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ALINA: efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage *ALK*+ NSCLC

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Declaration of interests

Benjamin J. Solomon has the following relationships to disclose:

- Advisory board role: Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, D3 Bio, Janssen, Lilly, Merck, Pfizer, Takeda, Roche/Genentech
- Invited speaker: Amgen, AstraZeneca, Pfizer, Roche/Genentech
- Member of board of directors: International Association for the Study of Lung Cancer, Thoracic Oncology Group of Australasia, Cancer Council of Victoria
- Research grant: Sanofi
- Sponsor/funding: Beigene, Bristol Myers Squibb, Lilly, Novartis, Nuvalent, Roche/Genentech, Pfizer

The unmet need in resectable *ALK*+ NSCLC

- Around 30–40% of patients with NSCLC are diagnosed with resectable disease.[1–4] Despite treatment, the risk of disease recurrence remains high (~45–76%, depending on stage)[5]*
- *ALK* rearrangements are found in 4–5% of patients with NSCLC; *ALK*+ NSCLC is typically:[6–13]
  - Seen in younger patients (median age at diagnosis ~55 years)
  - More common in non-smokers
  - Associated with a high risk of brain metastases (~50–60% of patients over the course of the disease)
- For patients with **resectable *ALK*+ NSCLC** the current standard-of-care after surgery is **adjuvant platinum-based chemotherapy;** immunotherapy is not recommended[14]

*Based on 5-year disease-free survival (DFS) event rates reported by Pignon et al. J Clin Oncol 2008

1. Cagle et al. Arch Pathol Lab Med 2013; 2. Le Chevalier. Ann Oncol 2010; 3. Datta et al. Chest 2003; 4. O'Reilly et al. ASCO Educational Book 2023; 5. Pignon et al. J Clin Oncol 2008; 6. Chen and Chaft. Transl Lung Cancer Res 2023; 7. Chaft et al. Lung Cancer 2018; 8. Chevallier et al. World J Clin Oncol 2021; 9. Tian et al. Lung Cancer 2017; 10. Barlesi et al. Lancet 2016; 11. Rangachari et al. Lung Cancer 2015; 12. Tan, et al. Int J Mol Sci 2020; 13. Zou et al. BMC Med 2022 14. NCCN Clinical practice guidelines in oncology: NSCLC v.3 2023

Alectinib is a potent oral ALK TKI with efficacy in the CNS

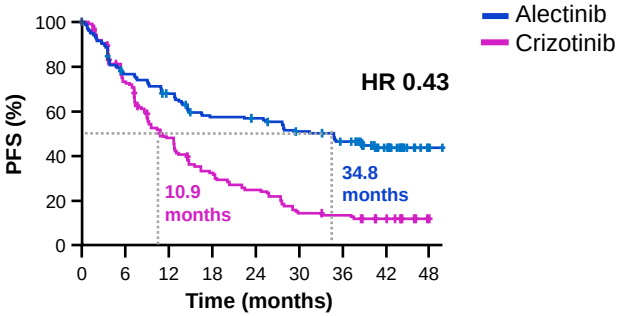
- In advanced *ALK*+ NSCLC, three phase III trials have shown statistically significant and clinically meaningful improvements in PFS with alectinib compared with crizotinib,[1–4] as well as high levels of intracranial activity[5–7]

ALEX[1]

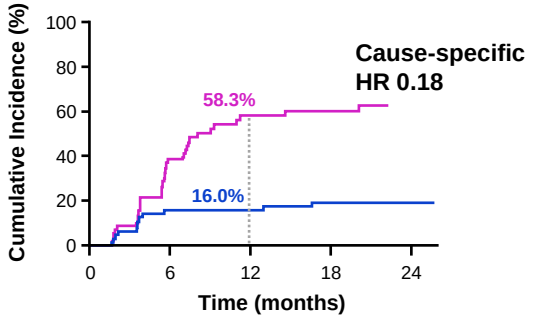
J-ALEX[2]

ALESIA[3]

PFS in the ITT population[4]



Cumulative incidence of CNS progression[6]*



- Long-term treatment with alectinib has been demonstrated to be well tolerated with a well-characterised, manageable safety profile[8]
- Alectinib is a recommended first-line treatment in advanced *ALK*+ NSCLC;[9] as of August 2023, an estimated cumulative total of >92,000 patients have been treated with alectinib in clinical practice[10]

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PFS, progression-free survival; *In patients with CNS metastases at baseline.

