| | | | |
|---|---|---|---|
| **Patient Name:** | Dummy | **Booking ID:** | XXXXXXX |
| **Age:** | 31 Years | **Sample Type:** | FFPE Tissue Block |
| **Gender:** | Male | **Sample collection date:** | 25-06-2024 |
| **Referring doctor:** | XXXXXXXX | **Sample receiving date:** | 26-06-2024 |
| **Test Requested:** | Lung Cancer Advanced Panel by NGS (DNA+RNA) | **Reporting date:** | 08-07-2024 |

# LUNG CANCER ADVANCED PANEL REPORT BY NGS

## CLINICAL INDICATION

Diagnosis: c/o Non-small cell lung cancer left upper lobe ling inferior lingular segment with left hilar metastatic nodes (Tumor content was 90%, test performed on FFPE Block ID 1181 B8).

## TEST RESULT SUMMARY

**(Clinically actionable gene fusion were detected in *EML4::ALK* fusion)**

## SUMMARY OF VARIANTS

**SNVs/InDels Table**

| Genes & transcript | Variants | Exon & Locus | Overall coverage & Allele frequency | Function of gene in cancer | *Tier Classification |
|---|---|---|---|---|---|
| None | | | | | |

**Fusions gene Table :**

| Genes/ transcript | Breakpoints/variants | Locus & Exon | Read counts & Function of gene in this cancer | *Tier Classification |
|---|---|---|---|---|
| *EML4::ALK* fusion | EML4-ALK.E13A20.COSF408.1 | chr2:42522656 - chr2:29446394 | 21924/53871.954591 Gain-of-Function | Tier: IA |
| *EML4::ALK* fusion | EML4-ALK.E13ins90A20 | chr2:42522656 - chr2:29446484 | 24/58.97313 Gain-of-Function | Tier: IA |

***Tier Reference:** Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Reviewed by Imran Haider
Senior Scientific Officer
Onco-Genomics

Approved by
Dr. Himani Pandey
Postdoc-SGPGIMS Lucknow
Lab Head-Clinical Genomics

## Variant description & clinical interpretation:

**Potential relevance of EML4::ALK fusion:** The first generation small molecule tyrosine kinase inhibitor (TKI), crizotinib10, was FDA approved (2011) for the treatment of ALK positive advanced NSCLC as well as ALK positive ALCL or inflammatory myofibroblastic tumor (IMT). Kinase domain mutations including L1196M, G1269A, F1174L, G1202R, as well as other variants have been shown to confer acquired resistance to crizotinib in ALK positive NSCLC11,12,13,14.
Other mechanisms of acquired resistance involve amplification of the ALK fusion gene and activation of alternate or bypass signaling pathways involving EGFR, KIT, MET, and IGF1R15. In order to overcome acquired resistance, second and third-generation ALK inhibitors including ceritinib16 (2014), alectinib17 (2015), brigatinib18 (2017), and lorlatinib19 (2018) were developed and approved by the FDA. Two phase III trials evaluating crizotinib and alectinib as first line therapy in NSCLC, including patients with asymptomatic central nervous system (CNS) disease, were conducted and both studies showed consistent higher objective response rates (ORR) with alectinib relative to crizotinib20,21. For this reason, alectinib is a preferred first-line treatment of ALK positive NSCLC22.

## COMMENT

- ✓ Please correlate clinically.
- ✓ Genetic counseling for accurate interpretation of test results is recommended.
- ✓ Correlation of the genetic findings with the clinical condition of the patient is required to arrive at an accurate diagnosis, prognosis or therapeutic decisions.
- ✓ We recommend the confirming of above variants by an alternate method i.e. Sanger sequencing technique/MLPA
- ✓ For questions about this report, or for assistance in locating nearby genetic counseling services, please contact the Laboratory: geneticcounselors@redcliffelabs.com, ccsupport@redcliffelabs.com.

