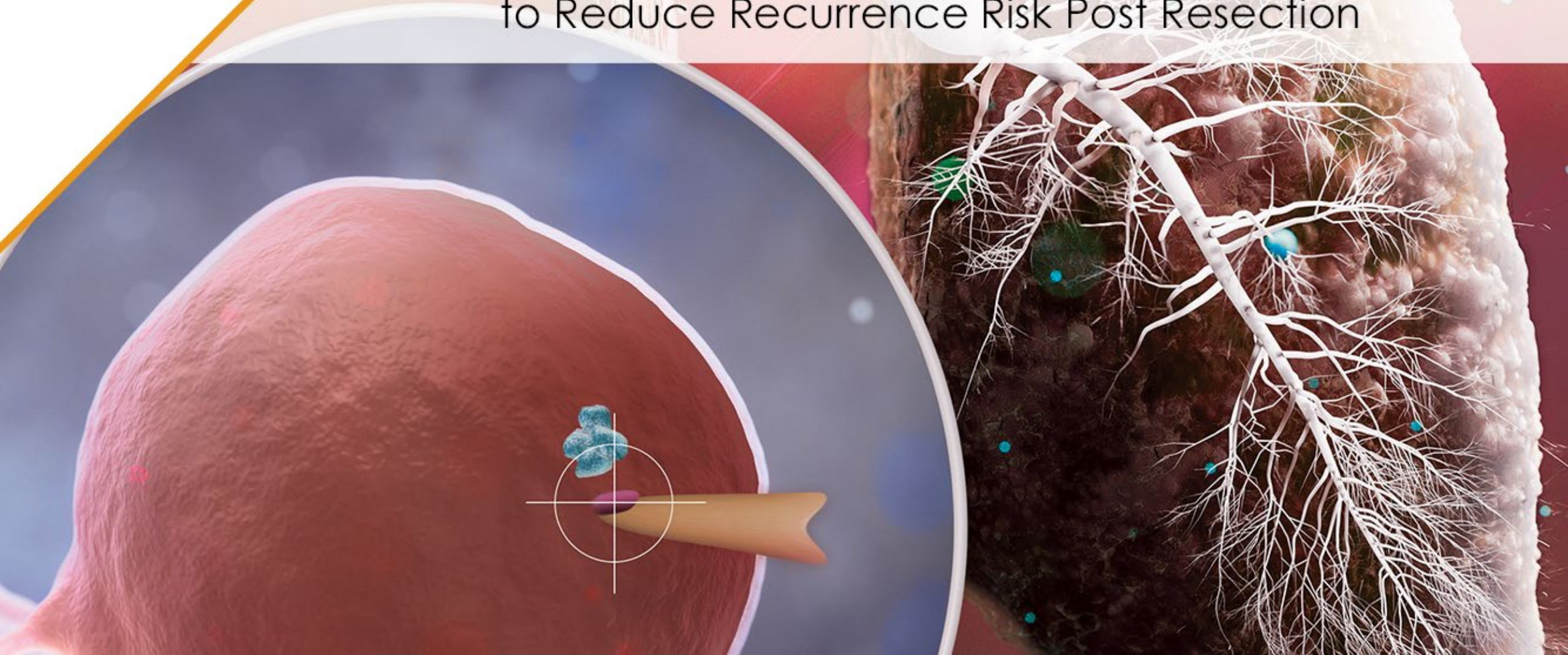
AXIS Medical Education

Advancing ALK Inhibition Into Early-Stage NSCLC:

Integrating Biomarker-Driven Therapies to Reduce Recurrence Risk Post Resection



DISCLAIMER

This slide deck in its original and unaltered format is for educational purposes and is current as of December 2024. All materials contained herein reflect the views of the faculty, and not those of AXIS Medical Education, the CME provider, or the commercial supporter. Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

AXIS Medical Education

DISCLOSURE OF UNLABELED USE

This activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

USAGE RIGHTS

Learning Objectives

Upon completion of this activity, participants should be better able to:

1. Identify ALK-positive patients with early-stage NSCLC at high risk for recurrence post resection across the interprofessional care team
2. Incorporate therapeutic strategies for biomarker driven treatment of early-stage patients with ALK-positive NSCLC post resection
3. Develop clinical practice skills and team-based strategies to adopt use of targeted therapies in the adjuvant setting in patients with early-stage NSCLC
4. Recognize the clinical value of oncology-relevant endpoints beyond overall survival in patients with early-stage NSCLC post resection

Overview of Key Oncogenic Drivers of NSCLC

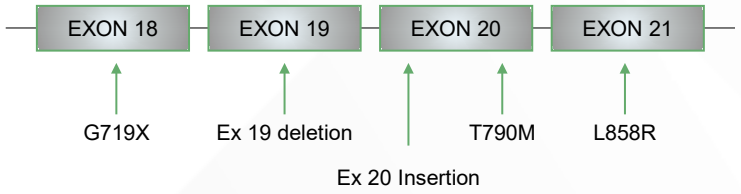
Common Genomic Alterations in NSCLC

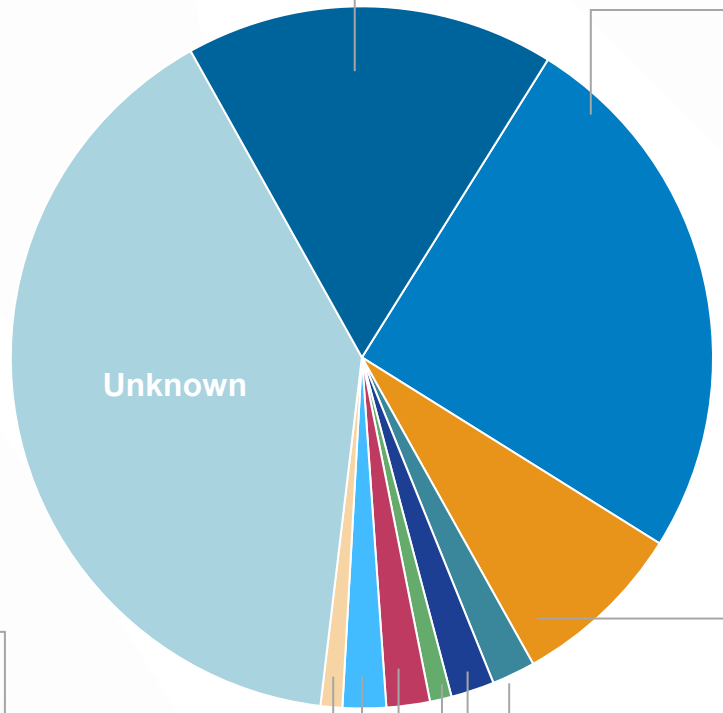
EGFR Mutation

17%

- Point mutations in tyrosine kinase domain
- *Erlotinib, gefitinib, afatinib, dacomitinib, osimertinib*

Tyrosine kinase domain of EGFR gene





KRAS Mutation

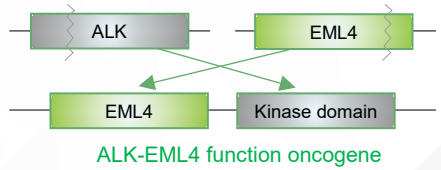
25%

- Activation of MAPK pathway
- Negative prognostic marker
- *KRAS^{G12C} – sotorasib, adagrasib*

ALK Rearrangement

4-8%

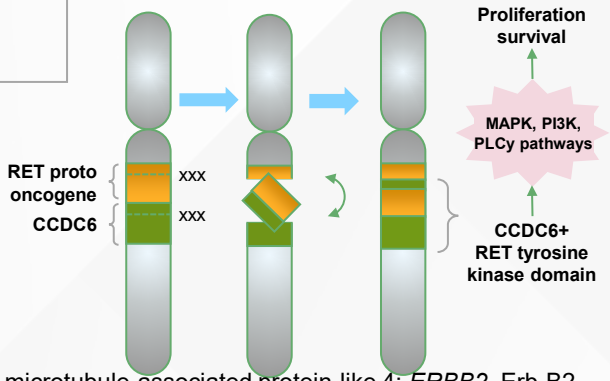
- Fusion between ALK and EML4
- Constitutive ALK kinase activity
- *Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib*



RET Rearrangement

2%

- Fusion between RET tyrosine kinase domain and partner gene
- *Pralsetinib, selpercatinib*



ERBB2 (*HER2*) Mutation

1%

- *Trastuzumab deruxtecan*

ROS1 Rearrangement

2%

- *Crizotinib, entrectinib, repotrectinib*

BRAF Mutation

2%

- *Dabrafenib + trametinib, encorafenib + binimetinib*

METex14 Skipping Mutation

2%

- *Capmatinib, tepotinib*

NTRK Rearrangement

1%

- *Larotrectinib, entrectinib, repotrectinib*

AXIS Medical Education

ALK, anaplastic lymphoma kinase; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *EGFR*, epidermal growth factor receptor; EML4, echinoderm microtubule-associated protein-like 4; *ERBB2*, Erb-B2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; *KRAS*, KRAS proto-oncogene, GTPase; MAPK, mitogen-activated protein kinase; *METex14*, mesenchymal–epithelial transition exon 14; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase c; *RET*, rearranged during transfection; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase.

Updated from Loh Z, et al. *Intern Med J*. 2019;49(12):1541-1545. Gupta R, et al. *Am J Clin Oncol*. 2019;42(4):337-344.

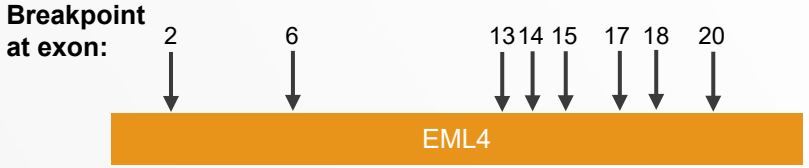
EML4-ALK Is the Most Common ALK-Fusion Protein

The most common rearrangement is between *EML4* and *ALK*, which produces the EML4-ALK-fusion protein[1,2]

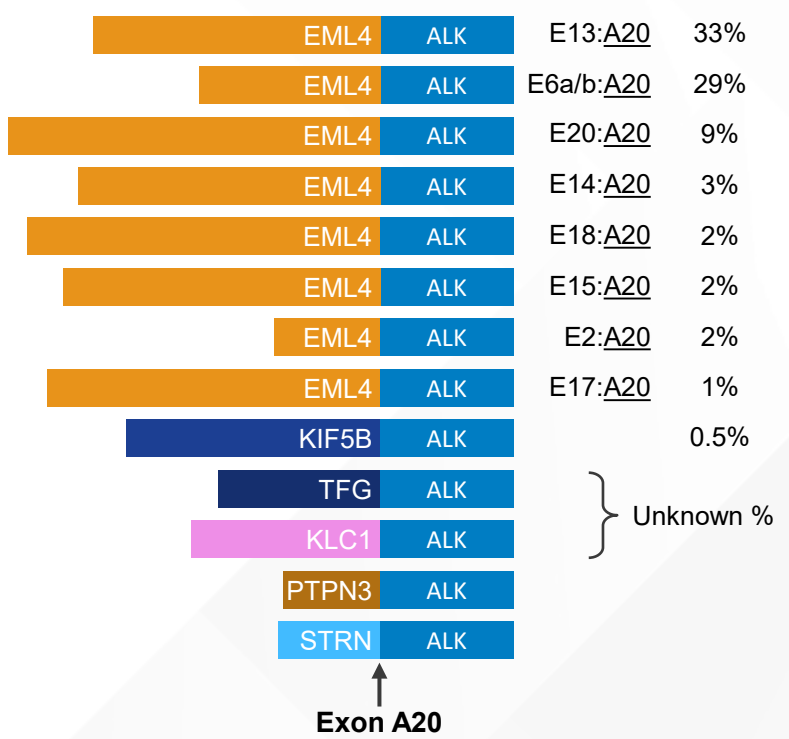
The breakpoint within *ALK* occurs at **exon 20** (A20)[1,2]

The breakpoint within *EML4* can differ, thus generating **different variants** of the fusion protein[1,2]

Breakpoints within EML4[1,2]



Summary of common variants of the ALK-fusion protein[1–4]

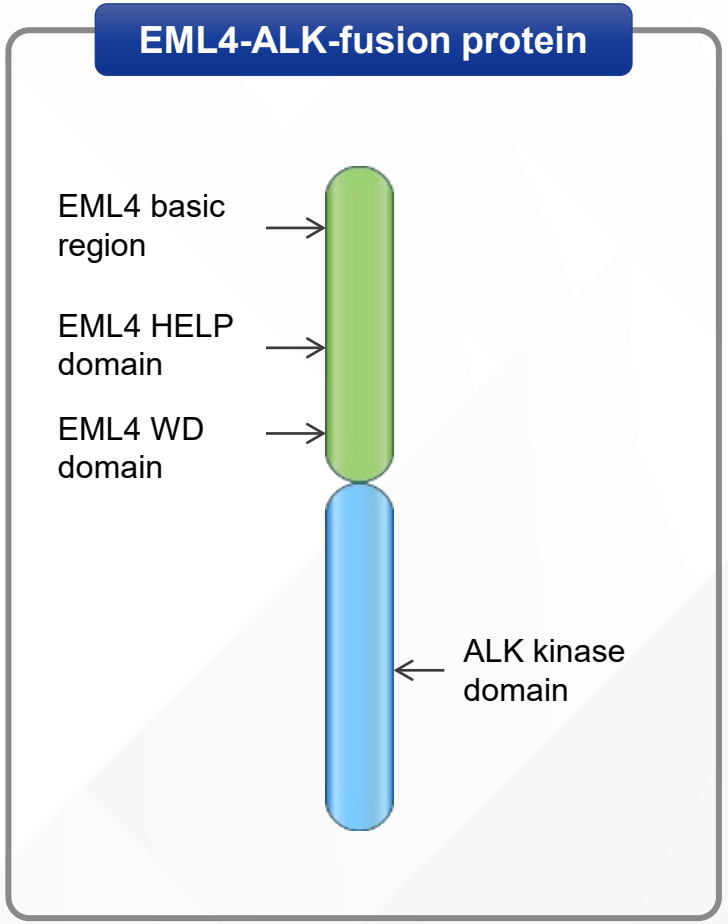


ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; NSCLC, non-small cell lung cancer.

1. Gridelli C, et al. *Cancer Treat Rev.* 2014;40(2):300-306.
2. D'Arcangelo M, et al. *Curr Opin Oncol.* 2013;25(2):121-129.
3. Hallberg B, Palmer RH. *Nat Rev Cancer.* 2013;13(10):685-700.
4. Ou SH, et al. *Oncologist.* 2012;17(11):1351-1375.

EML4-ALK-Fusion Proteins Are Constitutively Active

- In the *EML4-ALK* rearrangement, a region within chromosome 2 becomes inverted, resulting in the 5′ region of the *EML4* gene becoming fused to the 3′ region of the *ALK* gene[1,2]
- EML4-ALK-fusion proteins therefore consist of differing sections of the **amino-terminal of EML4 fused to the protein-kinase domain of ALK**[1,2]
- The EML4-ALK-fusion protein lacks the ALK transmembrane domain[1]
- EML4 promotes dimerization of the fusion protein resulting in constitutive activation of the ALK kinase domain[1]



ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; HELP, hydrophobic echinoderm microtubule-associated protein-like protein; WD domain, tandem repeats of the WD40 structural motif that form a β-propeller structure.

1. Soda M, et al. *Nature.* 2007;448(7153):561-566. 2. Rikova K, et al. *Cell.* 2007;131(6):1190-1203.

ALK Inhibitors in Clinical Use

↑ on-target potency, ↑ CNS penetration

ALK TKI		ADDITIONAL TARGETS	STATUS
1st generation	**Crizotinib**	MET, ROS1	▪ FDA / EMA approved, first line
2nd generation	**Alectinib**	RET, LTK	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line ▪ FDA / EMA approved, adjuvant setting
	Brigatinib	EGFR, IGF-1R, ROS1	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Ceritinib	IGF-1R, IR, ROS1	▪ FDA / EMA approved, post crizotinib ▪ FDA-approved, first line
	Ensartinib	MET, ABL, AXL	▪ FDA-approved, first line
	Entrectinib	NTRKs, ROS1	(FDA / EMA approved for ROS1 and NTRK, but not ALK)
3rd generation	**Lorlatinib**	ROS1	▪ FDA / EMA approved, in patients who have received 1 or more ALK inhibitors ▪ FDA / EMA approved, first line

AXIS Medical Education

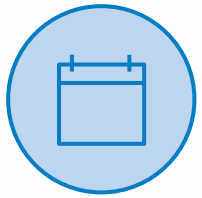
ABL1, ABL proto-oncogene 1, non-receptor tyrosine kinase; ALK, anaplastic lymphoma kinase; AXL, AXL receptor tyrosine kinase; CNS, central nervous system; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; IGF-1R, insulin-like growth factor 1 receptor; LTK, leukocyte receptor tyrosine kinase; MET, mesenchymal–epithelial transition; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor.

Adapted from: Awad MM, Shaw AT. *Clin Adv Hematol Oncol.* 2014;12(7):429-439. Roskoski R Jr. *Pharmacol Res.* 2017;117:343-356. FDA. https://www.fda.gov. EMA. https://www.ema.europa.eu/en.