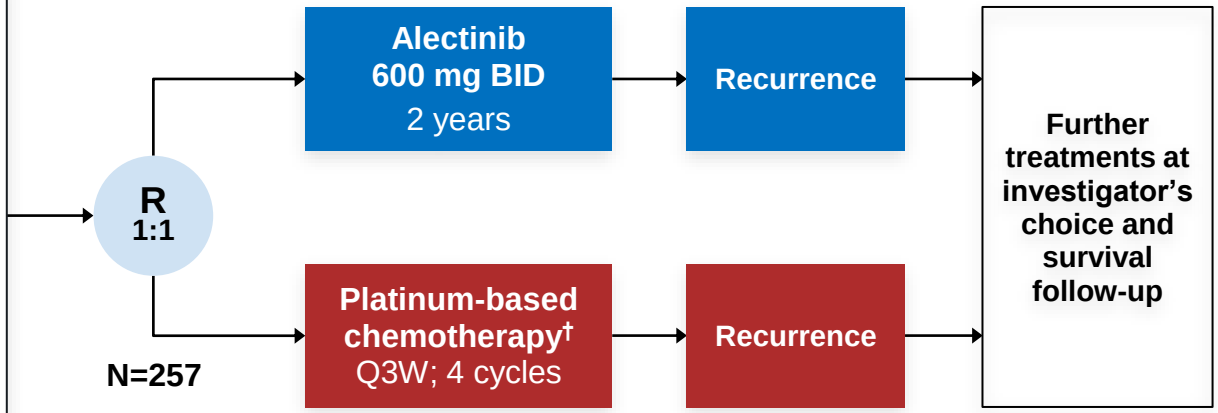
ALEX, NCT02075840; J-ALEX, JapicCTI-132316; ALESIA, NCT02838420;
1. Peters et al. N Engl J Med 2017; 2. Hida et al. Lancet 2017; 3. Zhou et al. Lancet Respir Med 2019; 4. Mok et al. ESMO Open 2020;
5. Gadgeel et al. J Clin Oncol 2016; 6. Gadgeel et al. Ann Oncol 2018; 7. Zou et al. BMC Med 2022; 8. Dziadziuszko et al. ESMO Open 2022;
9. NCCN Clinical practice guidelines in oncology: NSCLC v.3 2023; 10. PBRER/PSUR - Roche Data on file

ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian



Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

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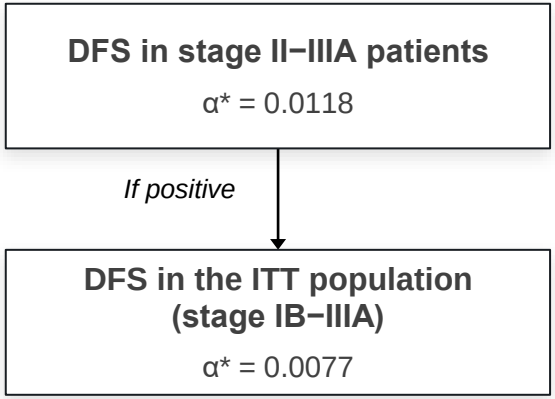
Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

ALINA statistical analysis plan

- ALINA was designed to demonstrate superiority of alectinib compared with chemotherapy, with 80% power to detect a DFS HR of:
  - 0.55 in the stage II–IIIA subpopulation
  - 0.58 in the ITT population (stage IB–IIIA)
- One interim analysis was pre-planned after ~67% (59) events in the stage II–IIIA subpopulation

DFS testing hierarchy



Here, we report the primary results from the pre-specified interim analysis (clinical cut-off date: 26 June 2023)

DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat
*The stopping boundaries for the DFS interim analysis were computed using the Lan-DeMets approximation to the O'Brien-Fleming boundaries