## METHODOLOGY & VARIANT ANALYSIS

**Methodology:** Next Generation Sequencing: The clinically relevant genes have been selected on the basis of their known impact as actionable targets of existing and emerging anti-cancer therapies, and prognostic features in various tumor types. The sensitivity of the assays depends on the quality of the FFPE tissue block/slide, and its tumor percentage (>10-15%). In the multiple validation studies, the limit of detection (LOD) were observed at 5% with depth >500x. In process quality controls were determined for prepared library. The libraries were sequenced at range mean depth: >500-1500x on Ion Torrent next generation sequencing platform. Reference sequence to the GRCh37 (hg19) assembly of the human genome were used. Genomic DNA and RNA were isolated from FFPE tissue block sample using commercial kit according to manufacturer's instructions and the target regions of interest were amplified using the targeted gene panel. Library preparation was performed and sequenced on the Ion Torrent Gene Studio S5 plus sequencer. The FASTQ/BAM file reads were aligned against the hg19 in the Torrent suite software (v5.18.1). Variant calling and annotations were done using Variant Annotator v3.3. AMP-ASCO-CAP guidelines were followed for variant classification. Clinically relevant mutations/fusions were annotated using published variants in literature and a set of databases. The effect of non-synonymous variant is calculated using multiple prediction algorithms such as PolyPhen, SIFT, Mutation Taster2.
**Tools and Databases employed for analysis:** COSMIC, HGMD, UCSC genome browser, Uniprot, Ensembl, dbSNP, gnomAD, ExAC, Pubmed, Dgap, icgc, Kaviar, Delly various bioinformatics analysis, predictive tools and disease specific databases used as available and appropriate. Such tools/databases would be mentioned wherever used.

## TEST LIMITATIONS

- ✓ It should be noted that this test is limited to a limited number of genes and does not include all intronic and non-coding regions.
- ✓ This report only includes variants that meets a level of evidence threshold for cause or contribute to disease. Test results are interpreted in the context of clinical & pathological findings and laboratory data.
- ✓ The accuracy and completeness may vary due to variable information available in different databases. Synonymous mutations were not considered while preparing this report.
- ✓ Variant with minimum or more as 500x are considered for clinical correlation with the disease. Only mutations having VAF >5% will be reported. PCR primer binding site polymorphisms or mutations might lead to allele dropout & cause false negative results.

- ✓ Mutations in under-performing amplicon (<100x coverage) may be missed. Fusions having deep intronic breakpoints might be missed. Indel exceeding 50 bp size may not be detected.
- ✓ The variants have not been confirmed using Sanger sequencing and/or alternate technologies. To rule out germ line mutations i.e. variant with variant allele frequency at nearly 50% or 100%, whole blood sample is recommended to process along with tissue sample.
- ✓ The sensitivity of this assay to detect small deletions/duplication is upto certain number of bases only. CNVs if detected with this assay have to be confirmed by alternate method such as MLPA & Micro-array.
- ✓ Variations with high minor allele frequencies which are benign/likely benign will be given upon request if required. Certain genes may not be covered completely, and few mutations could be missed.
- ✓ Due to inherent technology limitations, coverage is not uniform across all regions. Hence, pathogenic variants present in areas of insufficient coverage as well as those variants which currently do not correlate with the provided phenotype may not be analyzed/ reported. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity.
- ✓ This assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements. Incidental or secondary findings (if any) that meet the ACMG/AMP-ASCO-CAP guidelines can be given upon request.
- ✓ Genes with pseudo-genes, para-log genes and genes with low complexity may have decreased sensitivity and specificity of variant detection and interpretation due to inability of the data and analysis tools to unambiguously determine the origin of the sequence data in such regions. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS).
- ✓ All laboratory tests are associated with an error rate of ~1%. These could be due to sample mismatch, inappropriate labeling, processing or technological limitations. Please correlate with clinical features and other investigations for final conclusion and send a repeat sample for analysis if necessary.
- ✓ The transcript used for clinical reporting generally represents the canonical transcript, which is usually the longest coding transcript with strong/multiple supporting evidence. However, clinically relevant variants annotated in alternate complete coding transcripts could also be reported.

**DISCLAIMER**

- ❖ Test has been performed assuming that the sample received belongs to the above-named individual(s) and that any stated relationships between individuals are accepted as true. It is also assumed that consent for the same was provided after pre- test counseling at the point of collection/referral.
- ❖ The results should be interpreted in the context of the patient's medical evaluation, family history and racial/ethnic background. Please note that variant classification and/or interpretation may change over time if more information available. Re-interpretation of multi gene next generation sequencing data is recommended on an annual basis and may be requested by a medical provider.
- ❖ More evidence for disease association of genes and causal pathogenic variants are discovered every year, and it is recommended that genetic variants are re-interpreted with updated software and annotations periodically.
- ❖ Rare polymorphisms may lead to false negative or positive results. False negative results may be due to sampling error/errors in sample handling as well as clonal density below the limit of detection. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. Identification of a mutation in one or more of these genes does not guarantee activity of the drug in a given indication due to the presence of contraindicated mutation in the gene not covered by the panel.
- ❖ The information provided should only be utilized as a guide or aid and the decision to select any therapy option based on the information reported here resides solely with the discretion of the treating physician.
- ❖ Patient care and treatment decisions should only be made by the physician after taking into account all relevant information available including but not limited to the patient's condition, family history, findings upon examination, results of other diagnostic tests, and the current standards of care.
- ❖ This report should only be used as an aid and the physician should employ sound clinical judgment in arriving at any decision for patient care or treatment.

