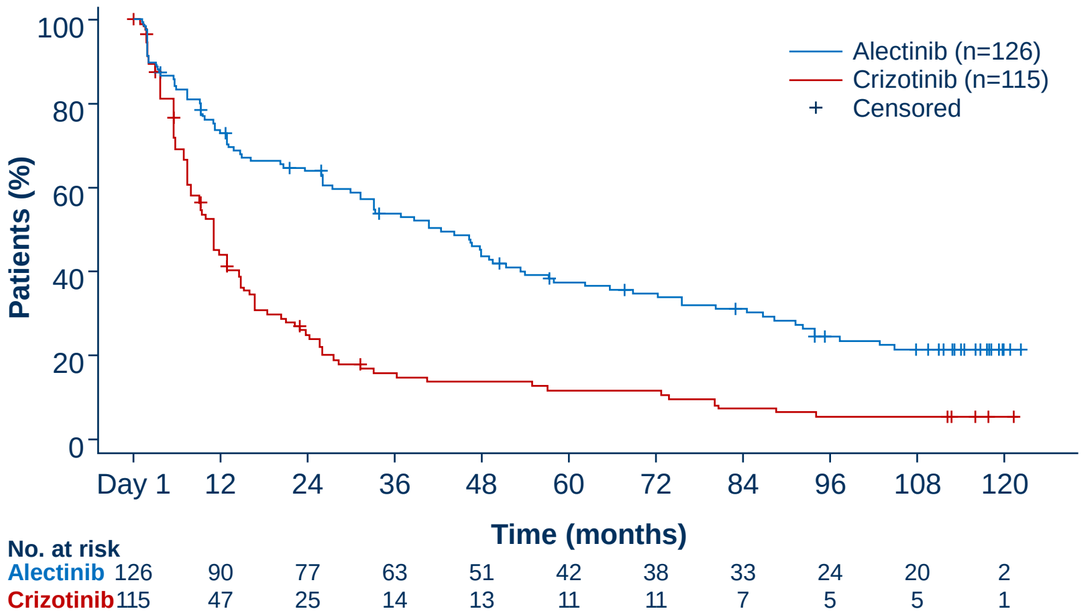


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*Assessed by investigator.

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Investigator-assessed DoR in responders*



	Alectinib (n=126)	Crizotinib (n=115)
Median, months (95% CI)	**42.3** (31.3–51.3)	**11.1** (7.9–13.0)
HR (95% CI)	**0.41** (0.30–0.56)	

Among responders, median DoR was **42.3** months with **alectinib** versus **11.1** months with **crizotinib**

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*Responders were defined as patients with investigator-assessed measurable disease at baseline.

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Safety summary

- Median duration of treatment was 28.1 months (range 0–127) with alectinib and 10.8 months (range 0–123) with crizotinib
- The most common AE leading to dose reduction and discontinuation of alectinib was **increased blood bilirubin** (5.3% and 3.3% of patients, respectively), while for crizotinib it was **increased ALT** (8.6% and 6.6%, respectively)

n (%)	Alectinib (n=152)	Crizotinib (n=151)
All-grade AEs	147 (**96.7**)	148 (**98.0**)
Grade 3−5 AEs	88 (**57.9**)	87 (**57.6**)
SAEs	70 (**46.1**)	48 (**31.8**)
Treatment-related AEs	125 (**82.2**)	135 (**89.4**)
AEs leading to death	10 (**6.6**)*	7 (**4.6**)
AEs leading to treatment discontinuation	27 (**17.8**)	22 (**14.6**)
AEs leading to dose reduction	35 (**23.0**)	30 (**19.9**)
AEs leading to dose interruption	49 (**32.2**)	43 (**28.5**)

*COVID-19 (n=1), pneumonia (n=1), blood creatinine increased (n=1), acute myeloid leukaemia (n=1), acute kidney injury (n=1), ovarian cyst ruptured (n=1), cardiac arrest (n=1), all considered unrelated to alectinib, and death with unknown cause and no autopsy performed (n=3), suspected to be related to other causes than alectinib treatment

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AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event.

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Most common (≥2%) grade 3–5 AEs

Preferred term, n (%)	Alectinib (n=152)	Crizotinib (n=151)
Anaemia	11 (**7.2**)	1 (**0.7**)
AST increased	8 (**5.3**)	16 (**10.6**)
Pneumonia	8 (**5.3**)	3 (**2.0**)
Urinary tract infection	8 (**5.3**)	1 (**0.7**)
ALT increased	7 (**4.6**)	25 (**16.6**)
Blood bilirubin increased	7 (**4.6**)	0
Blood CPK increased	5 (**3.3**)	7 (**4.6**)
Hypokalaemia	5 (**3.3**)	1 (**0.7**)
Acute kidney injury	5 (**3.3**)	0
Hyponatraemia	3 (**2.0**)	4 (**2.6**)
Back pain	3 (**2.0**)	0
Death	3 (**2.0**)*	0

Preferred term, n (%)	Alectinib (n=152)	Crizotinib (n=151)
Rash	3 (**2.0**)	0
Pulmonary embolism	2 (**1.3**)	5 (**3.3**)
Diarrhoea	2 (**1.3**)	3 (**2.0**)
Electrocardiogram QT prolonged	1 (**0.7**)	5 (**3.3**)
Nausea	1 (**0.7**)	5 (**3.3**)
Neutropenia	0	9 (**6.0**)
Vomiting	0	5 (**3.3**)
Neutrophil count decreased	0	4 (**2.6**)
Pneumonitis	0	3 (**2.0**)
Deep vein thrombosis	0	3 (**2.0**)

*Three (**2.0%**) on-study death events with unknown cause and no autopsy performed were suspected to be related to other causes than alectinib treatment. Alectinib treatment was ongoing at the time of these death events.

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AST, aspartate aminotransferase; CPK, creatine phosphokinase.

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Conclusions

- Final data from the randomised, Phase 3 ALEX study show that first-line alectinib induced a **clinically meaningful median OS** of **81.1** months and **median DoR** of **42.3** months in patients with previously untreated, advanced *ALK*+ NSCLC
  - **22% lower risk of death** with alectinib than with crizotinib (HR 0.78; 95% CI 0.56–1.08)
  - OS benefit with alectinib was observed across a number of pre-specified patient subgroups, including **patients with CNS metastases at baseline**
  - OS results may have been confounded by treatment crossover (25.2% of patients in the crizotinib arm received alectinib as subsequent therapy)
  - **Prolonged median DoR** with alectinib (42.3 months vs 11.1 months with crizotinib)
- No new or unexpected safety concerns were reported; safety data were in line with the known safety profile of alectinib

These data continue to support **first-line alectinib** as a **standard of care** in patients with **advanced *ALK*+ NSCLC**

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ORIGINAL ARTICLE

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For further information, please see the accompanying manuscript published in *Annals of Oncology* (Peters et al. 2025)

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