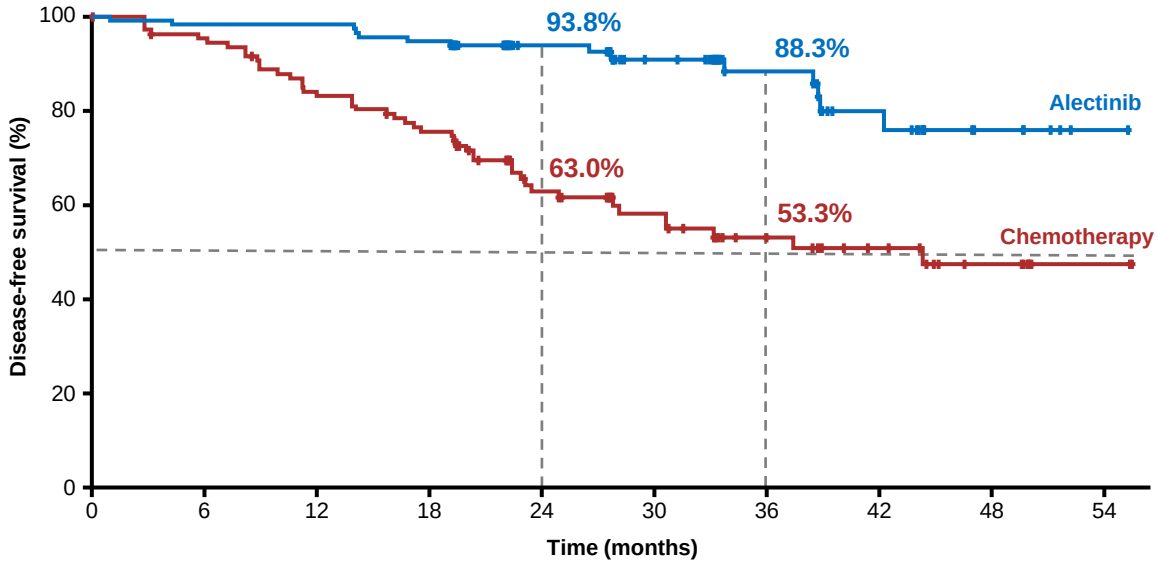
Patient demographics and baseline characteristics (ITT)

Characteristic	Alectinib (n=130)	Chemotherapy (n=127)
Median age <65 / ≥65 years, %	54 years 79 / 21	57 years 73 / 27
Sex: female / male, %	58 / 42	46 / 54
Smoking status: never / former / current, %	65 / 32 / 4	55 / 43 / 2
Race: Asian / non-Asian, %	55 / 45	56 / 44
ECOG PS: 0 / 1, %	55 / 45	51 / 49
Stage at diagnosis*: IB / II / IIIA, %	11 / 36 / 53	9 / 35 / 55
Nodal status: N0 / N1 / N2, %	16 / 35 / 49	14 / 34 / 52
Histology: squamous / non-squamous, %	5 / 95	2 / 98
Surgical procedure: Lobectomy / Other‡, %	97 / 3	92 / 8

Data cut-off: 26 June 2023

*Per UICC/AJCC 7th edition; ‡Pneumonectomy (alectinib arm, 2%; chemotherapy arm, 3%), bilobectomy (2%; 4%), sleeve lobectomy (0; 1%)