- By providing drug information for the reported diagnosis, Redcliffe Lab Pvt. Ltd. is not guaranteeing that any drug or clinical trial is necessarily appropriate for this patient.
- Healthcare providers should evaluate and interpret the information provided in this report, along with all other available clinical information about this patient, to determine the best treatment decisions in their own independent medical judgment. Patient management decisions should not be based on a single test, including this one, nor solely on the information contained in this report.

## LIST OF GENES ASSAYED

- **Genes Assayed for the Detection of DNA Sequence Variants**
  AKT1, ALK, AR, BRAF, CDK4, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR2, FGFR3, GNA11, GNAQ, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, PDGFRA, PIK3CA, RAF1, RET, ROS1, SMO
- **Genes Assayed for the Detection of Copy Number Variations**
  ALK, AR, BRAF, CCND1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FGFR4, KIT, KRAS, MET, MYC, MYCN, PDGFRA, PIK3CA
- **Genes Assayed for the Detection of Fusions**
  ALK, RET, ROS1, NTRK1, NTRK2, NTRK3, FGFR1, FGFR2, FGFR3, MET, BRAF, RAF1, ERG, ETV1, ETV4, ETV5, ABL1, AKT3, AXL, EGFR, ERBB2, PDGFRA, PPARG

## VARIANT REPORTING CLASSIFICATION BASED ON AMP-ASCO-CAP RECOMMENDATIONS

| **Variants** | **A change in a gene. This could be disease causing (pathogenic) or not disease causing(benign).** |
|---|---|
| **Tier I** | ***Variants with Strong Clinical Significance (Level A and B Evidence)***<br>**Level A**, biomarkers that predict response or resistance to US FDA-approved therapies for a specific type of tumor or have been included in professional guidelines as therapeutic, diagnostic, and/or prognostic biomarkers for specific types of tumors;<br>**Level B**, biomarkers that predict response or resistance to a therapy based on well- powered studies with consensus from experts in the field or have diagnostic and/or prognostic significance of certain diseases based on well-powered studies with expert consensus. |
| **Tier II** | ***Variants with Potential Clinical Significance (Level C and D Evidence)***<br>**Level C**, biomarkers that predict response or resistance to therapies approved by FDA or professional societies for a different tumor type (i.e., off-label use of a drug), serve as inclusion criteria for clinical trials, or have diagnostic and/or prognostic significance based on the results of multiple small studies. **Level D**, biomarkers that show plausible therapeutic significance based on preclinical studies or may assist disease diagnosis and/or prognosis themselves or along with other biomarkers based on small studies or multiple case reports with no consensus. |
| **Tier III** | ***Variants of Unknown Significance***<br>Not observed at a significant allele frequency in the general or specific sub population or pan cancer or tumor specific variant databases. No convincing published evidence of Cancer Association |
| **Tier IV** | ***Benign or Likely Benign*** |

## REFERENCES


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- Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
- 1000 Genomes Project Consortium et al., A global reference for human genetic variation. Nature, 526(7571): 68-74, 2015.
- Lek M. et al., Analysis of protein-coding genetic variation in 60,706 humans. Nature, 536(7616):285-91, 2016.
- McLaren, W., et al., Deriving the consequences of genomic variants with the Ensembl API and SNP Effect Predictor. Bioinformatics, 2010. 26(16): p. 2069-70.
- Schwarz JM, Cooper DN, Schuelke M and Seelow D. Mutationtaster2: mutation prediction for the deep- sequencing age. NatureMethods.2014; 11: 361-62.
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- Landrum et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018 Jan 4;46(D1):D1062-D1067. PMID: 29165669


**---------- End Of Report ---------**

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## Additional report for reference

## Sample Cancer Type: Non-Small Cell Lung Cancer

## Relevant Biomarkers

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

| Tier | Genomic Alteration | FDA | NCCN | EMA | ESMO | Clinical Trials |
|---|---|---|---|---|---|---|
| IA | *EML4::ALK fusion*<br>echinoderm microtubule associated protein like 4 - ALK receptor tyrosine kinase<br>Locus: chr2:42522656 - chr2:29446394 | ◑ (5) | ◑ (5) | ● (5) | ● (6) | ● (33) |

**FDA:** United States-Food and Drug Administration, **NCCN:** United States-National Comprehensive Cancer Network, **EMA:** European Medicine Agency, **ESMO:** European Society for Medical Oncology. Numbers in parentheses indicate the number of relevant therapies with evidence.
**Tier Reference:** Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