Identifying ALK-Positive Patients at High Risk for Recurrence in the Community Setting

ALK: A Distinct Subset of NSCLC

Patients with *ALK*+ NSCLC tend to be…



Younger[1–3]

Median age ~52 years versus ~70 years for other types of NSCLC

Never or light smokers[2,4,5]

~70% patients with *ALK*+ NSCLC have never smoked

Advanced disease at presentation[6–8]

- Pleural/pericardial effusion
- Multiple lesions/sites
- Symptomatic
- CNS metastases

ALK, anaplastic lymphoma kinase; CNS, central nervous system; NSCLC, non-small cell lung cancer.

1. Chia PL, et al. *Clin Epidemiol*. 2014;6:423-432. 2. Camidge DR, et al. *Lancet Oncol*. 2012;13(10):1011-1019. 3. NIH. SEER. https://seer.cancer.gov/statfacts/html/lungb.html. 4. Tao H, et al. *Thorac Cancer*. 2017;8(1):8-15. 5. Kayaniyil S, et al. *Curr Oncol*. 2016;23(6):e589-e597. 6. Solomon BJ, et al. *N Engl J Med*. 2014;371(23):2167-2177. 7. Soria JC, et al. *Lancet*. 2017;389(10072):917-929. 8. Peters S, et al. *N Engl J Med*. 2017;377(9):829-838.

PERIOPERATIVE SYSTEMIC THERAPY

Systemic Therapy Following Surgical Resection[a,c]

- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3–4, N2]).
  See Principles of Molecular and Biomarker Analysis (NSCL-H).
- Patients with completely resected tumors ≥4 cm or node-positive NSCLC should be evaluated for additional systemic therapy.

- Alectinib 600 mg twice daily for 24 months[14]
  - For patients with NSCLC positive for *ALK* rearrangements (category 1).
- Osimertinib 80 mg daily for 3 years[15]
  - For patients with NSCLC positive for *EGFR* (exon 19 deletion, exon 21 L858R) mutations who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy (category 1).
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[16]
  - For patients with NSCLC with PD-L1 ≥1% and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors (category 1).
  - Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to atezolizumab for intravenous infusion.
- Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks
  - For up to a year for patients with NSCLC negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors (category 1).[17] The benefit for patients with PD-L1 <1% is unclear.
  - For up to 39 weeks for patients who received previous neoadjuvant pembrolizumab + chemotherapy (category 1).[3]
- Durvalumab 1500 mg every 4 weeks for up to 12 cycles[4]
  - For patients who received previous neoadjuvant durvalumab + chemotherapy and no known *EGFR* mutations or *ALK* rearrangements (category 1).
- Nivolumab 480 mg every 4 weeks for up to 13 cycles[2]
  - For patients who received previous neoadjuvant nivolumab + chemotherapy and no known *EGFR* mutations or *ALK* rearrangements (category 1).

ALK, anaplastic lymphoma kinase; ; EGFR, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.
NCCN Guidelines. Non-Small Cell Lung Cancer (Version 1.2025). NCCN.org.

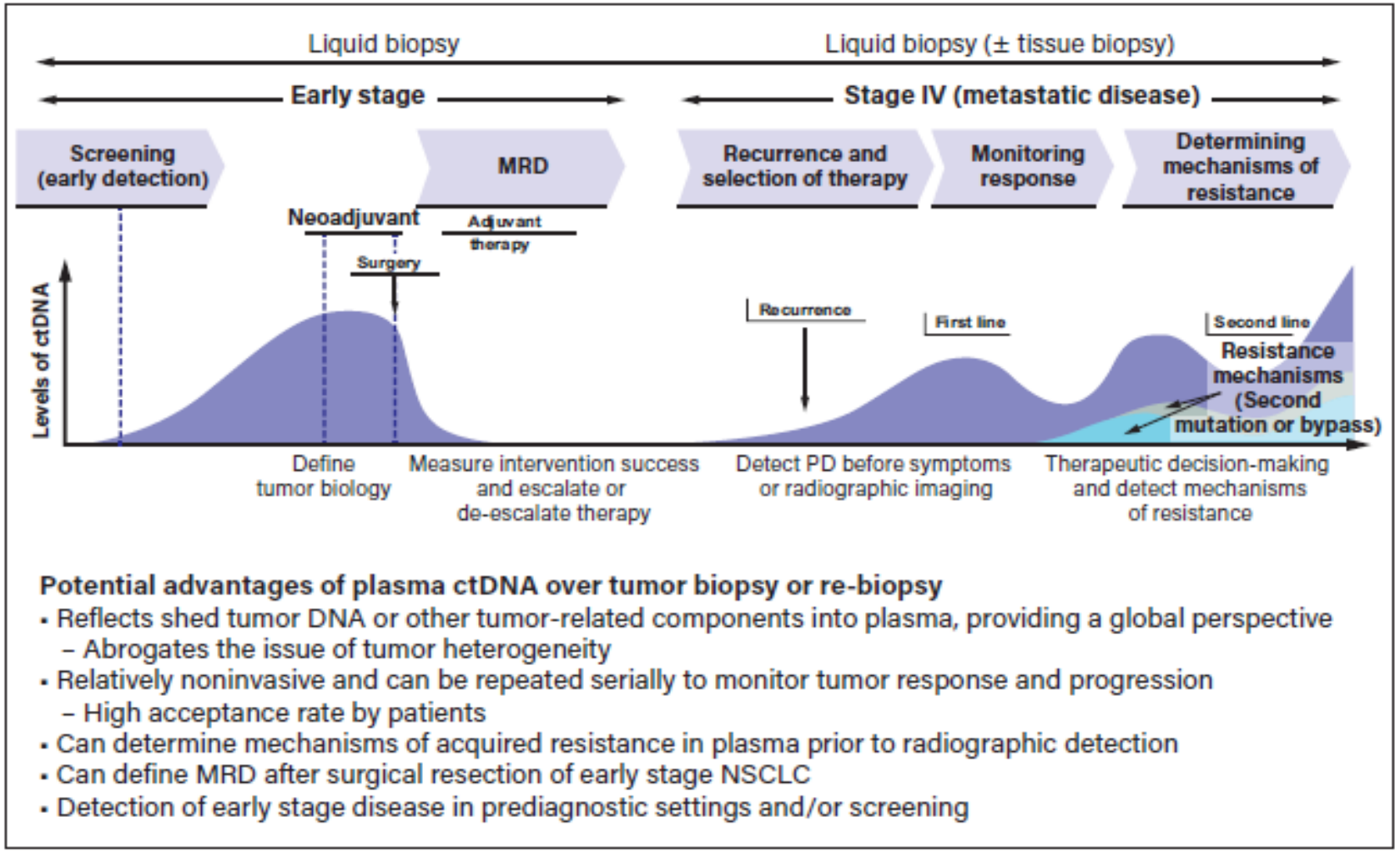
How Should the Testing Be Done?

Table 1. Molecular methods for biomarker testing in solid tumors

Technique	Application	Advantages	Limitations
Immunohistochemistry (IHC)	protein-based assay for detection of expression	• cheap, rapid, and widely available • direct visualization of protein expression	• antibody availability • subjective interpretation/ quantification
Fluorescence *in situ* hybridization (FISH)	hybridization using fluorescent-labeled probes to detect gene copy-number changes or gene rearrangements/fusions	• relatively simple assay design • direct visualization of signals within cells of interest	• probe availability • restricted to specific locus/gene tested
Polymerase chain reaction (PCR)	detection of targeted gene mutations, fusions, copy-number alterations, DNA methylation	• high sensitivity and specificity • relatively simple assay design • relatively low-cost	• limited throughput • restricted to targeted genes and regions of interest interrogated
Next-generation sequencing (NGS)	massively parallel sequencing of multiple genes for detecting mutations, fusions, copy-number alterations	• high throughput • high sensitivity and specificity • comprehensive coverage • site/tumor-specific applications	• high complexity • bioinformatics requirements • longer turnaround time
Gene expression profiling (GEP)	differential gene expression between tumor/normal or pre/post-treated tumor	• high throughput	• bioinformatics requirements • restricted to targeted genes

Passaro A, et al. *Cell*. 2024;187(7):1617-1635.

Role of Liquid Biopsy Across the Cancer Care Continuum



Potential advantages of plasma ctDNA over tumor biopsy or re-biopsy

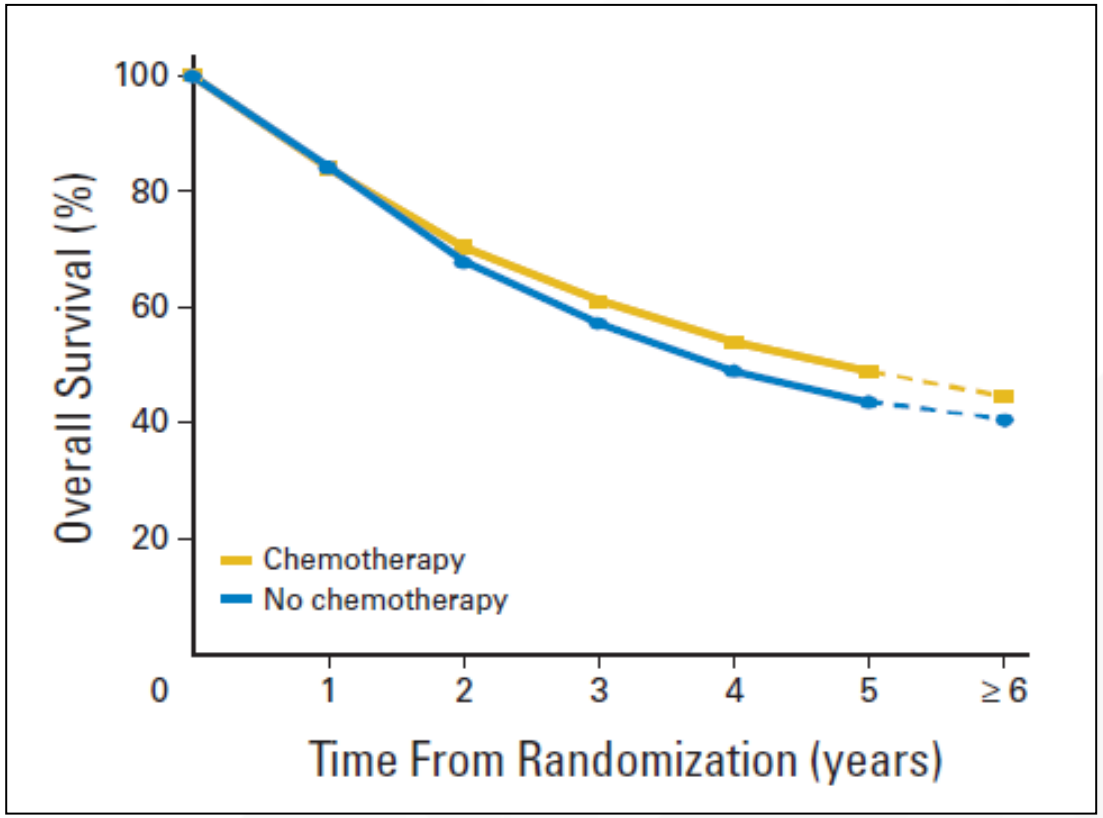
- Reflects shed tumor DNA or other tumor-related components into plasma, providing a global perspective
  - Abrogates the issue of tumor heterogeneity
- Relatively noninvasive and can be repeated serially to monitor tumor response and progression
  - High acceptance rate by patients
- Can determine mechanisms of acquired resistance in plasma prior to radiographic detection
- Can define MRD after surgical resection of early stage NSCLC
- Detection of early stage disease in prediagnostic settings and/or screening

ctDNA, circulating tumor DNA; MRD, minimal residual disease; NSCLC, non-small cell lung cancer.
IASLC. https://www.iaslc.org/iaslc-atlas-molecular-testing-targeted-therapy-lung-cancer.

Rationale to Improve Disease Control in Resected ALK-Positive NSCLC

Meta-Analysis: Lung Adjuvant Cisplatin Evaluation (LACE)

- 5 studies since 1995
  - BLT, ALPI, IALT, JBR.10, ANITA
- Pooled individual data
  - 4,585 patients
- Chemotherapy
  - ↓6.9% lung cancer death
  - ↑1.4% non-cancer death



ALPI, Adjuvant Lung Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; BLT, Big Lung Trial; IALT, International Adjuvant Lung Cancer Trial; JBR.10, National Cancer Institute of Canada Clinical Trials Group JBR.10.

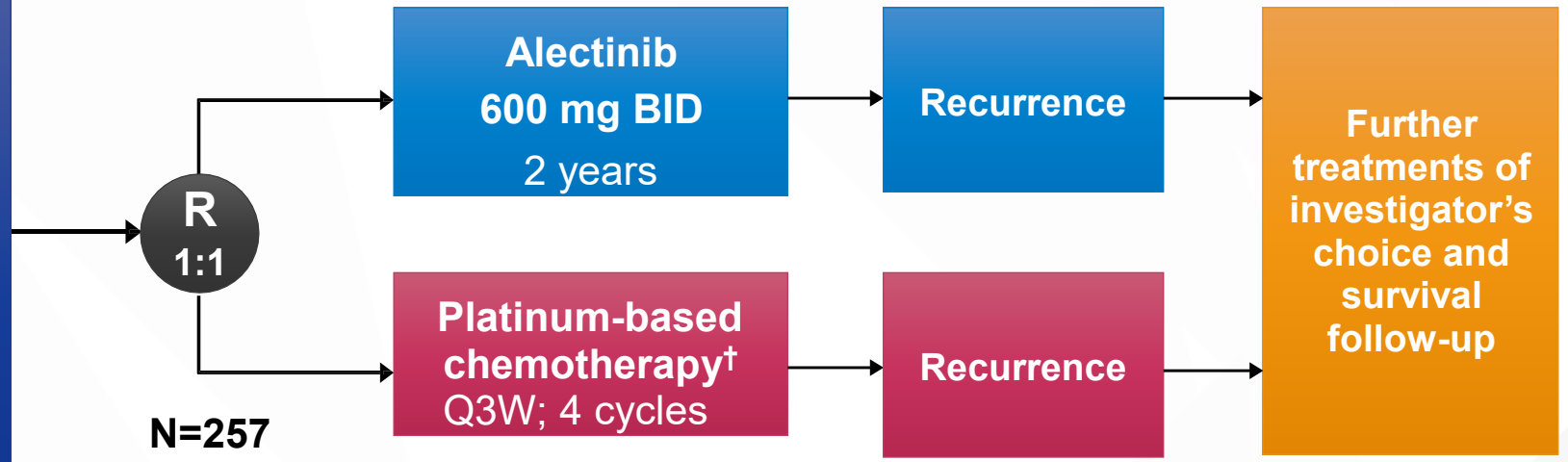
Pignon JP, et al. *J Clin Oncol*. 2008;26(21):3552-3559.

ALINA: A Global, Open-Label, Phase 3, Randomized Clinical Trial*

Resected Stage IB (≥4 cm)–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 (≥4 cm) vs II vs IIIA
- Race: Asian vs non-Asian



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

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

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

AXIS Medical Education

Data cutoff: June 26, 2023. *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 randomization 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 is not available.

ALK, anaplastic lymphoma kinase; BID, twice daily; CNS, central nervous system; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention to treat; NSCLC, non-small cell lung cancer; OS, overall survival; Q3W, once every 3 weeks; UICC/AJCC, International Union Against Cancer/American Joint Committee on Cancer.

Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276. ClinicalTrials.gov identifier: NCT03456076.