Disease-free survival: stage II–IIIA*



No. at risk

Alectinib	116	111	111	107	67	49	35	21	10	3
Chemo	115	102	88	79	48	35	23	17	10	2

	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

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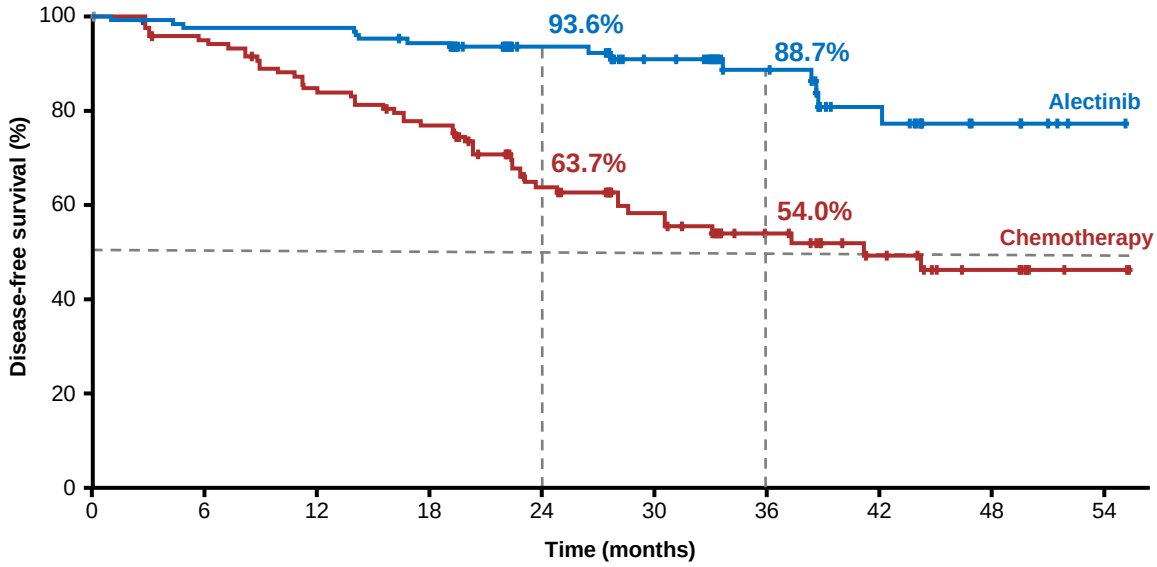
Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months
*Per UICC/AJCC 7th edition; †Stratified log rank; DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

Disease-free survival: ITT (stage IB–IIIA)*



No. at risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemo	127	112	98	89	55	41	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported‡

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

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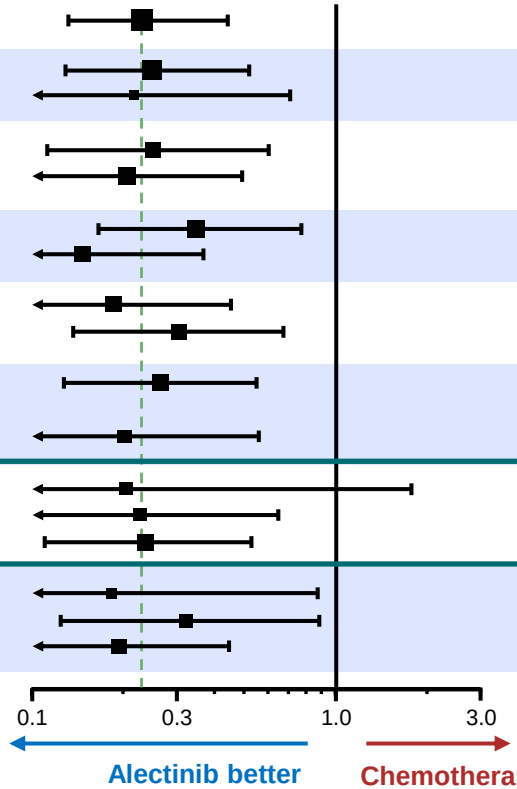
Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months

*Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

Disease-free survival subgroup analysis (ITT)

Subgroup		No. of events / patients	DFS HR (95% CI)
All patients		65 / 257	0.24 (0.14–0.43)
Age	<65	43 / 196	0.26 (0.13–0.52)
	≥65	22 / 61	0.24 (0.08–0.71)
Sex	Male	35 / 123	0.26 (0.11–0.60)
	Female	30 / 134	0.22 (0.10–0.50)
Race	Asian	31 / 143	0.36 (0.17–0.79)
	Non-Asian	34 / 114	0.16 (0.06–0.38)
ECOG PS at baseline	0	32 / 137	0.20 (0.09–0.46)
	1	33 / 120	0.31 (0.14–0.69)
Tobacco use history	Never	37 / 154	0.27 (0.13–0.55)
	Current	0 / 8	NE
	Previous	28 / 95	0.22 (0.08–0.57)
Stage*	Stage IB	6 / 26	0.21 (0.02–1.84)
	Stage II	22 / 92	0.24 (0.09–0.65)
	Stage IIIA	37 / 139	0.25 (0.12–0.53)
Regional lymph node status	N0	11 / 39	0.19 (0.04–0.88)
	N1	20 / 88	0.34 (0.13–0.89)
	N2	34 / 130	0.21 (0.09–0.47)