## Relevant Non-Small Cell Lung Cancer Findings

| Gene | Finding | Gene | Finding |
|---|---|---|---|
| ALK | ***EML4::ALK fusion*** | NTRK1 | None detected |
| BRAF | None detected | NTRK2 | None detected |
| EGFR | None detected | NTRK3 | None detected |
| ERBB2 | None detected | RET | None detected |
| KRAS | None detected | ROS1 | None detected |
| MET | None detected | | |

## Biomarker Descriptions

**EML4::ALK fusion**

*ALK receptor tyrosine kinase, echinoderm microtubule associated protein like 4*

Background: The ALK gene encodes the ALK receptor tyrosine kinase (RTK) with sequence similarity to the insulin receptor subfamily of kinases[1]. ALK is the target of recurrent alterations in cancer, the most common being chromosomal rearrangements that generate fusion genes containing the intact ALK tyrosine kinase domain combined with multiple partner genes[2]. ALK fusion kinases are constitutively activated and drive oncogenic transformation via activation of downstream STAT3, PI3K/AKT/MTOR, and RAS/RAF/MEK/ERK pathways[2,3,4,5].

Alterations and prevalence: ALK was discovered by positional cloning of translocations involving nucleophosmin (NPM) on 5q35 with a previously unidentified RTK on 2p23 (ALK), which occur in over 50% of anaplastic large cell lymphoma cases (ALCL)[1,6]. In contrast, about 5% of non-small cell lung cancer (NSCLC) cases generate recurrent ALK fusions with EML4, KIF5B, and HIP1[7,8,9].

Potential relevance: The first generation small molecule tyrosine kinase inhibitor (TKI), crizotinib[10], was FDA approved (2011) for the treatment of ALK positive advanced NSCLC as well as ALK positive ALCL or inflammatory myofibroblastic tumor (IMT). Kinase domain mutations including L1196M, G1269A, F1174L, G1202R, as well as other variants have been shown to confer acquired resistance

## Biomarker Descriptions (continued)

to crizotinib in ALK positive NSCLC[11,12,13,14]. Other mechanisms of acquired resistance involve amplification of the ALK fusion gene and activation of alternate or bypass signaling pathways involving EGFR, KIT, MET, and IGF1R[15]. In order to overcome acquired resistance, second and third-generation ALK inhibitors including ceritinib[16] (2014), alectinib[17] (2015), brigatinib[18] (2017), and lorlatinib[19] (2018) were developed and approved by the FDA. Two phase III trials evaluating crizotinib and alectinib as first line therapy in NSCLC, including patients with asymptomatic central nervous system (CNS) disease, were conducted and both studies showed consistent higher objective response rates (ORR) with alectinib relative to crizotinib[20,21]. For this reason, alectinib is a preferred first-line treatment of ALK positive NSCLC[22].

## Variant Details

### Gene Fusions

| Genes | Variant ID | Locus |
|---|---|---|
| EML4::ALK | EML4-ALK.E13A20.COSF408.1 | chr2:42522656 - chr2:29446394 |
| EML4::ALK | EML4-ALK.E13ins90A20 | chr2:42522656 - chr2:29446484 |

## Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

### EML4::ALK fusion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| crizotinib | ◑ | ◑ | ● | ● | ● (III) |
| alectinib | ● | ◑ | ● | ● | ● (IV) |
| ceritinib | ● | ◑ | ● | ● | ● (IV) |
| lorlatinib | ● | ◑ | ● | ● | ● (IV) |
| brigatinib | ● | ◑ | ● | ● | ● (II) |
| atezolizumab + bevacizumab + carboplatin + paclitaxel | ✖ | ✖ | ✖ | ● | ✖ |
| ensartinib | ✖ | ✖ | ✖ | ✖ | ● (IV) |
| alectinib, durvalumab | ✖ | ✖ | ✖ | ✖ | ● (III) |
| furetinib, crizotinib | ✖ | ✖ | ✖ | ✖ | ● (III) |
| sacituzumab tirumotecan | ✖ | ✖ | ✖ | ✖ | ● (III) |
| targeted therapy | ✖ | ✖ | ✖ | ✖ | ● (III) |
| TGRX-326, crizotinib | ✖ | ✖ | ✖ | ✖ | ● (III) |
| alectinib, crizotinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| brigatinib, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| chemotherapy, lorlatinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| IBI323, bevacizumab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