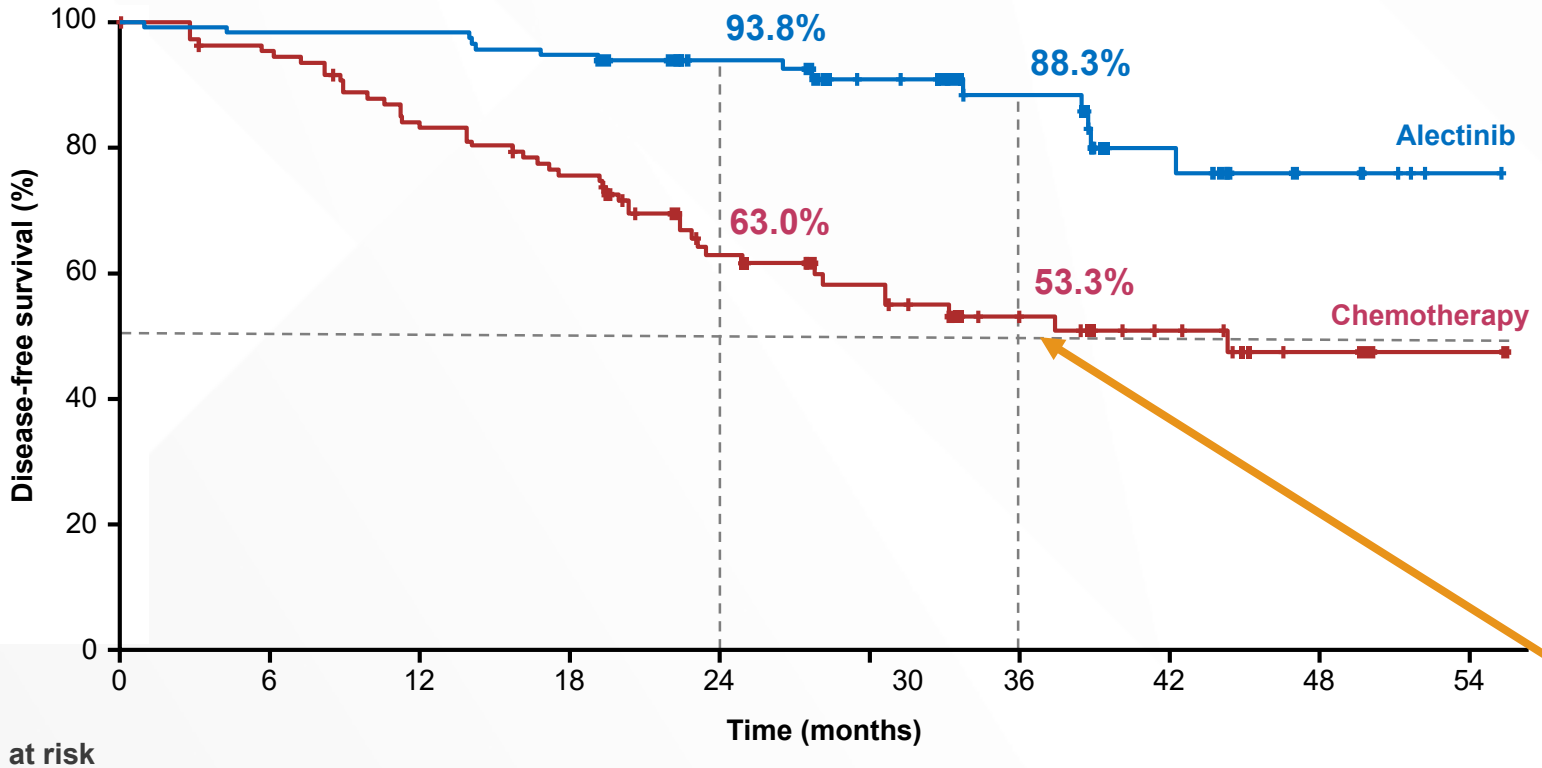
Patient Demographics and Baseline Characteristics (ITT)

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

Medical Education

Data cutoff: June 26, 2023.
*Per UICC/AJCC 7th edition; †Pneumonectomy (alectinib arm, 2%; chemotherapy arm, 3%), bilobectomy (2%; 4%), and sleeve lobectomy (0%; 1%).
ITT, intent to treat; ECOG PS, Eastern Cooperative Oncology Group performance status.
Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

Primary Endpoint: 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

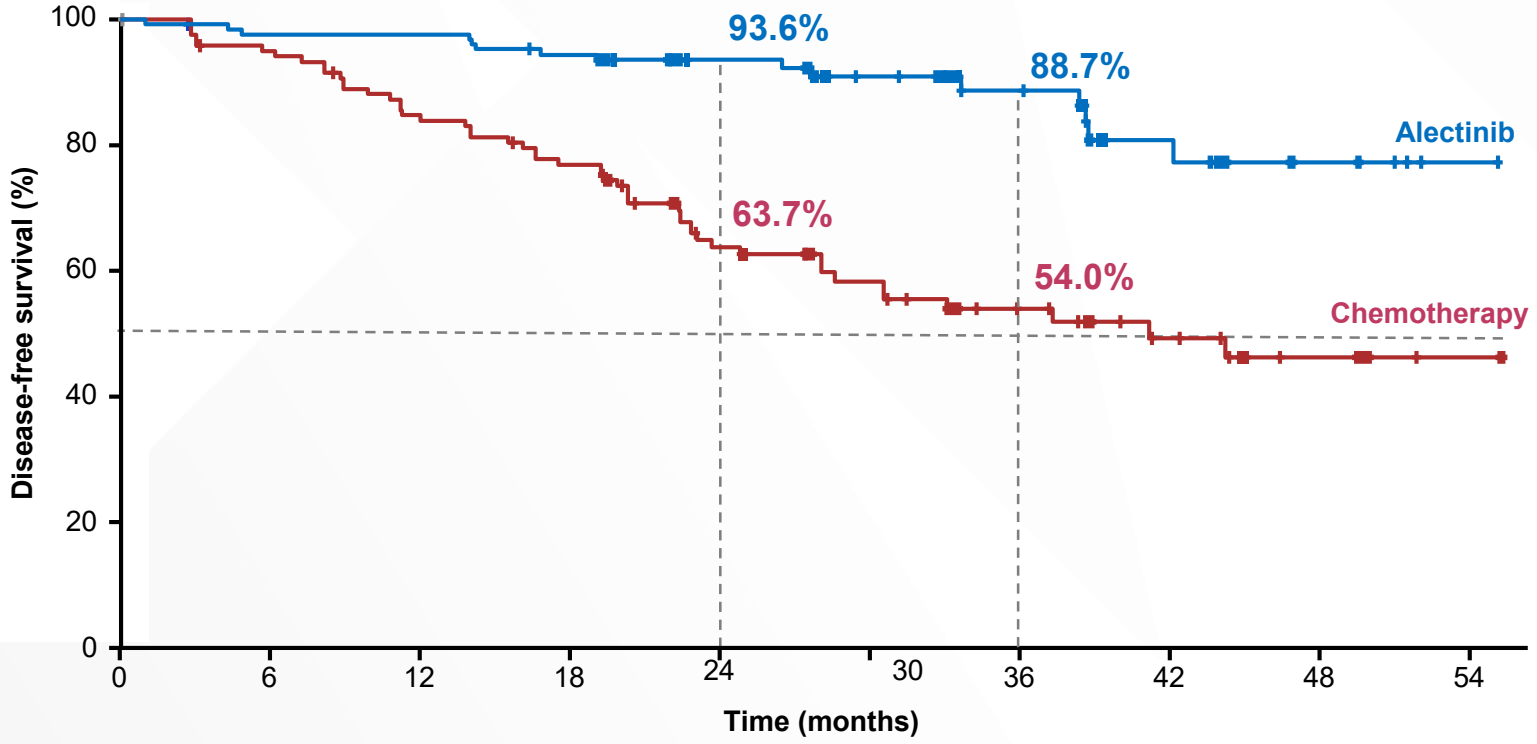
	Alectinib (n=116)	Chemotherapy (n=115)
Patients with event	14 (12%)	45 (39%)
Death	0	1
Recurrence	14	44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) P<0.0001†	

Nearly 50% have had recurrence or death by year 3

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

Data cutoff: June 26, 2023; time from last patient in to data cutoff was ≈18 months.
*Per UICC/AJCC 7th edition. †Stratified log rank; DFS was defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC as determined by the investigator or death from any cause, whichever occurs first.
DFS, disease-free survival; HR, hazard ratio; NE, not established; NSCLC, non-small cell lung cancer; UICC/AJCC, International Union Against Cancer/American Joint Committee on Cancer.
Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

Primary Endpoint: 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	15 (12%)	50 (39%)
Death	0	1
Recurrence	15	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†	

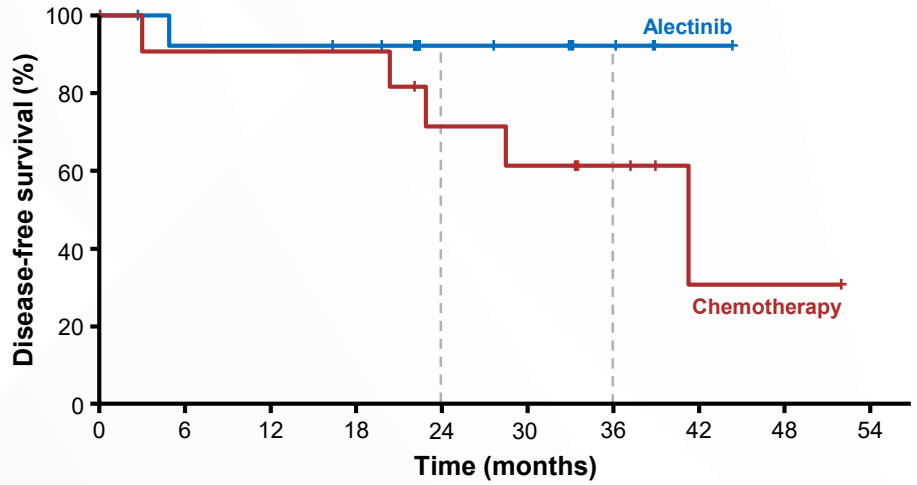
At the data cutoff, OS data were immature, with only 6 (2.3%) OS events reported‡

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

Data cutoff: June 26, 2023; time from last patient in to data cutoff 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 was defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC as determined by the investigator or death from any cause, whichever occurs first.
DFS, disease-free survival; HR, hazard ratio; ITT, intent to treat; NE, not established; NSCLC, non-small cell lung cancer; OS, overall survival; UICC/AJCC, International Union Against Cancer/American Joint Committee on Cancer.
Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

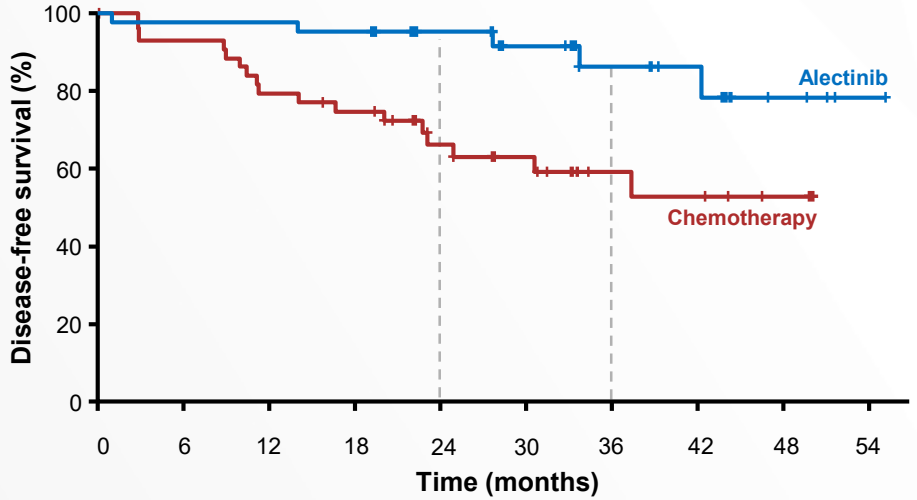
Disease-Free Survival by Disease Stage

Stage IB

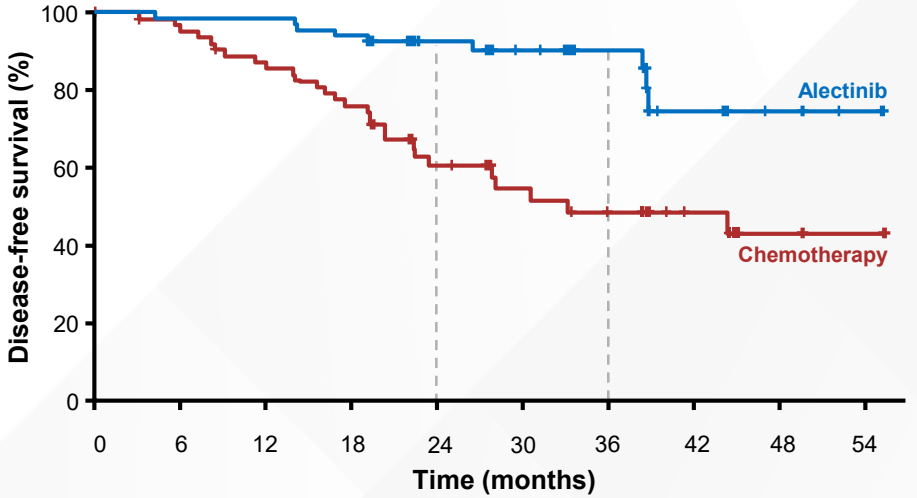


2-year DFS rate, % (95% CI)	Stage IB (n=26)	Stage II (n=92)	Stage IIIA (n=139)
Alectinib	**92.3** (77.8, 100.0)	**95.6** (89.5, 100.0)	**92.7** (86.4, 98.9)
Chemotherapy	**71.6** (44.2, 99.0)	**66.3** (51.7, 81.0)	**60.7** (47.9, 73.5)
HR† (95% CI)	**0.21** (0.02, 1.84)	**0.24** (0.09, 0.65)	**0.25**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

Stage II



Stage IIIA

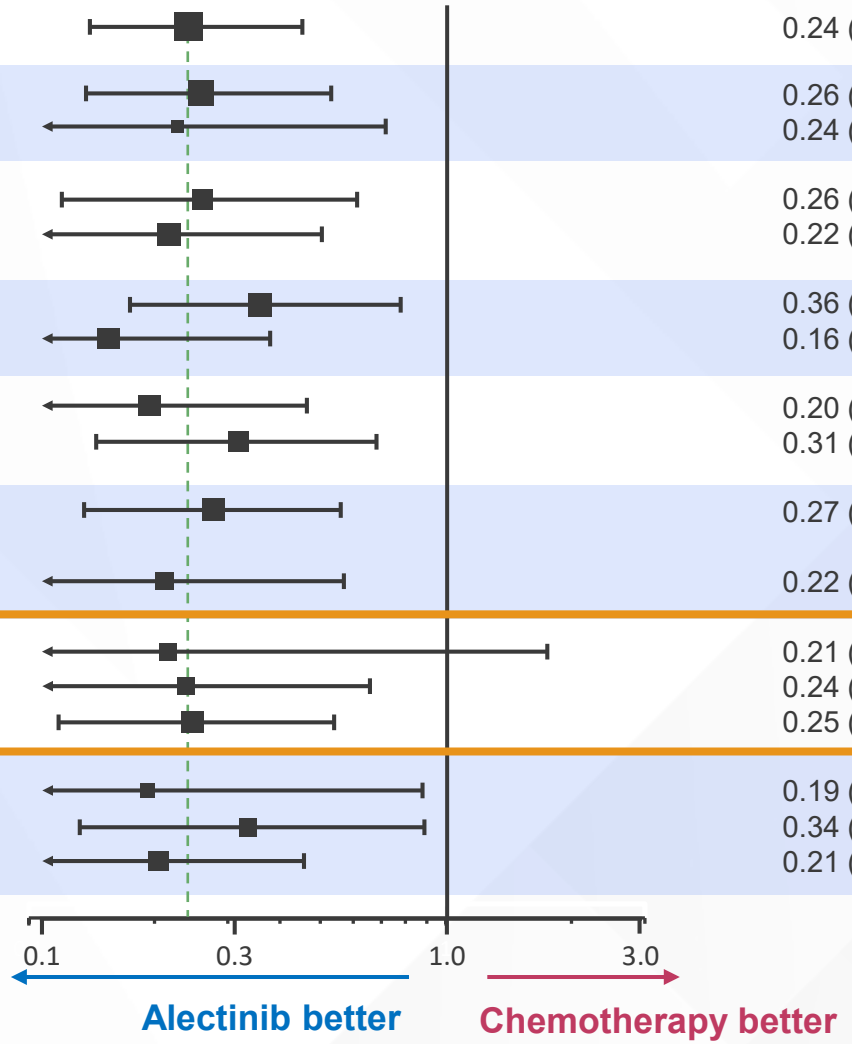


DFS, disease-free survival; HR, hazard ratio.

Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

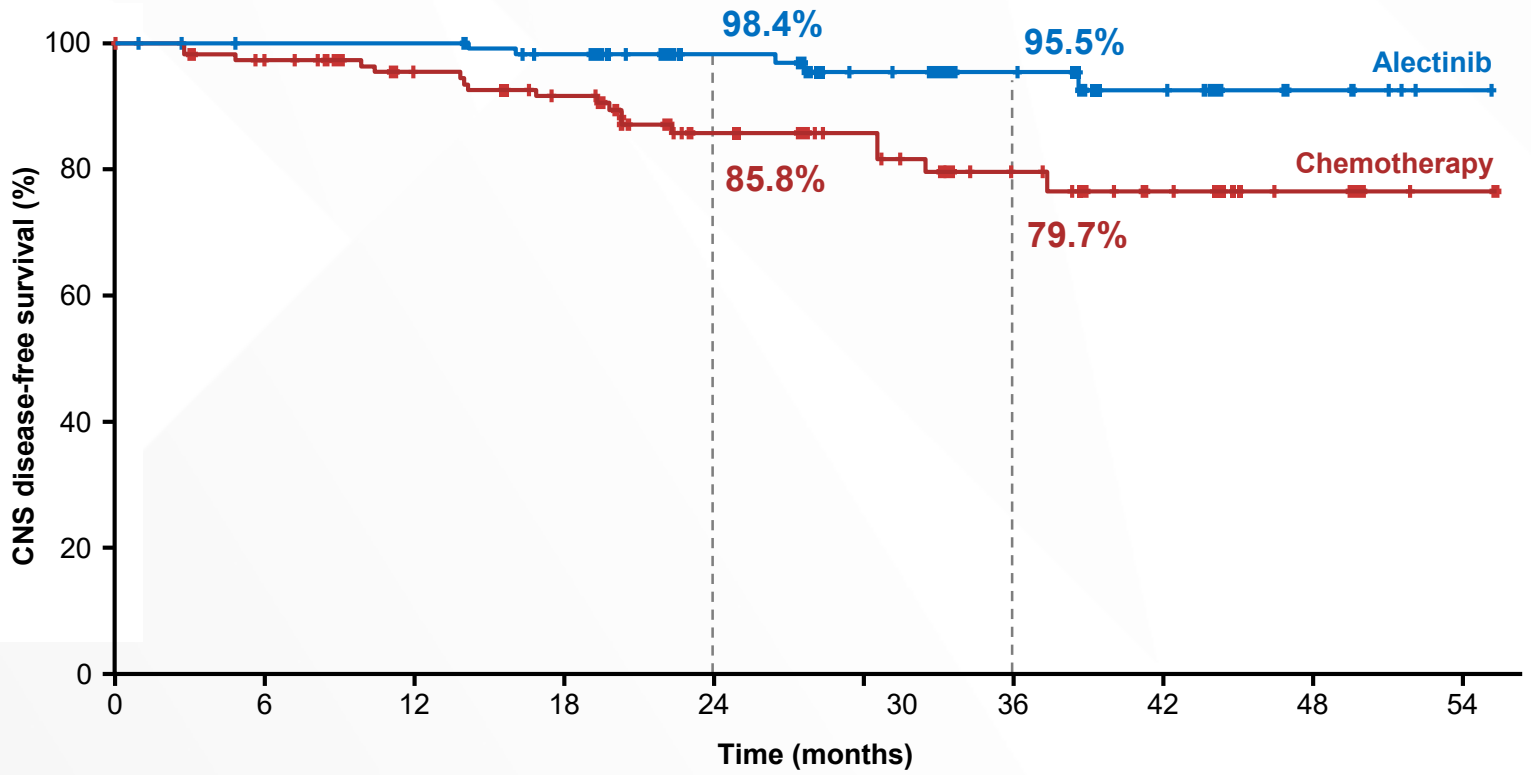
Disease-Free Survival Subgroup Analysis (ITT)

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)



Data cut-off: 26 June 2023; arrows indicate lower bound of the CI<0.1.
*Per UICC/AJCC 7th edition.
DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intent to treat.
Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

CNS Disease-Free Survival in the ITT Population



No. at risk

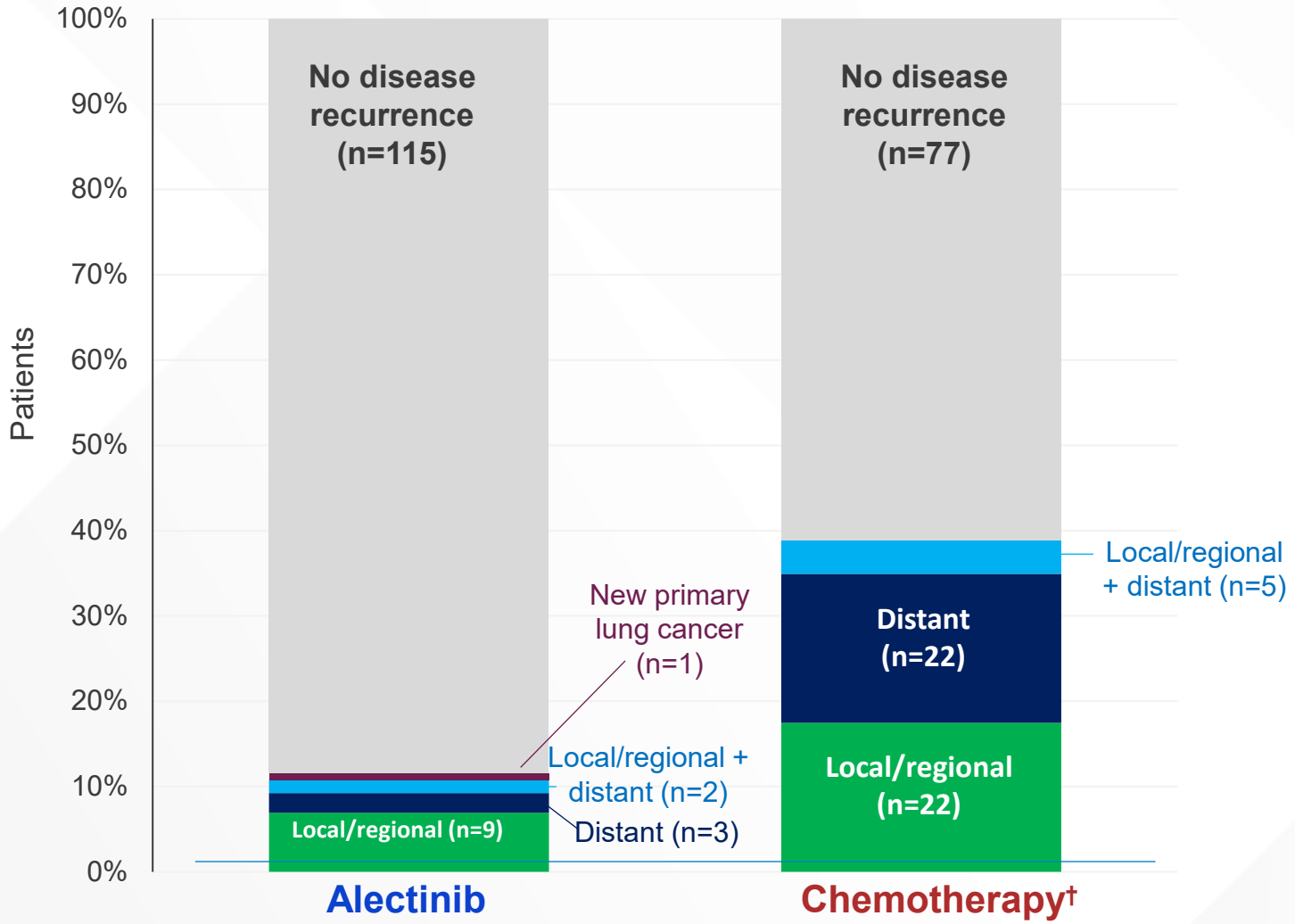
Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

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

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

Data cutoff: June 26, 2023.
*Stratified analysis with race and stage as stratification factors. CNS-DFS was defined as time from randomization to the first documented recurrence of disease in the CNS or death from any cause.
CNS, central nervous system; DFS, disease-free survival; HR, hazard ratio; ITT, intent to treat.
Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

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

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.
ITT, intent to treat.
Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

Safety Summary

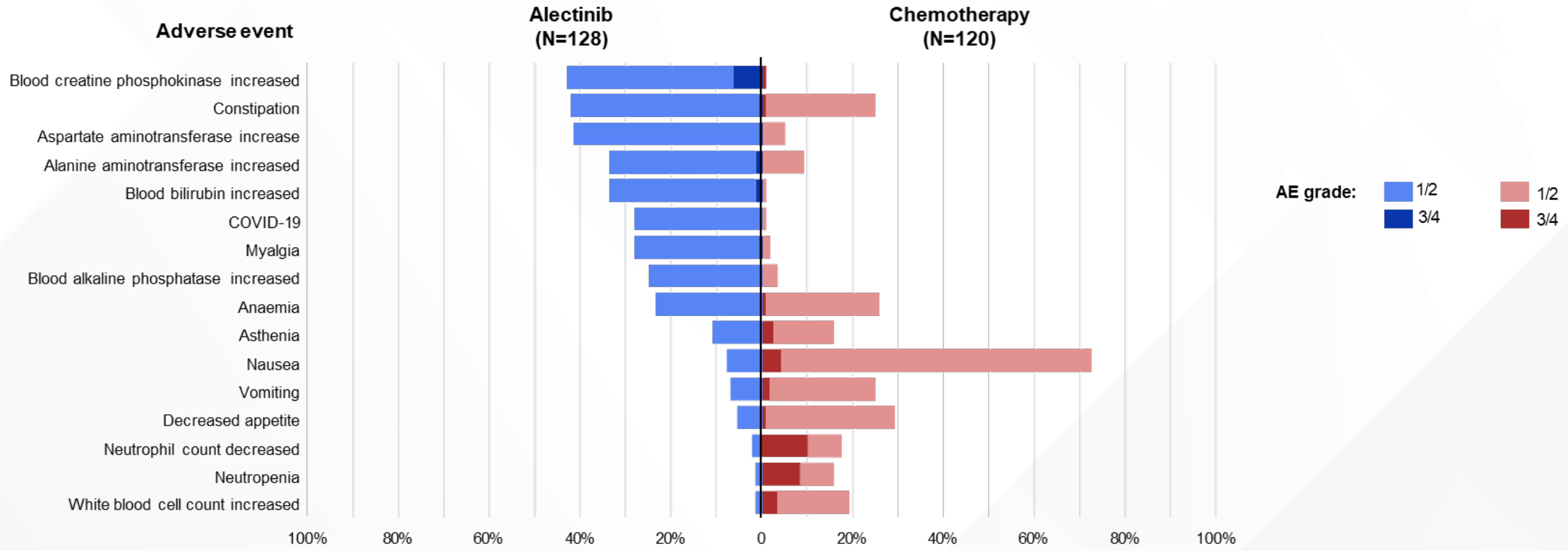
	Alectinib (n=128)	Chemotherapy (n=120)
Median treatment duration	**23.9 months**	**2.1 months**
Patients with any AEs, %	**98**	**93**
Grade 3/4 AEs	30	31
Grade 5 AEs	0	0
Serious AEs	13	8
Treatment-related serious AEs	2	7
AEs leading to dose reduction	26	10
AEs leading to dose interruption	27	18
AEs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

At data cutoff, **20.3%** of patients in the alectinib arm were receiving ongoing treatment

Medical Education

Data cutoff: June 26, 2023.
Multiple occurrences of the same AE in one individual are counted only once in each category.
AE, adverse event.
Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

AEs Occurring in ≥15% of Patients



Data cutoff: June 26, 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.
AE, adverse event.
Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

AEs Leading to Dose Interruption, Reduction, or Treatment Discontinuation in ≥3 Patients

Most AEs did not require any dose modification and had resolved by the data cut-off

Safety	Alectinib (n=128)
Median treatment duration	23.9 months
Median dose intensity, %	99.4
Any AE leading to dose interruption, n (%)	**35 (27.3)**
in ≥3 patients	
Blood CPK increased	7 (5.5)
ALT increased	7 (5.5)
AST increased	6 (4.7)
COVID-19	6 (4.7)
Blood bilirubin increased*	5 (3.9)
Myalgia	3 (2.3)
Any AE leading to dose reduction, n (%)	**33 (25.8)**
in ≥3 patients	
Blood CPK increased	8 (6.3)
Blood bilirubin increased*	5 (3.9)
Any AE leading to treatment discontinuation, n (%)	**7 (5.5)**
in ≥3 patients	
Pneumonitis	3 (2.3)

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase.

Horinouchi H, et al. WCLC 2024. Abstract OA13.04.

Summary

- ALINA is the first and only positive phase 3 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

AXIS Medical Education

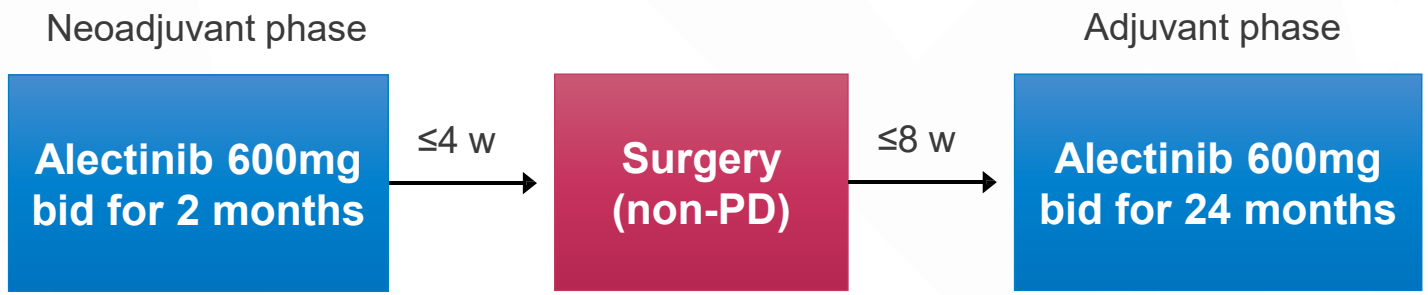
ALK, anaplastic lymphoma kinase; CNS, central nervous system; DFS, disease-free survival; HR, hazard ratio; NSCLC, non-small cell lung cancer.

Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

Emerging Directions in Early Stage ALK+ NSCLC

ALNEO: Study Design

- Resectable locally advanced stage III NSCLC
- Candidate for surgical resection after multidisciplinary discussion
- ALK positive (IHC/FISH/NGS)
- No Previous treatment
- ECOG PS 0-1



Primary endpoint: MPR by BICR
Secondary endpoints: pCR by BICR, OR, EFS, DFS, OS, AEs

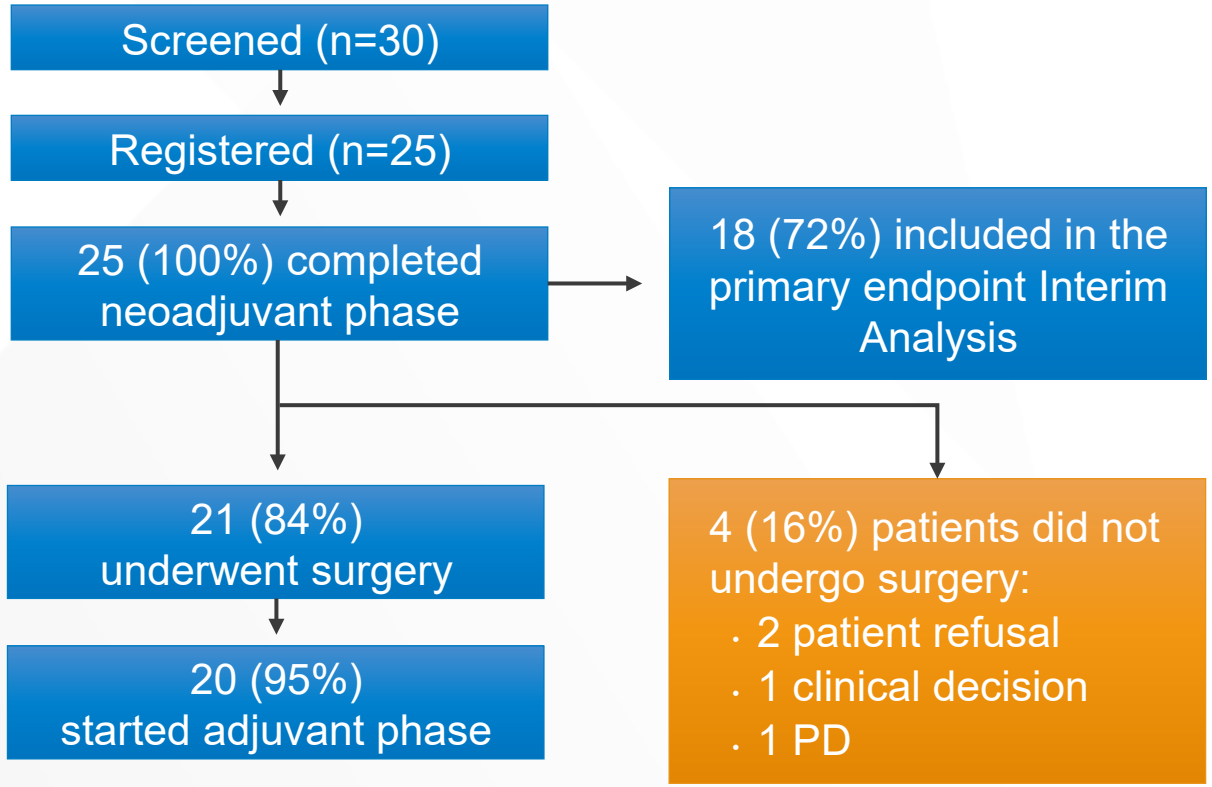
According to the Simon's two-stage mini-max design, the null hypothesis that the MPR is ≤20% will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 4 or fewer MPR in these 18 patients, the study will be stopped early for futility. Otherwise, 15 additional patients will be accrued for a total of 33. The null hypothesis will be rejected if 11 or more MPR are observed in 33 patients. This design yields a type I error rate of 0.05 and power of 0.80 when the true MPR is 40%

AXIS Medical Education

AE, adverse event; ALK, anaplastic lymphoma kinase; BICR, blinded independent central review ; bid, twice a day; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MPR, major pathological response; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OR, objective response; OS, overall survival; pCR, pathological complete response; PD, progressive disease.
Leonetti A, et al. WCLC 2024. Abstract MA01.03.