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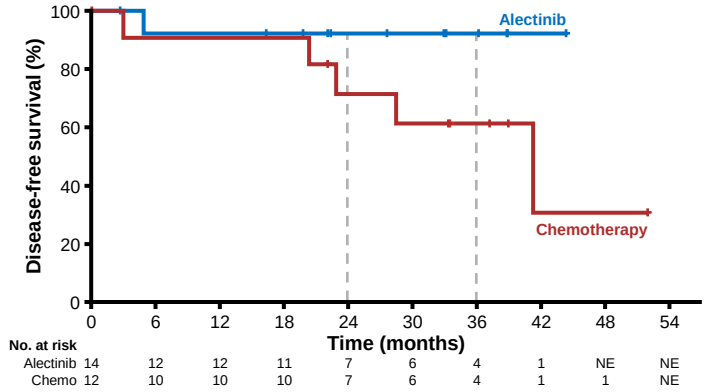
Data cut-off: 26 June 2023

Arrows indicate lower bound of the CI<0.1; *Per UICC/AJCC 7th edition

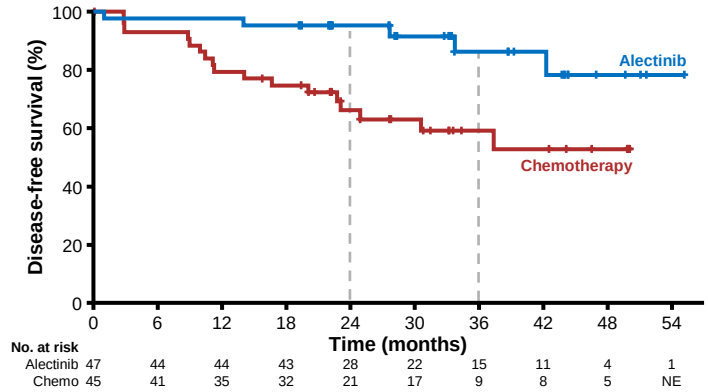
Disease-free survival by stage*

Stage IB

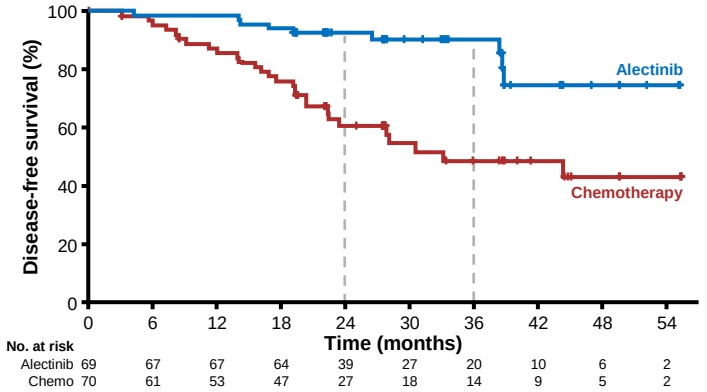


2-year DFS rate, % (95% CI)	Stage IB (n=26)	Stage II (n=92)	Stage IIIA (n=139)
Alectinib	92.3 (77.8, 100.0)	95.6 (89.5, 100.0)	92.7 (86.4, 98.9)
Chemotherapy	71.6 (44.2, 99.0)	66.3 (51.7, 81.0)	60.7 (47.9, 73.5)
HR† (95% CI)	0.21 (0.02, 1.84)	0.24 (0.09, 0.65)	0.25 (0.12, 0.53)