### EML4::ALK fusion (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| TGRX-326 | ✖ | ✖ | ✖ | ✖ | ● (II) |
| alectinib, radiation therapy | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| amivantamab, alectinib, brigatinib, lorlatinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| CBT-502, catequentinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| chemotherapy, cetuximab, natural killer cell therapy | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| DAJH-1050766 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| furetinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| HS-301 (Hanhui Pharmaceutical) | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| NVL-655 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| ramucirumab, lorlatinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| repotrectinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| SY-3505 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| APG-2449 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| gilteritinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| IBI-318, lenvatinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| IBI-363, IBI-325, lenvatinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| LZ-001 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| talazoparib, crizotinib | ✖ | ✖ | ✖ | ✖ | ● (I) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

# Relevant Therapy Details

## Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

FDA information is current as of 2024-05-15. For the most up-to-date information, search www.fda.gov.

## EML4::ALK fusion

### ◑ crizotinib

**Cancer type:** Inflammatory Myofibroblastic Tumor, Non-Small Cell Lung Cancer
**Label as of:** 2023-09-07
**Variant class:** ALK fusion

**Indications and usage:**

XALKORI® is a kinase inhibitor indicated for the treatment of

- adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test.
- pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.
  - Limitations of Use: The safety and efficacy of XALKORI® have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL.
- adult and pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202570s036lbl.pdf

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### ● alectinib

**Cancer type:** Non-Small Cell Lung Cancer
**Label as of:** 2024-04-18
**Variant class:** ALK fusion or ALK overexpression

**Indications and usage:**

ALECENSA® is a kinase inhibitor indicated for:

- adjuvant treatment in adult patients following tumor resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumors ≥ 4 cm or node positive) as detected by an FDA-approved test.
- treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208434s015lbl.pdf

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### ● brigatinib

**Cancer type:** Non-Small Cell Lung Cancer
**Label as of:** 2022-02-28
**Variant class:** ALK fusion

**Indications and usage:**

ALUNBRIG® is a kinase inhibitor indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208772s013lbl.pdf

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## EML4::ALK fusion (continued)

### ceritinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2021-10-07 **Variant class:** ALK fusion or ALK overexpression

**Indications and usage:**

ZYKADIA® is a kinase inhibitor indicated for the treatment of adults with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211225s004lbl.pdf

### lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2021-03-03 **Variant class:** ALK fusion or ALK overexpression

**Indications and usage:**

LORBRENA® is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210868s004lbl.pdf

## Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2024-05-01. To view the most recent and complete version of the guideline, go online to NCCN.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.



## EML4::ALK fusion

### ● alectinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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### ● alectinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Stage IIA, Stage IB , Stage IIIA, Stage IIIB (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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### ● brigatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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## EML4::ALK fusion (continued)

### ceritinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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### crizotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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### lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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### alectinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

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## EML4::ALK fusion (continued)

### alectinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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### brigatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

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### brigatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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### ceritinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

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## EML4::ALK fusion (continued)

### ceritinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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### crizotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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### lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

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### lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2024]

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## EML4::ALK fusion (continued)

### crizotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

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### alectinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

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### lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

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### alectinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2024]

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### alectinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 2.2024]

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## EML4::ALK fusion (continued)

### brigatinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2024]

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### brigatinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 2.2024]

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### ceritinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2024]

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### ceritinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 2.2024]

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### crizotinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2024]

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## EML4::ALK fusion (continued)

### crizotinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 2.2024]

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### lorlatinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2024]

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### lorlatinib

**Cancer type:** Inflammatory Myofibroblastic Tumor **Variant class:** ALK fusion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Recurrent, Metastatic (First-line therapy, Second-line therapy, Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 2.2024]

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## Current EMA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

EMA information is current as of 2024-05-15. For the most up-to-date information, search www.ema.europa.eu.

## EML4::ALK fusion

### ● alectinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2023-03-29 **Variant class:** ALK fusion or ALK overexpression

**Reference:**
https://www.ema.europa.eu/en/documents/product-information/alecensa-epar-product-information_en.pdf

### ● brigatinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2023-09-22 **Variant class:** ALK fusion

**Reference:**
https://www.ema.europa.eu/en/documents/product-information/alunbrig-epar-product-information_en.pdf

### ● crizotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-12-02 **Variant class:** ALK fusion

**Reference:**
https://www.ema.europa.eu/en/documents/product-information/xalkori-epar-product-information_en.pdf

### ● ceritinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-02-25 **Variant class:** ALK positive

**Reference:**
https://www.ema.europa.eu/en/documents/product-information/zykadia-epar-product-information_en.pdf

### ● lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2023-04-18 **Variant class:** ALK positive

**Reference:**
https://www.ema.europa.eu/en/documents/product-information/lorviqua-epar-product-information_en.pdf

## Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2024-05-01. For the most up-to-date information, search www.esmo.org.