ALNEO: Study Population

Data cut-off date: January 31st, 2024

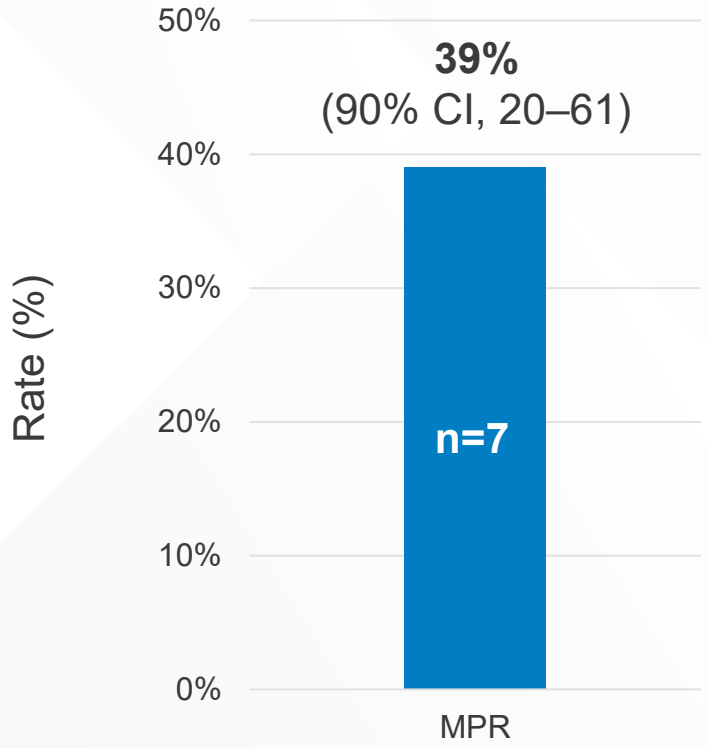


Baseline Characteristics		n=25
Median age, years (IQR)		56 (49-67)
Gender, n (%)	Male	8 (32)
	Female	17 (68)
Smoking, n (%)	Never	14 (56)
	Former	11 (44)
ECOG PS, n (%)	0	19 (76)
	1	6 (24)
Histology, n (%)	Adenocarcinoma	25 (100)
Stage*, n (%)	IIIA	14 (56)
	IIIB	11 (44)
N Stage*, n (%)	N0	2 (8)
	N1	1 (4)
	N2	22 (88)

AXIS Medical Education

*according to the 8th AJCC TNM; most represented stages were T3N2 (n=7, 28%), T1aN2 (n=4, 16%) and T4N2 (n=4, 16%).
AJCC TNM, American Joint Committee on Cancer tumor, node, metastases scoring system; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range.
Leonetti A, et al. WCLC 2024. Abstract MA01.03.

ALNEO: MPR (Primary Endpoint)



Pathologic Response	n=18
MPR, n (%)	7 (39)
pCR, n (%)	3 (17)
No MPR, n (%)	6 (33)
Not Assessed, n (%)	5 (28)[a]

Objective Response[b]	n=25
CR, n (%)	7 (39)
PR, n (%)	3 (17)
SD, n (%)	6 (33)
PD, n (%)	5 (28)[a]
ORR, (%)	20 (80)

	n=25
Underwent Surgery, n (%)	21 (84)
R0, n (% or surgery)	18 (86)
Type of surgery, n (%)	
Lobectomy	17 (81)
Pneumonectomy	2 (9.5)
Other Surgery	2 (9.5)
Received adjuvant, n (% of surgery)	20 (95)[c]
Median interval from surgery, weeks (IQR)	4.5 (2.7–6.0)
Median n of cycles, n (IQR)	6 (1–20)

- Neoadjuvant treatment was well tolerated. G1-2 TEAEs were reported in 14 (56%) cases. No Grade ≥3 treatment-related AEs were observed
- After a median follow-up of 10.8 months (IQR: 4.9–22.5), a total of 159 adjuvant courses were administered and the treatment appeared to be well tolerated

AXIS Medical Education

[a]4 patients did not undergo surgery, 1 patient underwent explorative thoracotomy; [b]at pre-surgical evaluation; [c]2 patients received adjuvant even though surgery was not radical.
AE, adverse event; CR, complete response; IQR, interquartile range; MPR, major pathological response; ORR, objective response rate; pCR, pathological complete response; PD, progressive disease; PR, partial response; R0, no residual tumor; SD, stable disease; TEAE, treatment-emergent adverse event.
Leonetti A, et al. WCLC 2024. Abstract MA01.03.

ALNEO: Summary

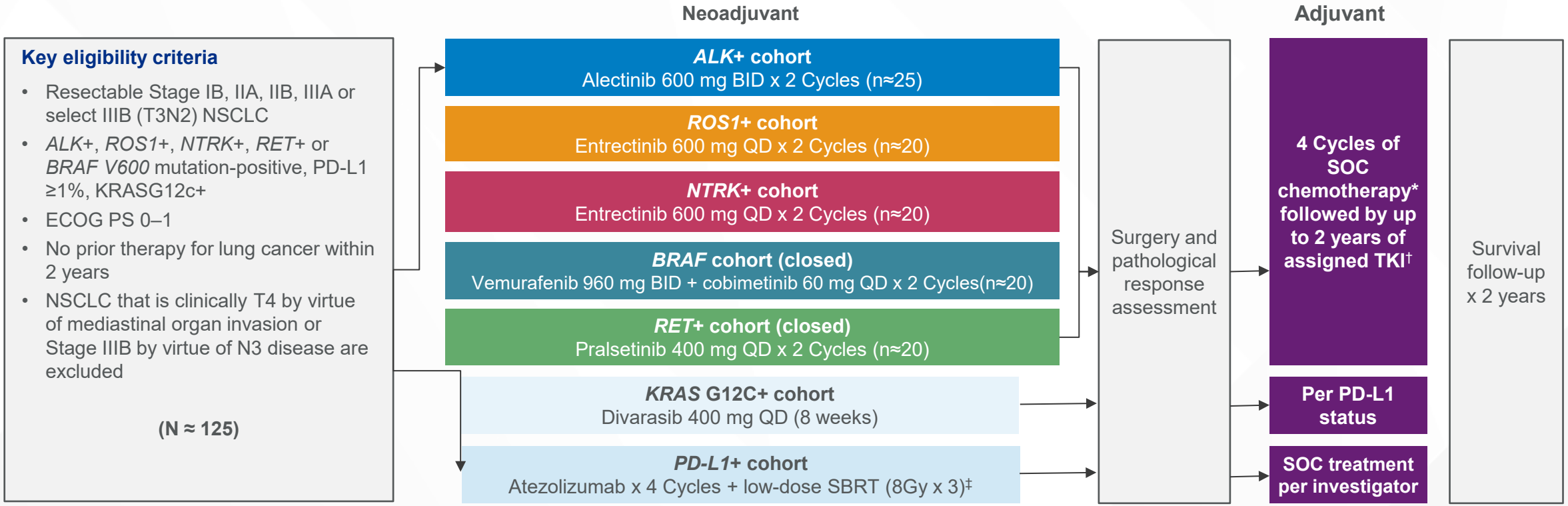
- Resectable stage IIIA/B ALK+ NSCLC
- Perioperative alectinib 600 mg BID
- Primary endpoint: MPR 39% with pCR 17%
- 86% underwent surgery (81% lobectomy); R0 resection 86%
- ORR: 80%
- No grade ≥3 AEs during neoadjuvant alectinib

AXIS Medical Education

AE, adverse event; ALK, anaplastic lymphoma kinase; BID, twice daily; MPR, major pathologic response; NSCLC, non-small cell lung cancer; ORR, objective response rate; pCR, pathological complete response; R0, no residual tumor.

Leonetti A, et al. WCLC 2024. Abstract MA01.03.

NAUTIKA1: Study Design



Primary Endpoint

- TKI cohorts: MPR (≤10% residual viable tumor cells)
- CPI cohort: pCR
- KRAS cohort: safety

Key Secondary Endpoints

- MPR per central assessment
- pCR
- Investigator-assessed ORR, DFS, EFS, OS
- Surgical outcomes
- Safety
- ctDNA clearance rate

Study ML41591. *At the discretion of the investigator; the following options are permitted for this study: cisplatin + pemetrexed (carboplatin allowed if cisplatin is contraindicated) and carboplatin + paclitaxel (nab-paclitaxel allowed if hypersensitivity occurred). †Patients will receive the same TKI as was given during the neoadjuvant phase. ‡to be given during Cycle 1 concurrently with atezolizumab.
ALK, anaplastic lymphoma kinase; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; CPI, checkpoint inhibitor; ctDNA, circulating tumor DNA; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; *KRAS*, KRAS proto-oncogene, GTPase; MPR, major pathological response; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; ORR, overall response rate; OS, overall survival; pCR, pathological complete response; PD-L1, programmed death ligand-1; QD, once a day; *RET*, rearranged during transfection; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase; SOC, standard of care; TKI, tyrosine kinase inhibitor.
Lee JM, et al. WCLC 2023. Abstract P2.01-06.

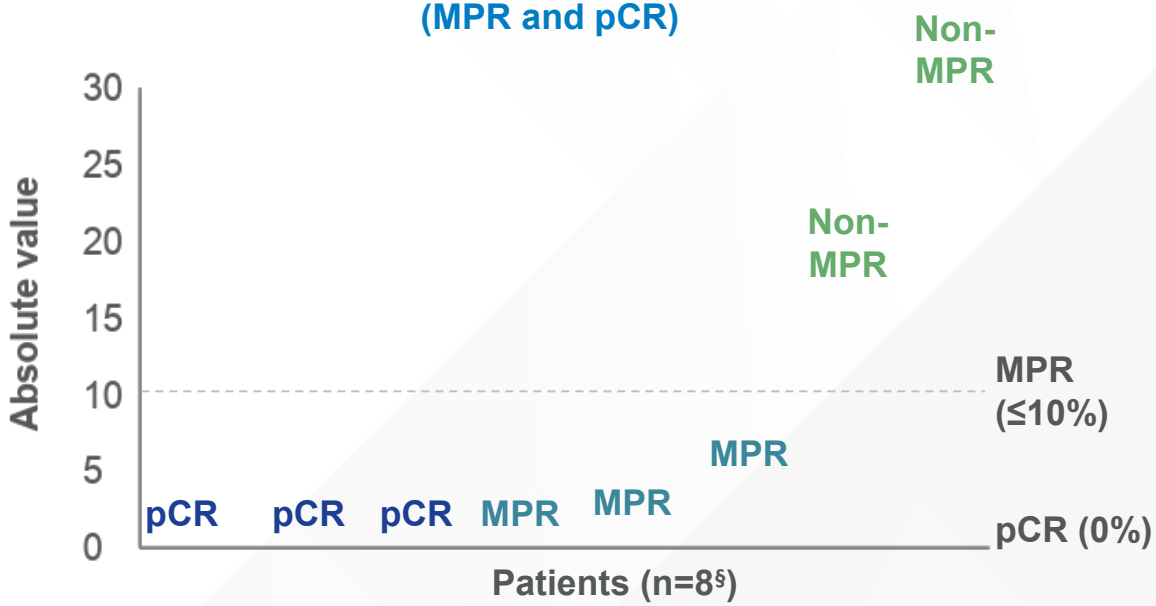
Response Outcomes

- Median neoadjuvant alectinib treatment duration was 8 weeks (range: 7.9–8.7); all patients received ≥2 cycles of alectinib treatment.
- One patient downstaged from stage IIIB to IIIA; one patient downstaged from stage IIIA to IIB after neoadjuvant treatment.

Response outcomes of patients from the *ALK*+ cohort

Pathological response, n (%)*	ALK+ cohort (n=9)
Major pathological response†	6 (66.7)
Pathological complete response‡	3 (33.3)
Radiographic response, n (%)	**ALK+ cohort (n=9)**
Complete response	0
Partial response	4 (44.4)
Stable disease	5 (55.6)
Progressive disease	0

Weighted percentage viable tumour cells (MPR and pCR)



MPR defined as ≤10% residual viable tumour cells; pCR defined as 0% of viable tumour cells.
*Assessed locally. †One evaluable patient did not undergo resection and was treated as a non-major pathological response patient. ‡Pathological complete response in the patient with squamous histology. §In one evaluable patient, resection was not done during surgery, so pathological response was not assessed.
ALK, anaplastic lymphoma kinase; MPR, major pathological response; pCR, pathological complete response.
Lee JM, et al. WCLC 2023. Abstract P2.01-06.

SAKULA: Neoadjuvant Ceritinib in ALK+ Locally Advanced NSCLC

- 7 patients: median age 50 years; 71% male; all stage IIIA
- Three 28-day cycles of ceritinib at 750 mg QD
- ORR: 100%
- Six patients went to resection; 5 had R0 resection
- Pathologic response: 2 pCR, 4 MPR
- Most common AEs were GI toxicities

ALK, anaplastic lymphoma kinase; AE, adverse event; GI, gastrointestinal; MPR, major pathologic response; ORR, objective response rate; pCR, pathological complete response; QD, once a day; R0, no residual tumor.

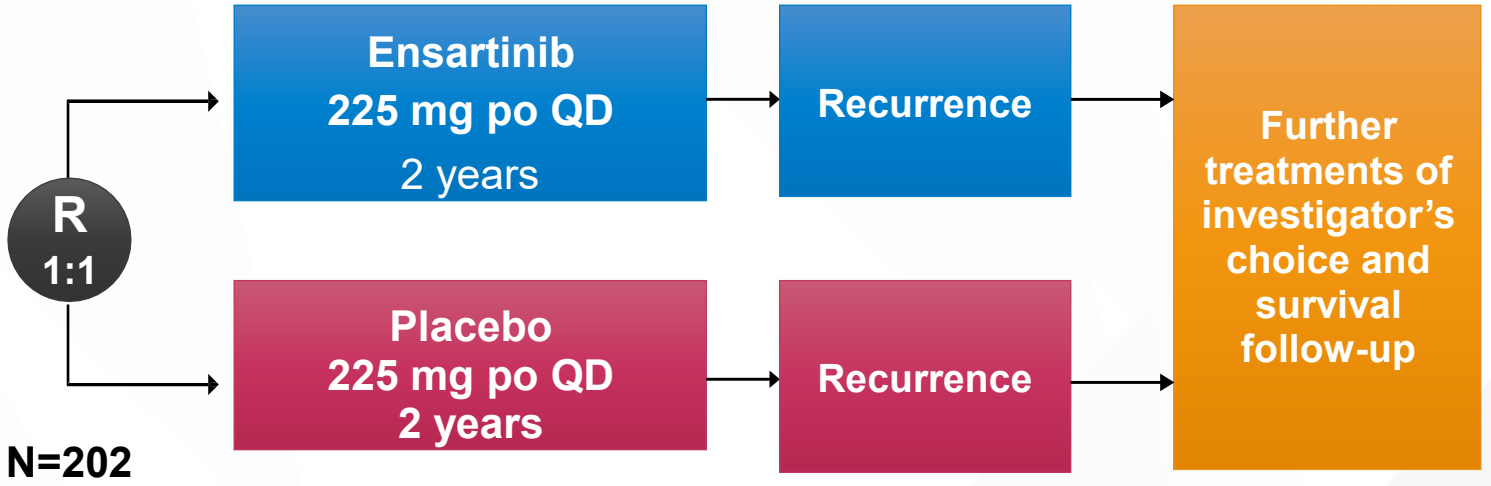
Zenke Y, et al. WCLC 2019. Abstract P1.18-04.

Ensartinib as Adjuvant Therapy in ALK+ Resected NSCLC: Double Blind, Placebo-Controlled, Multi-Center Phase 3 Trial

Resected Stage IB (≥4 cm)–IIIB (T3N2)
***ALK*+ NSCLC**

Other key eligibility criteria:

- ECOG PS 0/1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy



Chemotherapy optional and per investigator's discretion

Primary endpoint

- DFS

Other endpoints

- DFS at 3 and 5 years
- OS
- Safety

AXIS Medical Education

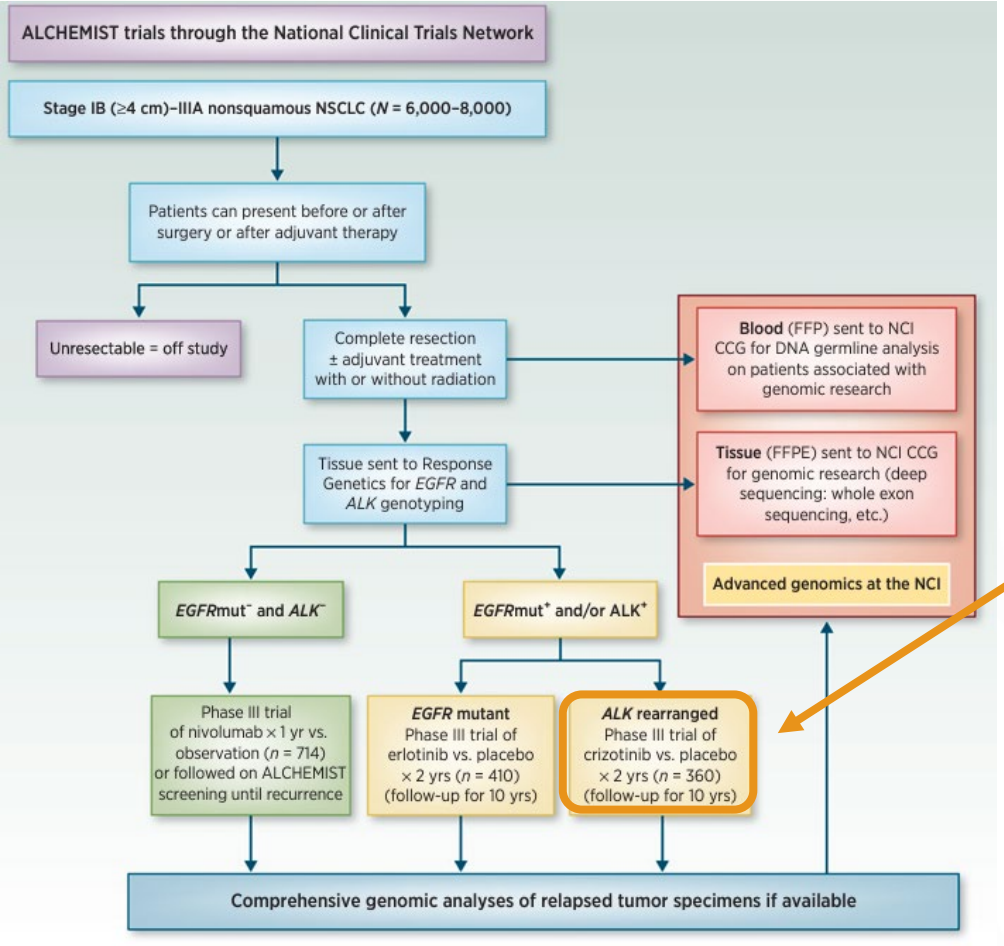
ALK, anaplastic lymphoma kinase; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; OS, overall survival; QD, once daily.
ClinicalTrials.gov identifier: NCT05341583.