Stage II



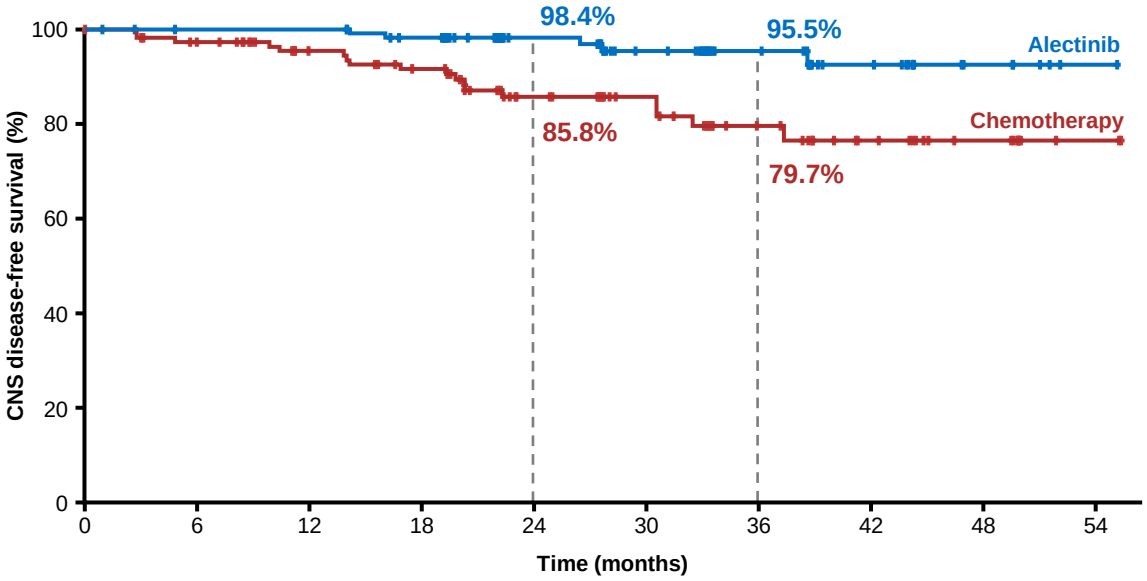
Stage IIIA



Data cut-off: 26 June 2023

*Per UICC/AJCC 7th edition; †Unstratified analysis

CNS disease-free survival in the ITT population



No. at risk

Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	**0.22** (0.08, 0.58)	

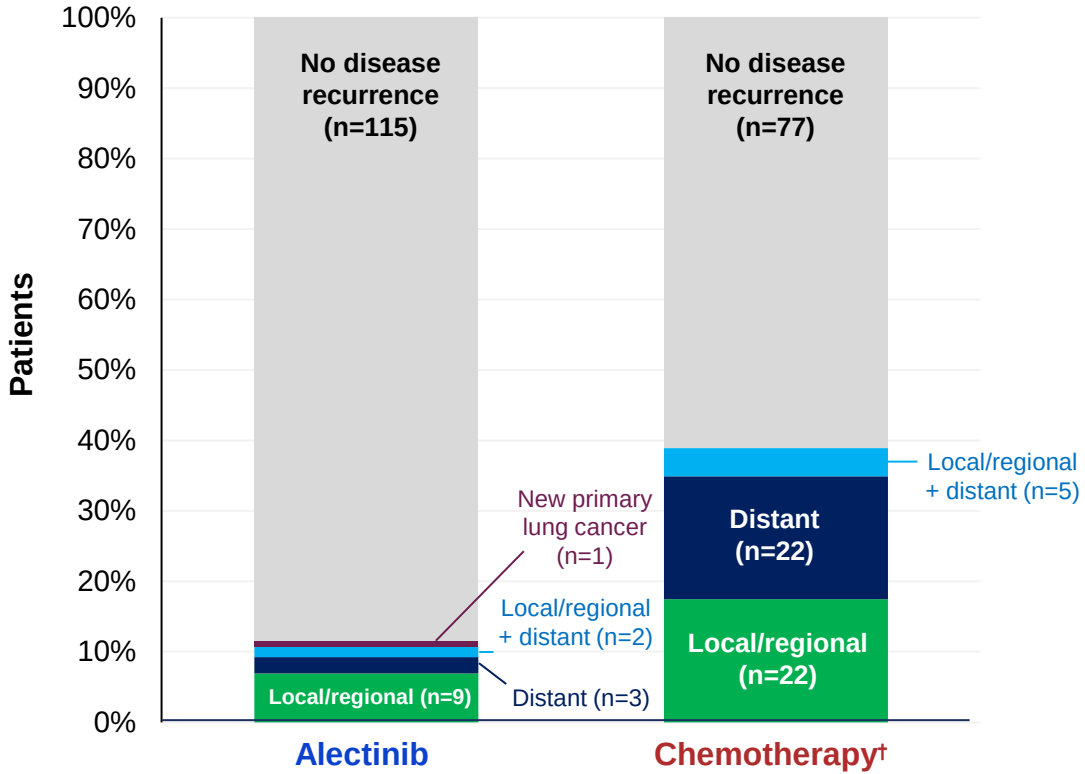
Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Data cut-off: 26 June 2023