## EML4::ALK fusion

### ● alectinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 4
- Stage IV; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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### ● brigatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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### ● ceritinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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### ● lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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## EML4::ALK fusion (continued)

### ceritinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**ESMO Level of Evidence/Grade of Recommendation:** I / B

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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### crizotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**ESMO Level of Evidence/Grade of Recommendation:** I / B

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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### brigatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**ESMO Level of Evidence/Grade of Recommendation:** III / A

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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### lorlatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**ESMO Level of Evidence/Grade of Recommendation:** III / A

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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## EML4::ALK fusion (continued)

### atezolizumab + bevacizumab + carboplatin + paclitaxel

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** ALK fusion

**ESMO Level of Evidence/Grade of Recommendation:** III / B

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 3

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

# Clinical Trials Summary

## EML4::ALK fusion

| NCT ID | Title | Phase |
|---|---|---|
| NCT02201992 | A Randomized Phase III Trial for Surgically Resected Early Stage Non-small Cell Lung Cancer: Crizotinib Versus Observation for Patients With Tumors Harboring the Anaplastic Lymphoma Kinase (ALK) Fusion Protein | III |
| NCT05525338 | Standard Dosed Alectinib Versus Therapeutic Drug Monitoring Guided Alectinib Dosing | IV |
| NCT05498064 | A Real World Study of Ensartinib in Advanced ALK-positive Non-small Cell Lung Cancer (NSCLC) | IV |
| NCT05170204 | A Phase I-III, Multicenter Study Evaluating the Efficacy and Safety of Multiple Therapies in Cohorts of Patients Selected According to Biomarker Status, With Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer | III |
| NCT06074588 | A Randomized, Open-label, Phase III Study of MK-2870 vs Chemotherapy (Docetaxel or Pemetrexed) in Previously Treated Advanced or Metastatic Nonsquamous Non-small Cell Lung Cancer (NSCLC) With EGFR Mutations or Other Genomic Alterations | III |
| NCT05522660 | A Multicentre Randomised Open-label Phase III Study of Stereotactic Radiosurgery, in Addition to Standard Systemic Therapy for Patients With Metastatic Melanoma or Newly Diagnosed Metastatic NSCLC and Asymptomatic or Oligo-symptomatic Brain Metastases | III |
| No NCT ID | A Single arm, Open Label, Phase II Trial Of Tumour Response To Alectinib In Patients With Advanced Tumours Harbouring ALK Gene Alterations Detected By Comprehensive Genomic Profiling | II |
| NCT04302025 | NAUTIKA1: Multicenter, Phase II, Neoadjuvant and Adjuvant Study of Multiple Therapies in Biomarker-Selected Patients With Resectable Stages IB-III Non-Small Cell Lung Cancer | II |
| NCT05718297 | A Multicentre, Randomised, Phase II Trial of Brigatinib Consolidation Versus Observation or Durvalumab in Patients With Unresectable Stage III NSCLC and ALK-rearrangement, After Definitive Chemo-radiotherapy | II |
| No NCT ID | Randomized, Open Label Phase II Study Of Brigatinib, Carboplatin Plus Pemetrexed And Brigatinib For Chemotherapy-Naive Patients With ALK-Rearranged Non-Squamous Non-Small Cell Lung Cancer (WJOG14720L) | II |
| NCT05200481 | A Phase II Randomized, Open-Labelled, Multicenter Study of Safety and Efficacy of Combination Brigatinib and Carboplatin-Pemetrexed Therapy or Brigatinib Monotherapy as First-Line Treatment in Advanced ALK-Positive Non-Small Cell Lung Cancer | II |
| NCT05178511 | A Prospective, Open Phase II Clinical Study in Patients With alK-positive Non-small Cell Lung Cancer Treated With Ensatinib After Second-generation ALK-TKI Resistance | II |
| NCT05241028 | Adjuvant Therapy of Ensatinib in Patients With Stage IB-IIIA ALK-positive Non-small Cell Lung Cancer: a Prospective, Multi-center, Single-arm Exploratory Study | II |