Ensartinib: Other Ongoing Trials

- A Phase 2 Study Comparing Ensartinib Versus Platinum-Based Chemotherapy as Adjuvant Treatment for Stage II-IIIA ALK-Positive Non-Small Cell Lung Cancer (NCT05186506)
- Adjuvant Therapy of Ensartinib in Patients With Stage IB-IIIA ALK-positive Non-Small Cell Lung Cancer: a Prospective, Multi-center, Single-arm Exploratory Study (NCT05241028)
- A Study of Ensartinib as Neoadjuvant Therapy for Patients With ALK-Positive Resectable Non-Small Cell Lung Cancer (NCT05380024)

ALK, anaplastic lymphoma kinase.
ClinicalTrials.gov identifier: NCT05186506.
ClinicalTrials.gov identifier: NCT05241028.
ClinicalTrials.gov identifier: NCT05380024.

ALCHEMIST Trials: A Golden Opportunity to Transform Outcomes in Early-Stage Non-Small Cell Lung Cancer



Enrolled 166 of the planned 160 – now closed to accrual
1^0 endpoint changed from OS to DFS

ALK, anaplastic lymphoma kinase; CCG, Center for Cancer Genomics; DFS, disease-free survival; EGFR, epidermal growth factor receptor; FFP, fresh frozen plasma; FFPE, formalin-fixed, paraffin-embedded; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; OS, overall survival.

Govindan R, et al. *Clin Cancer Res*. 2015;21(24):5439-5444.

HORIZON-01 (Cohort A1): Alectinib vs Durvalumab Following cCRT or sCRT in Locally Advanced, Unresectable, Stage III *ALK*+ NSCLC

- **Locally advanced, unresectable, stage III *ALK*+ NSCLC**
- Age ≥18 years old
- Post SOC cCRT or sCRT
- ECOG PS 0–2

R
1:1

N=120

Alectinib 600 mg PO BID
3 years

Durvalumab 1500 mg IV Q4W
1 year

Primary endpoint:
PFS

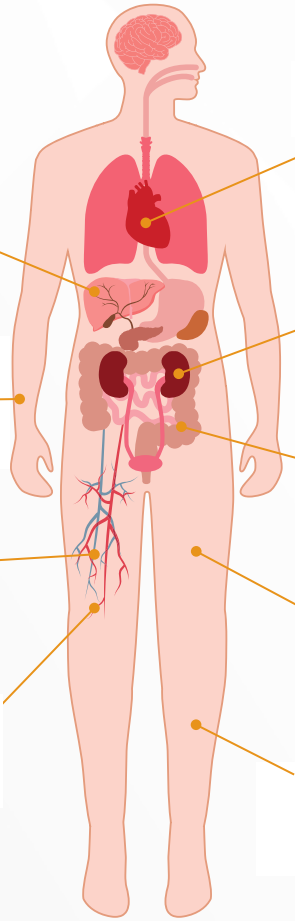
Key Secondary endpoints:
- Time to CNS progression
- ORR, DoR
- OS
- Safety

AXIS Medical Education

ALK, anaplastic lymphoma kinase; BID, twice a day; cCRT, concurrent chemoradiation; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q4W, every 4 weeks; sCRT, sequential chemoradiation; SOC, standard of care.
ClinicalTrials.gov identifier: NCT05170204.

Skills and Interprofessional Team-Based Strategies Needed to Adopt Adjuvant Targeted Therapies in the Community Setting

Clinically Relevant AEs in the ALINA Alectinib Arm



Liver function abnormalities
All grades: **60.9%**
Grade 3–4: **4.7%**

Rash
All grades: **14.1%**
Grade 3–4: **0.8%**

Anemia
All grades: **23.4%**
Grade 3–4: **0%**

Blood CPK increased
All grades: **43.0%**
Grade 3–4: **6.3%**

Bradycardia
All grades: **7.8%**
Grade 3–4: **0%**

Renal impairment
All grades: **15.6%**
Grade 3–4: **0.8%**

Constipation
All grades: **42.2%**
Grade 3–4: **0.8%**

Myalgia
All grades: **28.1%**
Grade 3–4: **0.8%**

Peripheral edema
All grades: **10.2%**
Grade 3–4: **0%**

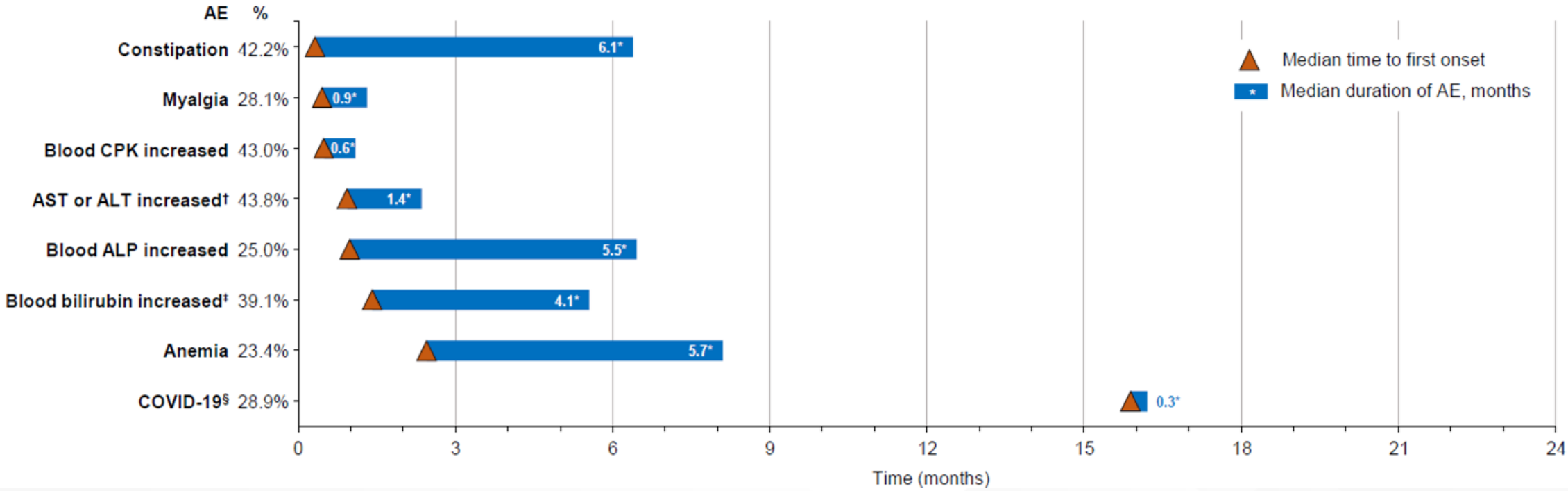
- Most clinically relevant AEs experienced with alectinib were low grade; higher-grade AEs could be well managed with dose interruption or reduction
- The safety profile of alectinib in the ALINA trial was consistent with that observed in previous trials in patients with metastatic ALK+ NSCLC

AXIS Medical Education

AE, adverse event; ALK, anaplastic lymphoma kinase; CPK, creatine phosphokinase; NSCLC, non-small cell lung cancer.
Horinouchi H, et al. WCLC 2024. Abstract OA13.04.

Time to Onset and Duration of Any AEs Occurring in ≥15% of Patients in the Alectinib Arm

- For the most frequent AEs, the median time to onset occurred mostly during the **first month** of alectinib.
- AEs of longer duration were mostly **Grade 1–2** in severity, **manageable** and did not lead to **treatment discontinuation**



AE, adverse event; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase.
Horinouchi H, et al. WCLC 2024. Abstract OA13.04.

Cardiac Toxicity With Alectinib

Cardiac Toxicity With Alectinib

Cardiac Follow-Up in Patients With ALK Positive Lung Cancer Treated With Alectinib

53 patients with *ALK* positive NSCLC treated with alectinig

Prospective cardiac evaluation at cardio-oncology clinic

- 22 of 34 patients with echocardiograms while on alectinib (median 24 months, range 7-38); no LV systolic dysfunction
- 13 of 19 patients with echocardiograms prior to and 6 months after alectinib; no significant changes in LVEF

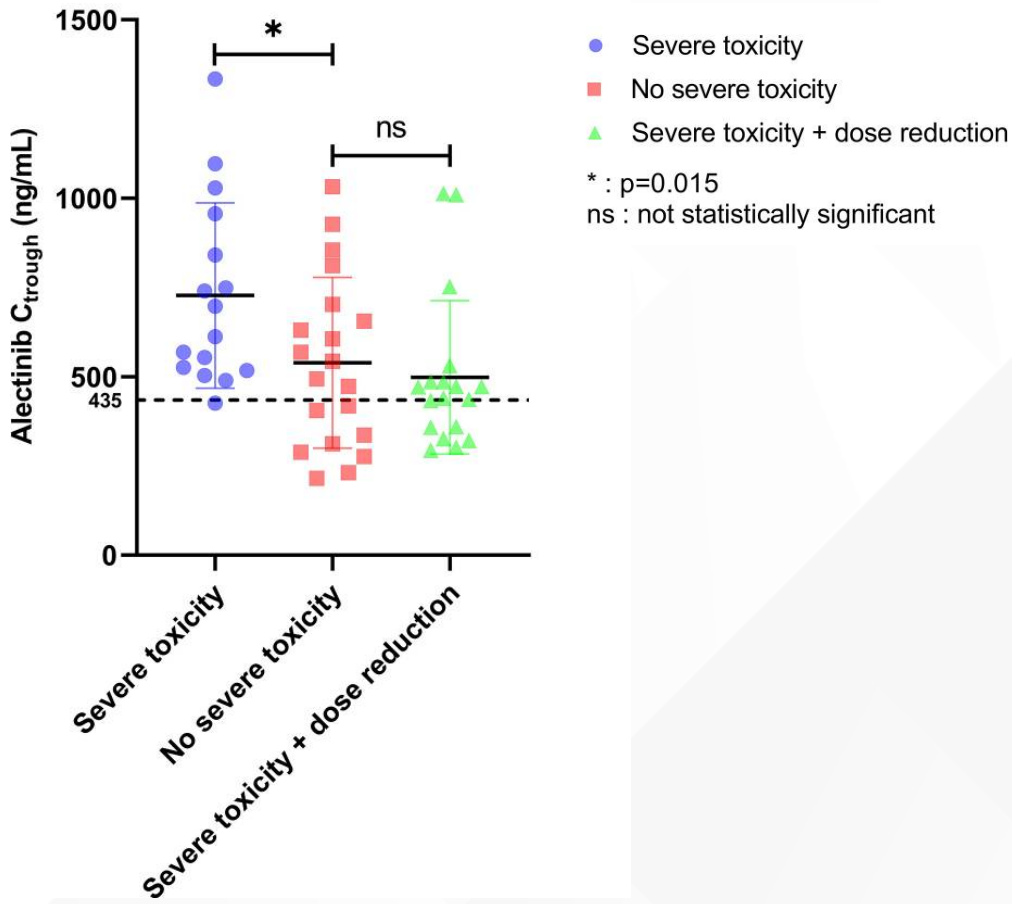
Adverse events data collection

- Median heart rate decreased by 17 bpm
- 42% developed bradycardia; 17% required dose reduction
- 13% developed edema, 3.7% required dose reduction

Blood sampling for alectinib exposure (N=47)

- Higher mean plasma exposure in patients with severe toxicity

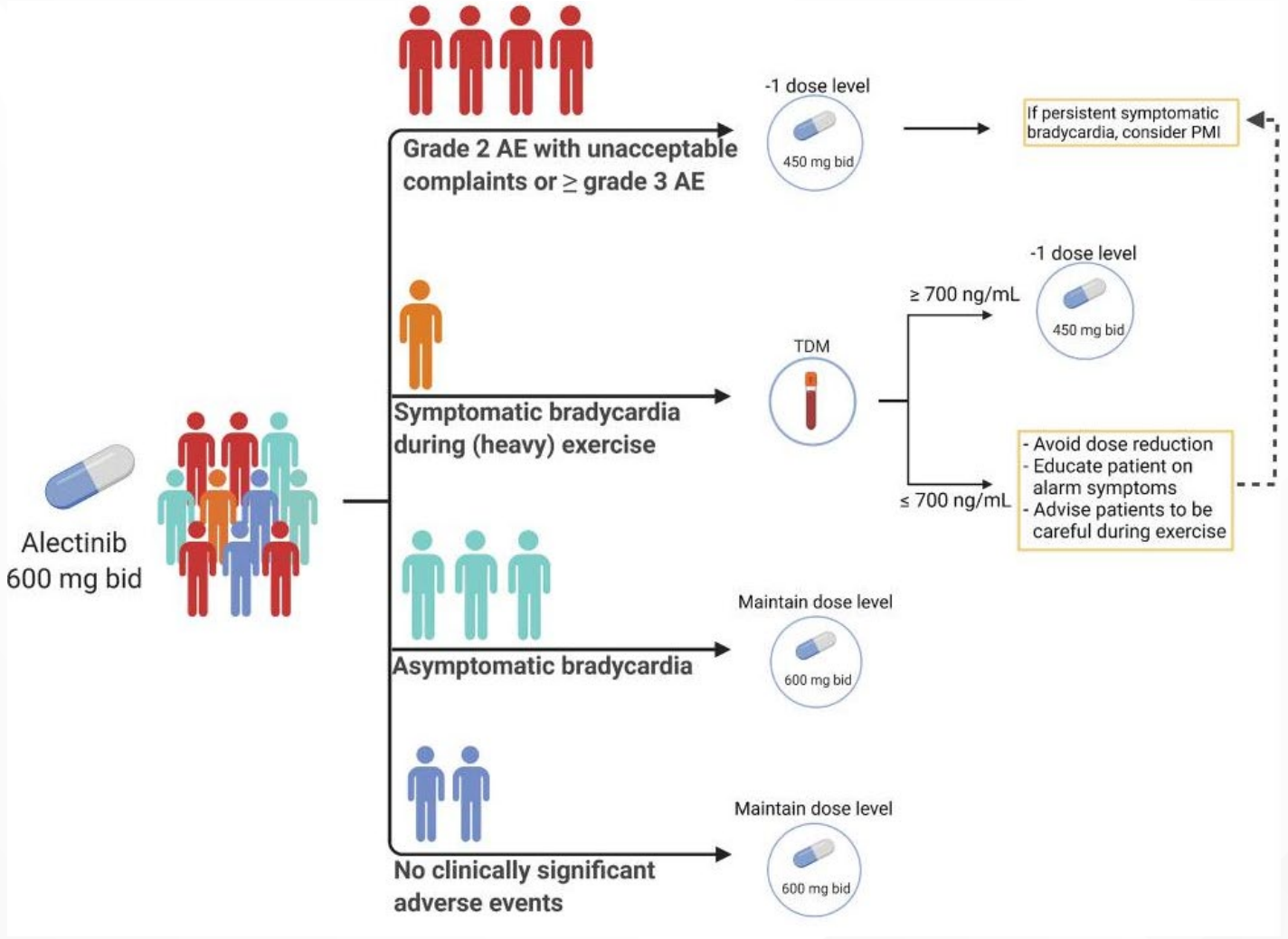
Alectinib exposure in patients with and without severe toxicity



ALK, anaplastic lymphoma kinase; LVEF, left ventricular ejection fraction; NSCLC, non-small cell lung cancer.

Pruis MA, et al. *JACC CardioOncol*. 2023;5(1):102-113.