*Stratified analysis with race and stage as stratification factors

CNS-DFS defined as time from randomisation to the first documented recurrence of disease in the CNS or death from any cause

Sites of disease recurrence (ITT)



Site(s) of distant recurrence*	Alectinib (n=130)	Chemotherapy (n=127)
Brain	4	14
Bone	1	8
Adrenal gland	0	3
Lymph node	0	2
Kidney	0	1
Peritoneum	0	1
Other	1	0

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Data cut-off: 26 June 2023; *At disease assessment where first recurrence detected; patients may have multiple sites of disease recurrence counted; †One patient died without a recurrence event reported

Post-recurrence subsequent therapy

Number of patients with disease recurrence, n (%)	Alectinib (n=15)	Chemotherapy (n=49)
Patients with any subsequent therapy	13 (87)	43 (88)
Systemic therapy	13 (87)	38 (78)
ALK TKI	7 (47)	37 (76)
Alectinib	4 (27)	29 (59)
Brigatinib	4 (27)	4 (8)
Crizotinib	0	4 (8)
Lorlatinib	0	2 (4)
Ceritinib	0	1 (2)
Chemotherapy	6 (40)	2 (4)
Immunotherapy	1 (7)	1 (2)
Other anti-cancer therapy	1 (7)	1 (2)
Radiotherapy	5 (33)	9 (18)
Surgery	1 (7)	3 (6)

Data cut-off: 26 June 2023

Includes any subsequent therapy reported on or after date of earliest contributing event to disease recurrence; Patients may have received more than one subsequent anticancer therapy