## Clinical Trials Summary (continued)

### EML4::ALK fusion (continued)

| NCT ID | Title | Phase |
|---|---|---|
| NCT05380024 | A Study of Ensartinib as Neoadjuvant Therapy for Patients With ALK Positive Resectable Non-Small Cell Lung Cancer | II |
| NCT05296278 | Efficacy and Biomarker Explanation of IBI-323 Combined With Bevacizumab Plus Platinum Based Chemotherapy on ALK-Rearranged Non-Small Cell Lung Cancer Who Failed From First Line Alectinib | II |
| NCT05740943 | Induction Lorlatinib for ALK Fusion Locally Advanced Non-small Cell Lung Cancer: A Prospective, Single Arm, Open-label Phase II Study | II |
| NCT06092086 | A Patient-Centric, Open-Label, Multicenter, Phase II Study of Lorlatinib Monotherapy in The First-Line Treatment of Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer | II |
| NCT05713006 | A Phase I/II Open-label Clinical Trial to Evaluate the Pharmacokinetics of Alectinib With Sequential Dose Escalation in Patients Diagnosed With ALK-rearranged Advanced Non-small Cell Lung Cancer. | I/II |
| NCT05724004 | A-SAB - Alectinib Followed by Concomitant Consolidation SBRT/Hypofractionated Radiation Therapy/ SRS in Advanced NSCLC With ALK-rearrangement | I/II |
| NCT05845671 | A Phase I/II , Open Label, Study of Amivantamab (JNJ-61186372) Among Participants With Advanced NSCLC Harboring ALK, ROS1, and RET Gene Fusions in Combination With Tyrosine Kinase Inhibitors | I/II |
| NCT03983928 | A Phase Ib, Open-label, Single Center, Non-randomized Study for Safety and Efficacy of TQB2450 Combined With Anlotinib in Subjects With Advanced Mutation Positive Non-Small Cell Lung Cancer | I/II |
| NCT04237805 | A Phase I/II, Multi-center Clinical Study: Dose-finding Phase I Study of Foritinib Succinate in Advanced ALK-positive NSCLC Patients and Phase II Study of Foritinib Succinate in ALK or ROS1-positive NSCLC Patients | I/II |
| NCT05384626 | A Phase I/II Study of the Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor NVL-655 in Patients With Advanced NSCLC and Other Solid Tumors (ALKOVE-1) | I/II |
| NCT06007937 | A Phase I/II Study of Combination Lorlatinib and Ramucirumab in Patients With Advanced ALK-rearranged Lung Cancers | I/II |
| NCT05257512 | A Phase I/II, Open-label, Multicenter Study of the Safety, Pharmacokinetics, and Antitumor Activity of SY-3505 Capsule in Patients With ALK-positive Advanced Non-small Cell Lung Cancer | I/II |
| NCT03917043 | A Phase I Study of the Safety, Pharmacokinetic and Pharmacodynamic Properties of Orally Administered APG-2449 in Patients With Advanced Solid Tumors | I |
| NCT06225427 | Phase I Study of Gilteritinib for ALK Positive Non-Small Cell Lung Cancer | I |
| NCT04777084 | A Prospective, Multi-cohort Clinical Research of Efficacy and Safety of Bispecific Anti-PD-1 / PD-L1 Antibody IBI318 Combined With Lenvatinib in the Treatment of Advanced NSCLC | I |
| NCT06081907 | A Prospective, Multi-cohort Study on Efficacy and Safety of IBI363 for Advanced Solid Tumors | I |
| NCT05769075 | A Phase I, Multicenter, Open-label Study of TY-2136b, Administered Orally in Patients With Advanced or Metastatic Solid Tumors Harboring ALK, ROS1 or NTRK1-3 Alterations | I |
| No NCT ID | A Multi-Center, Open-Label, Randomized Controlled Phase III Clinical Study: Comparing The Efficacy And Safety Of Foritinib Succinate And Crizotinib In Newly Treated ALK-Positive Advanced Or Metastatic Non-Small Cell Lung Cancer (NSCLC) Patients | III |
| No NCT ID | A Real-world, Open-label, Multi-center, Prospective, Non-interventional (Observational) Study to Evaluate the Effectiveness and Tolerability of Ceritinib in Indian Patients With ALK Positive Metastatic Non-Small Cell Lung Cancer Who Have Progressed or are Intolerant to Crizotinib | IV |
| NCT02584933 | An Open-label, Multi-center, Phase IV Roll-over Study in Patients With ALK Positive Malignancies Who Have Completed a Novartis-sponsored Ceritinib (LDK378) Study and Are Judged by the Investigator to Benefit From Continued Treatment With Ceritinib | IV |