Managing Cardiac Toxicity With Alectinib

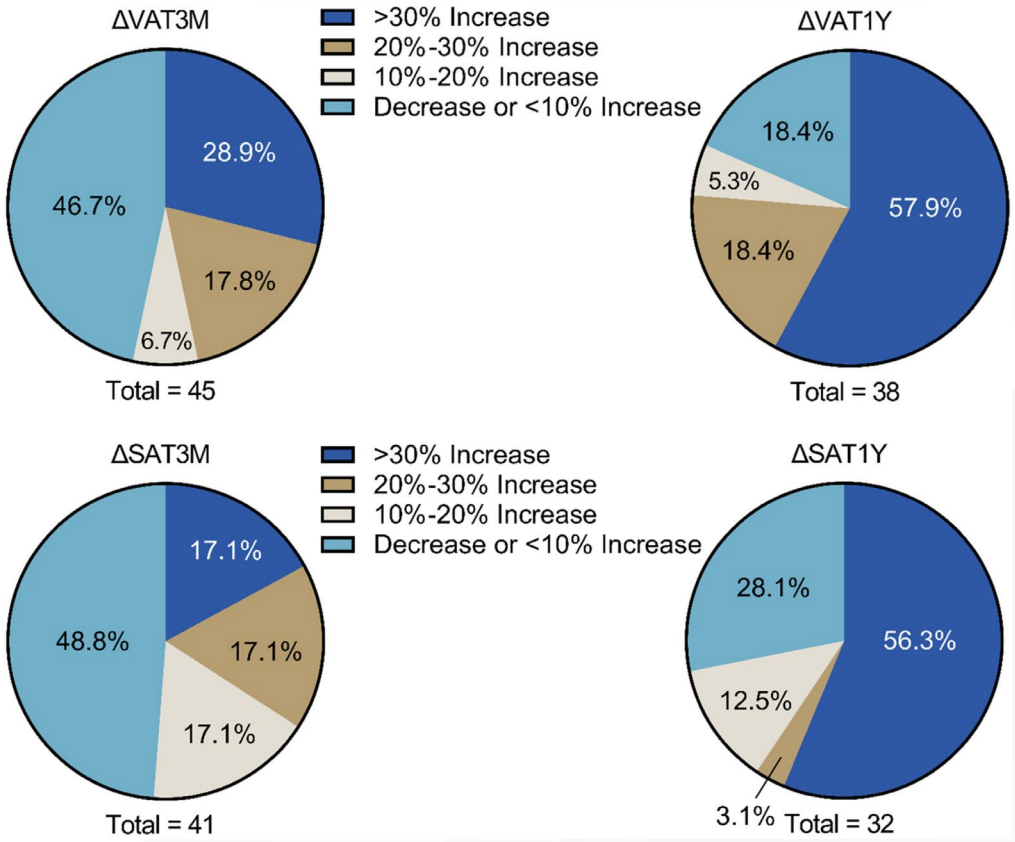


AE, adverse event; bid, twice a day; PMI, pacemaker implantation; TDM, therapeutic drug monitoring .
Pruis MA, et al. *JACC CardioOncol*. 2023;5(1):102-113.

Weight Gain With Alectinib

- 46 ALK+ patients
- Waist circumference, VAT, SAT and skeletal muscle measured
- Mean ↑ in waist circ – 9.7%
- Incidence of sarcopenic obesity increased from 23.7% to 47.4% at 1 year

Change is VAT and SAT at 3 mos and 1 yr

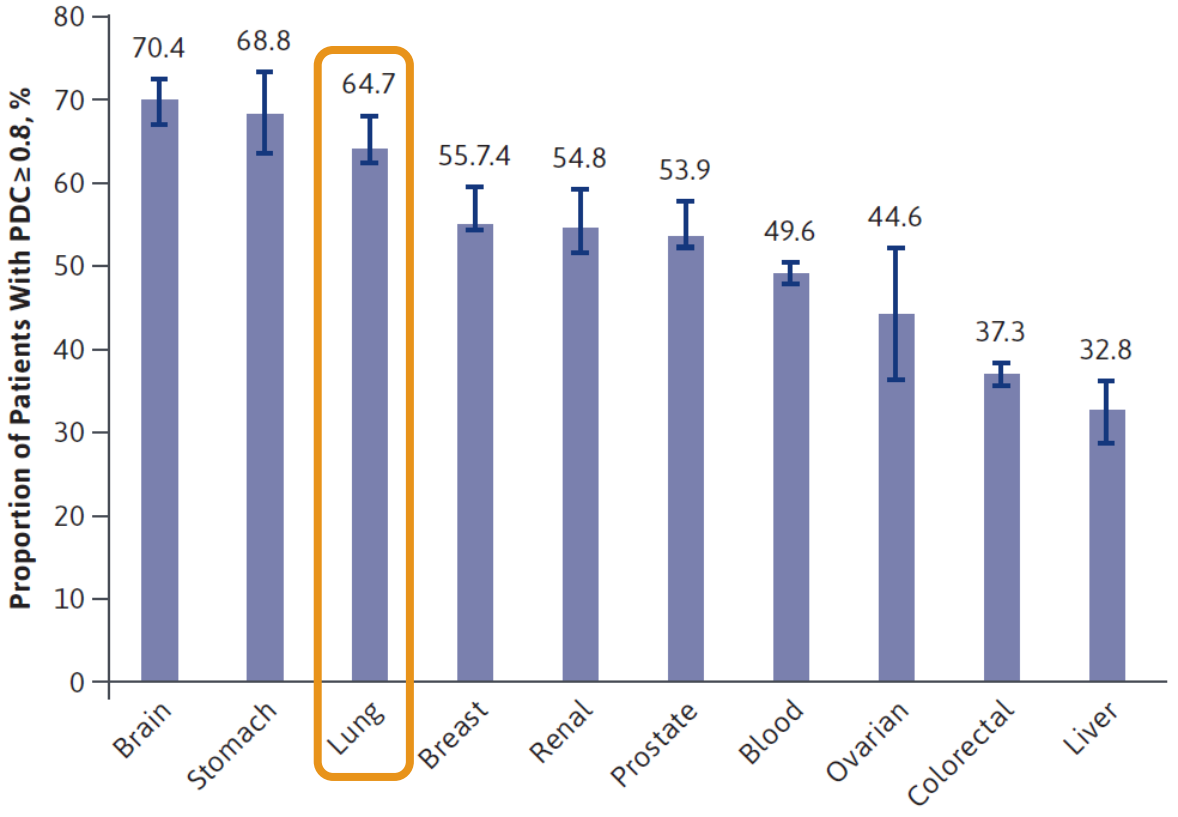


ALK, anaplastic lymphoma kinase; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

de Leeuw SP, et al. *J Thorac Oncol.* 2023;18(8):1017-1030.

Defining the Magnitude of Poor Adherence to Oral Oncolytics

- Retrospective cohort study
- Optum Clinformatics Data Mart commercial claims database 2010-18
- Adherence defined as proportion of days covered (PDC) > 0.8
- 37938 pts included
- Adherence rate – 51.9%
- Adherence worse with increased OOP costs, hospitalization and Medicare low-income subsidy



OOP, out of pocket.

Vyas A, et al. *J Manag Care Spec Pharm.* 2022;28(8):831-844.

Adherence Barriers and Tools in Oncology

Adherence Barriers Include:

- Low health literacy
- Limited patient knowledge
- Complex administration schedules
- Adverse effects
- OOP costs

Adherence Tools Include:

- Pill diaries
- Pill counts
- Electronic medication monitors
- Cellphone apps/alarms
- Refill rates
- Direct observation
- Biological assays

AXIS Medical Education

OOP, out of pocket.

Mackler E, et al. *J Oncol Pract*. 2019;15(4):e346-e355.

2018 HOPA Best Practices for Oral Oncolytics

Optimal adherence involves:

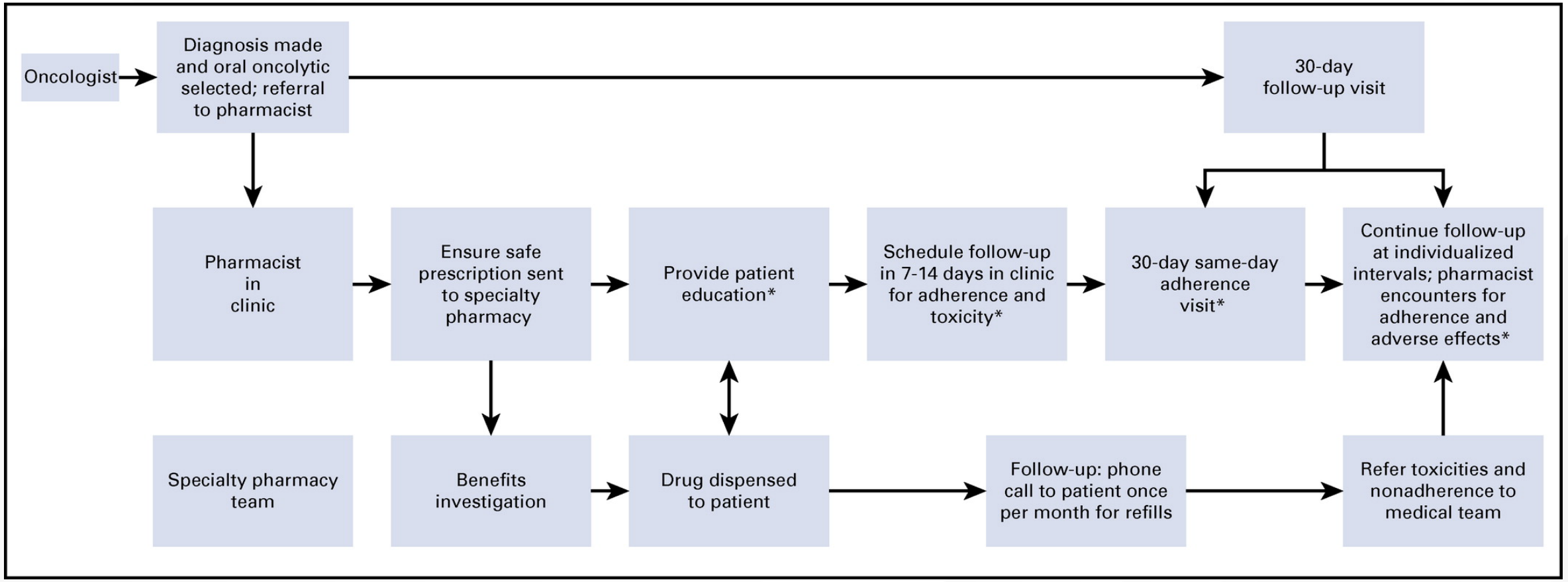
- Prescribing
- Education
- Dispensing/distribution
- Monitoring/follow-up
- Practice management

Best Practices
Prescribing
Patient consent, including intent of therapy, should be obtained for oral oncolytic therapy
Pharmacists should provide a comprehensive review of new oral oncolytics and determine their place in therapy via an interprofessional formulary committee
When feasible, pharmacists should support oral oncolytic prescribing on an individual patient level, taking into consideration both patient- and medication-specific characteristics
Pharmacists should be involved in the creation of oral oncolytic templates for electronic prescribing that include all required components and any standard supportive care measures or monitoring
Pharmacists should perform a comprehensive medication review at the time of prescription
Oral oncolytic safety and quality standards should be consistent with intravenous treatment standards
The oncology team should communicate the intent of oral oncolytic therapy, pertinent drug–drug interactions, and potential implications for the patient's comorbidities and management strategies to the patient's PCP
Education
Pharmacists should be involved in the development or endorsement of standardized education materials, and education should be consistent across the oncology care team
A separate education visit—in person or over the phone—should occur after the oncologist's initial prescribing visit and before the start of oral oncolytic therapy to supplement and reiterate the information provided during the oncologist visit
Education should be comprehensive (see Education) and focus on patient self-care management of oral oncolytic adverse effects and the importance of medication adherence
An assessment of patient knowledge, confidence to manage adverse effects, and need for follow-up should occur during the education session
Patient caregiver attendance at the education session is encouraged
Dispensing/distribution
A dedicated medication assistance team—nonpharmacist—should prospectively screen and provide financial support for oral oncolytic medications
The dispensing pharmacy should have access to necessary information for safely filling the oral oncolytic medication, including laboratory values and progress notes
The dispensing pharmacy should have a dedicated liaison for the clinic and provide information that includes financial toxicities, refills, medication adherence, and any identified medication adverse effects
Specialty pharmacists and oncology pharmacy organizations should partner to promote the education of oncology pharmacists and optimize oncology patient care
Monitoring and follow-up
A consistent process with standardized tools should be used in the oncology clinic setting for monitoring and follow-up
An oncology pharmacist should be involved in the creation of monitoring and follow-up materials and, ideally, in the assessment and monitoring of a patient's symptoms and medication adherence
Initial monitoring of symptoms and adherence, including PROs, should occur between 7 and 14 days after the start of treatment
Ongoing monitoring of symptoms and adherence, including PROs, should occur at each clinical encounter, at least before each refill
Medication reconciliation should occur at each assessment point above, ideally by a pharmacist
Adherence assessment should be user friendly, reliable, cost effective, and practical
Collaborative practice agreements, including laboratory and symptom monitoring, should exist in settings in which clinical oncology pharmacists are part of the interdisciplinary oncology care team
Communication within the oncology team and with the patient's PCP should be ongoing
Practice management
Oncology practices should have an oral oncolytic program with pharmacist involvement where possible
Before oral oncoloytic program development, a baseline gap assessment should be performed to assess areas for improvement and baseline performance on oral oncolytic quality measures
Pre- and postfinancial, clinical quality measures, including interprofessional and patient experience, should be assessed for continuous quality improvement
Sufficient resources should be provided to meet the above quality measures

AXIS Medical Education

HOPA, Hematology/Oncology Pharmacist Association.
Mackler E, et al. *J Oncol Pract.* 2019;15(4):e346-e355.

Oral Oncolytic Management – Optimal Workflow



Mackler E, et al. *J Oncol Pract*. 2019;15(4):e346-e355.

Adherence to ALK Inhibitors* - RWE

- Retrospective observational study – US commercial claims July 2015 – December 2018
- 1st line – 1482 pts (445 alectinib, 1037 crizotinib)
- 2nd line – 880 pts (604 alectinib, 142 brigatinib, 134 ceritinib)
- Adherence similar for all ALK inhibitors
- 1st line – median time to d/c – Alectinib 27.1 mos, crizotinib 8.8 mos
- 2nd line – d/c risk for Alectinib was 64% lower than ceritinib and 34% lower than brigatinib

AXIS Medical Education

*Data represents patients with stage IV disease.
ALK, anaplastic lymphoma kinase; d/c, discontinuation; RWE, real-world evidence.
Ganti AK, et al. *J Manag Care Spec Pharm*. 2022;28(3):305-314.

ASCO/FDA Action Plan to Improve Adherence to Oral Anticancer Agents

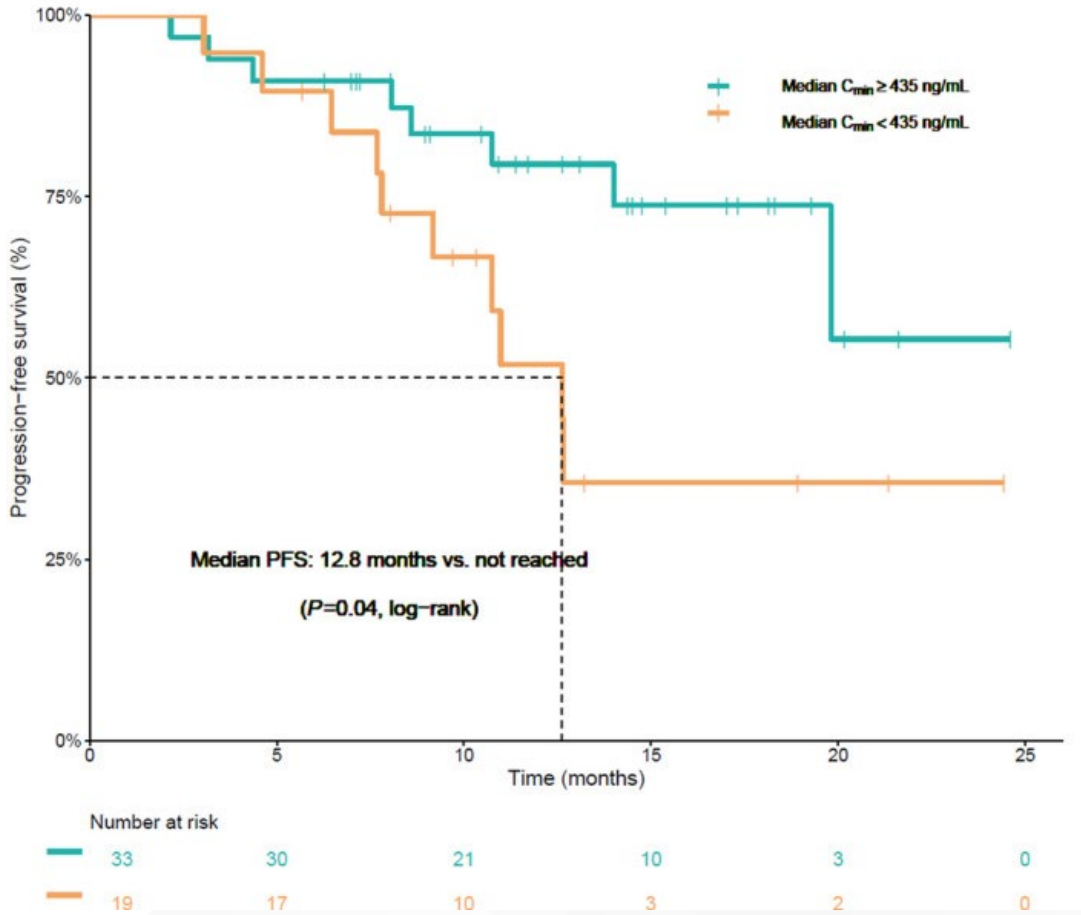
- Action 1: Pharmaceutical companies and regulators should consider adherence early and throughout drug development
- Action 2: Pharmaceutical companies and regulators should expand efforts to characterize toxicity and tolerability
- Action 3: Pharmacists should assume a primary role in the care team in supporting oral anticancer agent adherence
- Action 4: Cancer organizations should advocate for policies that ensure the affordability of oral anticancer drugs
- Action 5: Research funders should support more studies on oral anticancer agent adherence

AXIS Medical Education

ASCO, American Society of Clinical Oncology; FDA, Food and Drug Administration.
Levit LA, et al. *J Clin Oncol.* 2022;40(10):1036-1041.