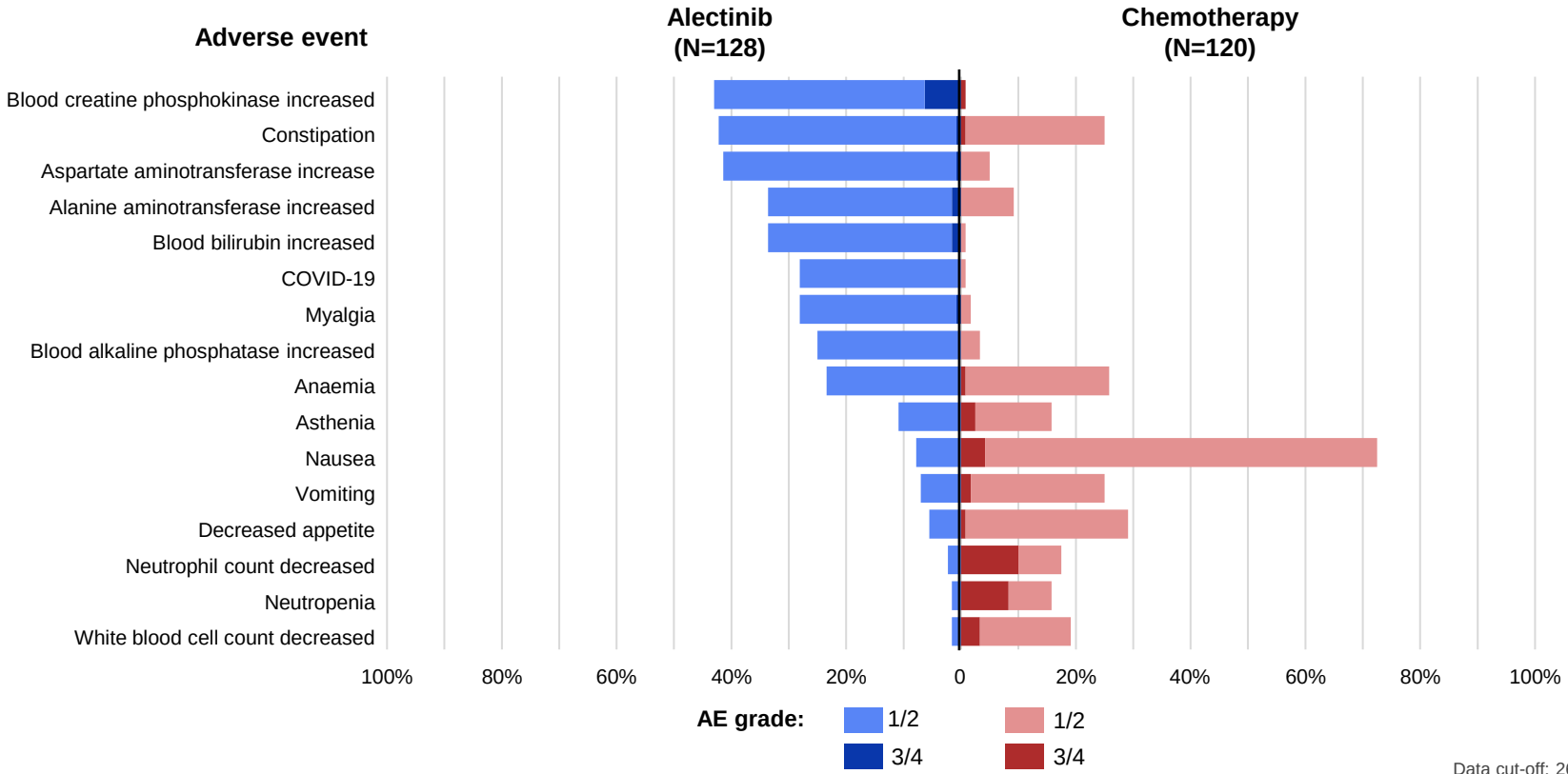
Safety summary

	Alectinib (n=128)	Chemotherapy (n=120)
Median treatment duration	**23.9 months**	**2.1 months**
Patients with any AEs, %	**98**	**93**
Grade 3/4 AEs	30	31
Grade 5 AEs	0	0
Serious AEs	13	8
Treatment-related serious AEs	2	7
AEs leading to dose reduction	26	10
AEs leading to dose interruption	27	18
AEs leading to treatment withdrawal	5	13

At data cut off, **20.3%** of patients in the alectinib arm were ongoing treatment

Data cut-off: 26 June 2023
Multiple occurrences of the same AE in one individual are counted only once in each category

AEs occurring in ≥15% of patients



Data cut-off: 26 June 2023

Median treatment duration was 23.9 months in the alectinib arm and 2.1 months in the chemotherapy arm. No grade 5 events were observed

Other key trials of alectinib in stage I–III NSCLC are ongoing

NAUTIKA1
USA
NCT04302025

Phase II study in in **resectable stage IB–IIIA NSCLC,** which includes a cohort of patients receiving **perioperative alectinib** (neoadjuvant and adjuvant) + adjuvant chemotherapy[1]

ALNEO
Italy
NCT05015010

Phase II study of **perioperative alectinib** in patients with **resectable stage III, *ALK*+ NSCLC**[2]

HORIZON-01
International
NCT05170204

Phase III, open-label, randomised cohort of patients with **unresectable stage III, *ALK*+ NSCLC** receiving **alectinib** vs durvalumab following chemoradiotherapy[3]

1. Lee et al. WCLC 2023 (Abs EP02.04); 2. Leonetti et al. Clin Lung Cancer 2021; 3. Paz-Ares et al. ELCC 2023 (Abs 131TiP)

Summary

- ALINA is the first and only positive phase III trial of an ALK inhibitor in resected, stage IB–IIIA NSCLC
- Treatment with adjuvant alectinib resulted in a statistically significant and clinically meaningful improvement in DFS compared with chemotherapy (HR 0.24; 95% CI 0.13, 0.43; p<0.0001)
  - The DFS benefit was seen consistently across subgroups
- An improvement in CNS-DFS was observed (HR 0.22; 95% CI 0.08, 0.58)
- Adjuvant alectinib was tolerable and in line with the known safety profile of alectinib

Adjuvant alectinib represents an important new treatment strategy for patients with resected, stage IB–IIIA, *ALK*+ NSCLC

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