## Clinical Trials Summary (continued)

### EML4::ALK fusion (continued)

| NCT ID | Title | Phase |
|---|---|---|
| NCT05144997 | Lorlatinib (PF-06463922) Continuation Protocol: An Open-Label, Single-Arm Continuation Study For Participants With ALK-Positive or ROS1-Positive Non-Small Cell Lung Cancer (NSCLC) Continuing From Pfizer Sponsored Lorlatinib Clinical Studies | IV |
| NCT06082635 | A Multi-centered, Randomized, Open-label Phase III Study to Evaluate the Efficacy and Safety of TGRX-326 Comparing With Crizotinib in Patients of Advanced ALK-positive or Metastatic Non-Small Cell Lung Cancer | III |
| NCT05015010 | A Phase II, Open-label, Single-arm, Multicenter Study to Assess the Activity and Safety of ALectinib as NEO-Adjuvant Therapy in Patients with Anaplastic Lymphoma Kinase-Positive (ALK+) Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC) | II |
| NCT06378892 | A Multicenter Single-arm Phase II Interventional Study to Evaluate the Activity and Safety of the Combination of Platinum-pemetrexed Based Chemotherapy Plus Lorlatinib in ALK Positive Non-Small Cell Lung Cancer (NSCLC) With Exclusively Extracranial Disease Progression on Lorlatinib. | II |
| NCT05955391 | A Multi-centered, Open-label, Single-arm Phase II Study to Evaluate the Safety and Efficacy of TGRX-326 Monotherapy in Patients of Advanced ALK-positiveNon-Small Cell Lung Cancer Who Failed 2nd-Generation ALK Inhibitor Therapies | II |
| No NCT ID | A Dose-Escalation, Open-Label Phase I/II Clinical Study Of The Safety, Tolerability, Pharmacokinetics And Efficacy Of DAJH-1050766 Tablets In Patients With Advanced Non-Small Cell Lung Cancer | I/II |
| NCT04872634 | A Phase I/IIa, Open, Single-Center Clinical Trial Evaluating the Safety and Anti-Tumor Activity of SNK01 (Natural Killer Cells) Administered in Combination With Gemcitabine/Carboplatin or Gemcitabine/ Carboplatin/Cetuximab to Locally Advanced or Metastatic Non-small Cell Lung Cancer Patients Who Have Failed Prior Tyrosine Kinase Inhibitor (TKI) Therapy (SNK_ASTER) | I/II |
| No NCT ID | Investigator-initiated Clinical Trial of Alectinib in Patients with ALK Positive Rare Cancer | II |
| NCT04116541 | MegaMOST - A Multicenter, Open-label, Biology Driven, Phase II Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations /Characteristics in Advanced / Metastatic Tumors. | II |
| NCT04551521 | Continuous ReAssessment With Flexible ExTension in Rare Malignancies - CRAFT: The NCT-PMO-1602 Phase II Trial | II |
| NCT04423185 | Platform Study of Genotyping Guided Precision Medicine for Rare Tumors in China | II |
| NCT03155620 | NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol | II |
| NCT03213652 | NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)-Phase II Subprotocol of Ensartinib in Patients With Tumors Harboring ALK or ROS1 Genomic Alterations | II |
| NCT04925609 | A Phase I/II Study of Brigatinib in Pediatric and Young Adult Patients With ALK+ Anaplastic Large Cell Lymphoma, Inflammatory Myofibroblastic Tumors or Other Solid Tumors | I/II |
| No NCT ID | A phase I/II clinical study evaluating the safety and efficacy of HS301 in the treatment of NTRK or ROS1 or ALK gene mutation-positive locally advanced or metastatic solid tumors | I/II |
| No NCT ID | A Phase IB study of Crizotinib Either in Combination or as Single Agent in Pediatric Patients with ALK, ROS1 or MET Positive Malignancies | I |
| No NCT ID | Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of LZ001 Monotherapy in Patients with Advanced Solid Tumors Carrying NTRK1/2/3, ROS1 or ALK Gene Fusions | I |
| NCT04693468 | Modular Phase IB Hypothesis-Testing, Biomarker-Driven, Talazoparib Combination Trial (TalaCom) | I |

## Clinical Trials Summary (continued)

### EML4::ALK fusion (continued)

| NCT ID | Title | Phase |
|---|---|---|
| NCT05722886 | DETERMINE (Determining Extended Therapeutic Indications for Existing Drugs in Rare Molecularly Defined Indications Using a National Evaluation Platform Trial): An Umbrella-Basket Platform Trial to Evaluate the Efficacy of Targeted Therapies in Rare Adult, Paediatric and Teenage/Young Adult (TYA) Cancers With Actionable Genomic Alterations, Including Common Cancers With Rare Actionable Alterations | II/III |
| NCT04094610 | A Phase I/II, Open-Label, Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects With Advanced or Metastatic Malignancies Harboring ALK, ROS1, NTRK1-3 Alterations | I/II |

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