Exposure-Response Analysis With Alectinib

- Observational study in 52 ALK+ patients with NSCLC receiving alectinib
- Standard dose 600 mg bid
- PFS is prolonged in patients with Cmin ≥435 ng/mL
- Implication:
  - Would monitoring levels make a difference in patients with minimal or no toxicity?
  - Should therapeutic drug monitoring be part of routine clinical management?

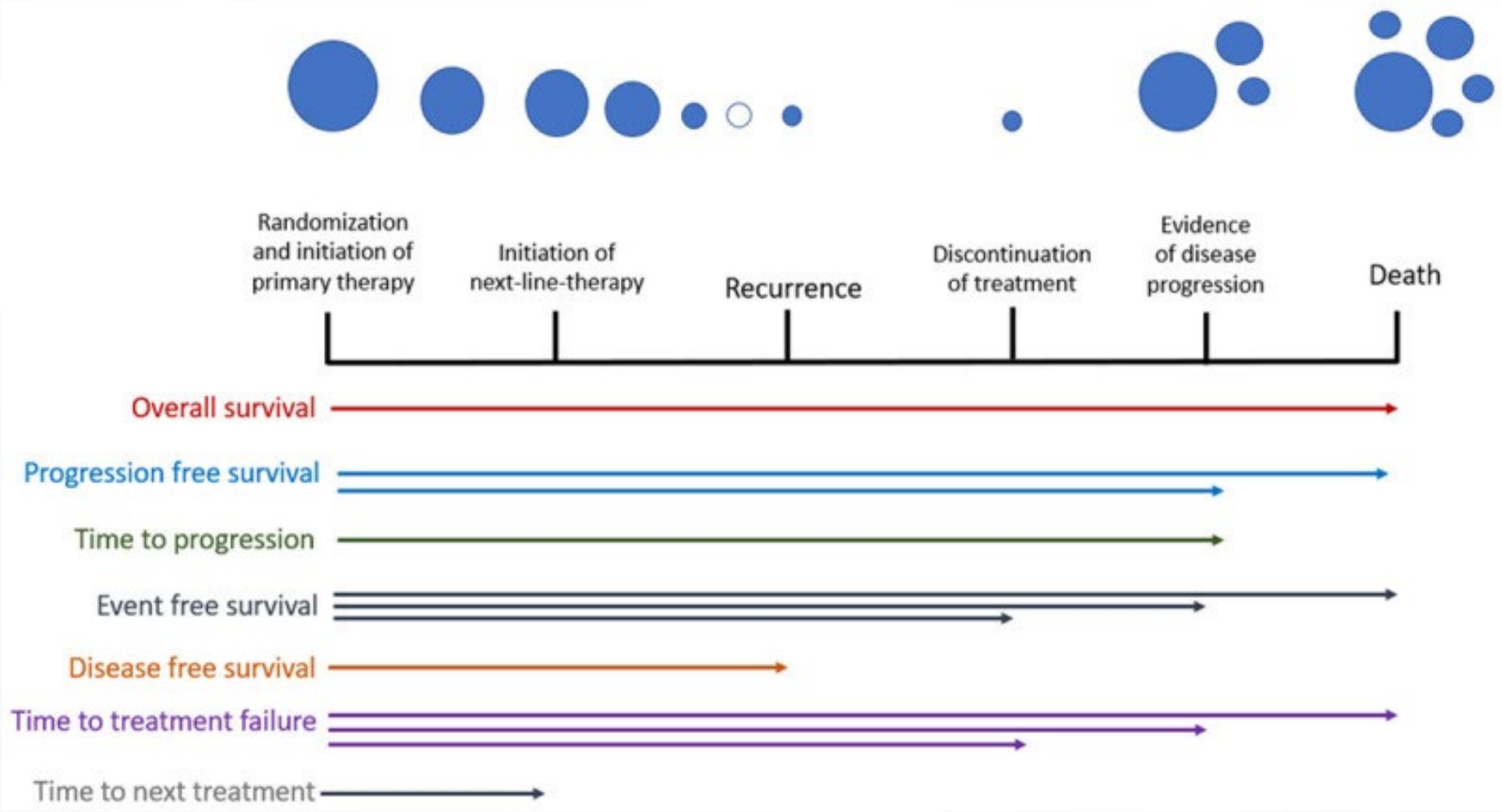


ALK, anaplastic lymphoma kinase; bid, twice a day; Cmin, minimum plasma concentration; NSCLC, non-small cell lung cancer; PFS, progression-free survival.
Groenland SL, et al. *Clin Pharmacol Ther*. 2021;109(2):394-402.

AXIS Medical Education

Addressing the Absence of Mature OS Data for Targeted Therapies in the Adjuvant Setting

Endpoints Used in Oncology Clinical Trials



Delgado A, Guddati AK. *Am J Cancer Res*. 2021;11(4):1121-1131.

Issues with Endpoints in the Adjuvant Setting

- Treatment is “blind” – no visible tumor – only micro-metastatic disease
- Risk of micro-metastatic disease varies
- Patients may be cured with surgery alone or recur
- despite treatment

- Potential utility of adjuvant therapy is only known at a distant time point
- QoL can be difficult to assess versus a no treatment/ placebo control arm
- Demonstrating an OS benefit takes a much longer time than in the metastatic setting

OS, overall survival; QoL, quality of life.
Mittal A, et al. *eClinicalMedicine.* 2024;76:102824.

Endpoints in Operable NSCLC

- DFS – valid surrogate endpoint for OS in trials of adjuvant chemotherapy[1,2]
- DFS benefit in ADAURA translated to an OS benefit[3]

- Other meaningful endpoints…….
  - CNS DFS (brain mets common in ALK+ NSCLC)
  - PROs (impact of toxicity)
  - Adherence (long duration of therapy)

ALK, anaplastic lymphoma kinase; CNS, central nervous system; DFS, disease-free survival; NSCLC, non-small cell lung cancer; OS, overall survival; PRO, patient-reported outcome.

1. Mauguen A, et al. *Lancet Oncol*. 2013;14(7):619-626. 2. Fiteni F, et al. *Expert Rev Anticancer Ther*. 2017;17(5):447-454. 3. Tsuboi M, et al. *N Engl J Med*. 2023;389(2):137-147.

Will DFS Benefit Drive OS Benefit in ALINA?

ADAURA – DFS Benefit Translated to an OS Benefit

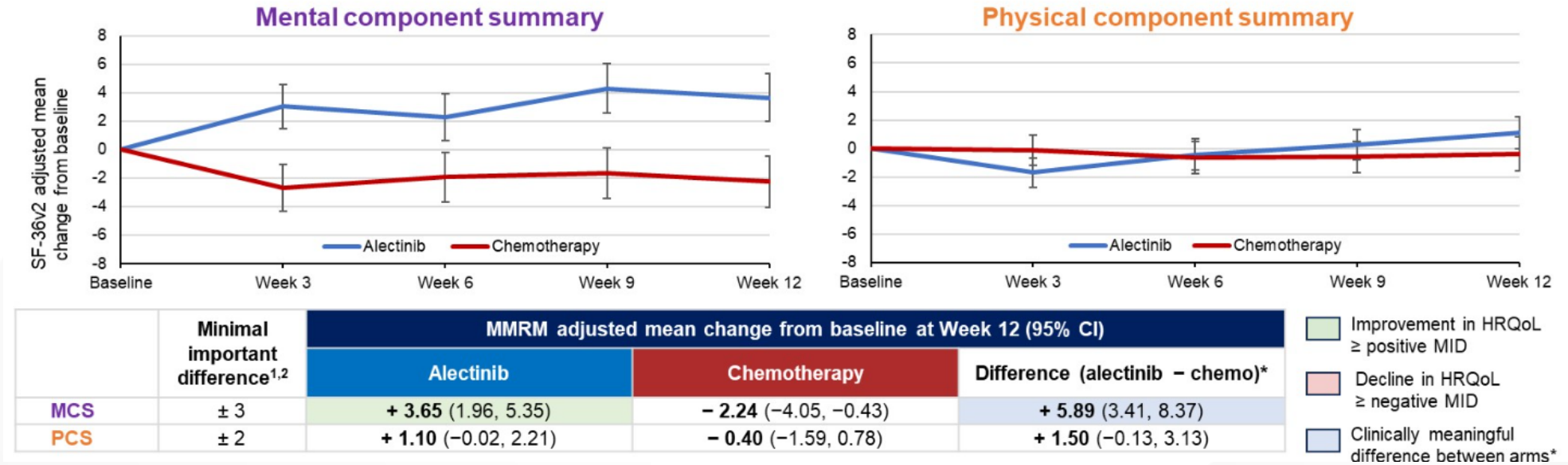
	ADAURA[1,2]	ALINA[3]
DFS HR	**0.17**	**0.24**
OS HR	**0.49 (*P* < 0.001)**	**?**
CNS DFS HR	**0.18**	**0.22**

CNS, central nervous system; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

1. Wu YL, et al. *N Engl J Med.* 2020;383(18):1711-1723. 2. Tsuboi M, et al. *N Engl J Med.* 2023;389(2):137-47. 3. Wu YL, et al. *N Engl J Med*. 2024;390(14):1265-1276.

ALINA: HRQoL Results

Adjusted mean change from baseline in MCS and PCS to week 12



	Minimal important difference[1,2]	MMRM adjusted mean change from baseline at Week 12 (95% CI)		
		Alectinib	Chemotherapy	Difference (alectinib − chemo)*
MCS	± 3	**+ 3.65** (1.96, 5.35)	**− 2.24** (−4.05, −0.43)	**+ 5.89** (3.41, 8.37)
PCS	± 2	**+ 1.10** (−0.02, 2.21)	**− 0.40** (−1.59, 0.78)	**+ 1.50** (−0.13, 3.13)

Improvement in HRQoL ≥ positive MID

Decline in HRQoL ≥ negative MID

Clinically meaningful difference between arms*

- Within arms, change from baseline for MCS and PCS were compared with the respective MID:
  - For MCS, a clinically meaningful improvement from baseline was seen with alectinib but not chemotherapy
  - PCS scores remained stable
- Clinically meaningful improvements from baseline in MCS were seen for alectinib versus chemotherapy

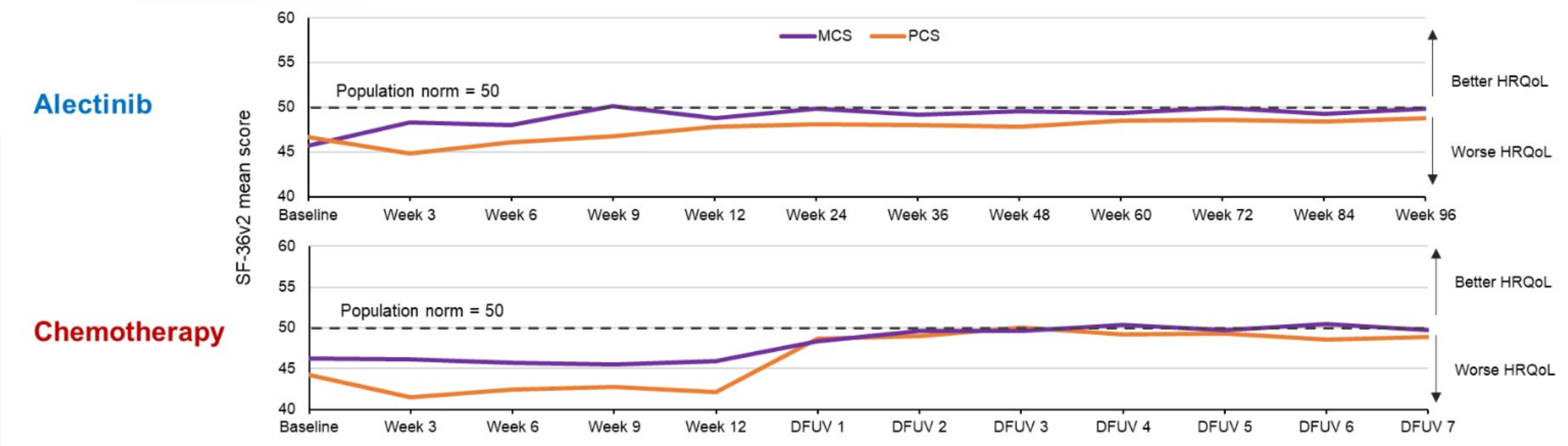
AXIS Medical Education

HRQoL, health-related quality of life; MCS, mental component summary; MID, minimal important difference; MMRM, mixed model repeated measures; PCS, physical component summary.

Nishio M, et al. ASCO 2024. Abstract 8006.

ALINA: Long-Term HRQoL Outcomes

- During active treatment with alectinib, MCS and PCS generally improved through to week 96 and were similar to the general population
- With chemotherapy, MCS and PCS improved after treatment was completed
- Similar trends were observed across health domains



HRQoL, health-related quality of life; MCS, mental component summary; PCS, physical component summary.

Nishio M, et al. ASCO 2024. Abstract 8006.

Case-Based Learning Lab

Case Study Description

- Mr. Anderson, a 55-year-old male, never smoker, presented with a persistent cough
- CXR – 4.5 cm RUL mass
- Chest CT – 4.3 cm RUL mass – no mediastinal adenopathy
- PET – Hypermetabolism noted in RUL mass (SUV 15) – no evidence of hypermetabolic adenopathy – no distant metastases
- EBUS – negative R2, R4 and station 7 FNAs – RUL bx positive for adenocarcinoma
- Brain MRI – negative
- Robotic RUL lobectomy and MLND – T2bN1 adenocarcinoma (1+ N1 node) – Stage IIB
- NGS – EML4-ALK fusion

AXIS Medical Education

ALK, anaplastic lymphoma kinase; CT, computed tomography; CXR, chest x-ray; EBUS, endobronchial ultrasound; EML4, echinoderm microtubule-associated protein-like 4; FNA, fine needle aspiration; MLND, mediastinal lymph node dissection; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PET, positron emission tomography; RUL, right upper lobe; SUV, standardized uptake value.

Case Study Audience Question

What would you recommend?

a) Alectinib
b) Brigatinib
c) Lorlatinib
d) Platinum + pemetrexed for 4 cycles
e) Unsure

Case Study Continuation

- Mr. Anderson starts on adjuvant alectinib 4 weeks after his surgical resection
- One month later he notes some mild constipation
- Physical exam identified asymptomatic bradycardia
- Routine laboratory studies show grade 1 AST/ALT elevations
- CBC and other chemistries including bilirubin are normal

ALT, alanine transaminase; AST, aspartate transaminase; CBC, complete blood count.

Case Study Audience Question

How would you manage his asymptomatic bradycardia?

a) Continue alectinib with a reduced dose
b) Continue alectinib with the same dose
c) Withhold alectinib until bradycardia is resolved
d) Permanently discontinue alectinib
e) Unsure

Conclusion

Key Takeaways

- Targeted therapies are now standard of care in molecularly defined subsets of early stage, resectable NSCLC
- Molecular profiling, ideally NGS, should be performed in early-stage NSCLC
- Adjuvant alectinib improves DFS and CNS DFS in stage IB-IIIA ALK-fusion positive resected NSCLC
  - DFS is a valid surrogate endpoint for OS in the adjuvant setting of NSCLC
- Strategies to ensure adherence should be prioritized
- Side effect profile of alectinib in the post-surgical setting is manageable

AXIS Medical Education

ALK, anaplastic lymphoma kinase; CNS, central nervous system; DFS, disease-free survival; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OS, overall survival.

AXIS Medical Education

Advancing ALK Inhibition Into Early-Stage NSCLC:

Integrating Biomarker-Driven Therapies to Reduce Recurrence Risk Post Resection