Alectinib (Alecensa®) as adjuvant treatment following complete tumour resection for adult patients with ALK-positive non-small cell lung cancer (NSCLC)

General information

Drug description [1]

Alectinib (Alecensa®) is a highly selective and potent ALK rearranged during transfection (RET) tyrosine kinase inhibitor.

Indication [2]

Alectinib (Alecensa®) as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence.

Incidence [3]

In Austria, in 2022, 5,203 persons were newly diagnosed with cancer of the lung, bronchia and trachea. The age-standardised[1] incidence rate was 68.0/100,000 in men and 45.8/100,000 in women.

Current treatment [4]

- Regarding the adjuvant systemic therapy of NSCLC, Onkopedia draws the following conclusions from the results of individual studies, from meta-analyses, and from subgroup analyses:
  - Adjuvant chemotherapy significantly increased 5-year survival rates in patients with stage II-III NSCLC after R0 resection and may also be considered in stage IB (UICC 7th edition) with additional risk factors.
  - The benefit of adjuvant chemotherapy is not limited to specific age groups. However, there are insufficient data for patients >75 years of age.
  - Adjuvant chemotherapy should start 4-8 weeks after surgery. A benefit is only proven if chemotherapy is started within 60 days after surgery.
  - Adjuvant chemotherapy should consist of a cisplatin-containing combination. The efficacy of carboplatin has been prospectively demonstrated in only one study in stage IB (UICC 7th edition).
  - Most data are available for the combination of cisplatin and vinorelbine, given over 4 courses of treatment. Other cisplatin-containing combinations may be chosen depending on comorbidity, side effects, and approval status, e.g., with docetaxel, etoposide, gemcitabine, or pemetrexed.
  - Combining chemotherapy with an anti-angiogenesis inhibitor did not prolong survival or increase survival.
  - Data on the value of immune checkpoint inhibitors in adjuvant systemic therapy are available with the Impower 010 trial using atezolizumab. Here, an improvement in disease-free survival was shown. The approval is limited to patients with a high risk of recurrence after R0 resection, a PD-L1 expression on tumour cells of >50% and an EGFR/ALK WT constellation after adjuvant chemotherapy.

Regulatory status

EMA [2]	FDA [5, 6]
Approval status for this indication: On April 25 2024, the CHMP adopted a positive opinion, recommending a change to the terms of the marketing authorisation for Alecensa®. The CHMP adopted a new indication as follows: ❖ Alecensa® as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence. **Other indications**: ❖ Alecensa® as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC.	**Approval status for this indication**: On April 18, 2024, the FDA approved alectinib (Alecensa®) for adjuvant treatment following tumour resection in patients with ALK-positive NSCLC (tumours ≥ 4 cm or node-positive), as detected by an FDA-approved test. ✓ Priority review ✓ Orphan drug designation

[1] European Standard Population 2013.

❖ Alecensa® as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib. ✓ **Medicine under additional monitoring**	**Other indications**: Alecensa® is indicated for ❖ treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test.

Manufacturer

Alecensa® is manufactured by Roche.

Costs [7]

224 Alecensa® hard capsules 150 mg = € 4,652.88 (ex-factory price)

Posology [1]

❖ A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. ALK-positive NSCLC status should be established prior to initiation of Alecensa® therapy.

Warnings and precautions [1]

❖ **Interstitial lung disease (ILD)/pneumonitis**
- Cases of ILD/pneumonitis have been reported in clinical trials with Alecensa®.
- Patients should be monitored for pulmonary symptoms indicative of pneumonitis.
- Alecensa should be immediately interrupted in patients diagnosed with ILD/pneumonitis and should be permanently discontinued if no other potential causes of ILD/pneumonitis have been identified.

❖ **Hepatotoxicity**
- Elevations in ALT and AST greater than 5 times the ULN as well as bilirubin elevations of more than 3 times the ULN, occurred in patients in pivotal clinical trials with Alecensa®. The majority of these events occurred during the first 3 months of treatment. In the pivotal Alecensa® clinical trials, it was reported that three patients with Grade 3-4 AST/ALT elevations had drug-induced liver injury.
- Concurrent elevations in ALT or AST greater than or equal 3 times the ULN and total bilirubin greater than or equal 2 times the ULN, with normal alkaline phosphatase, occurred in one patient treated in Alecensa® clinical trials.
- Liver function, including ALT, AST, and total bilirubin should be monitored at baseline and then every 2 weeks during the first 3 months of treatment. After that, monitoring should be performed periodically since events may occur later than 3 months, with more frequent testing in patients who develop aminotransferase and bilirubin elevations. Based on the severity of the adverse drug reaction, Alecensa® should be withheld and resumed at a reduced dose or permanently discontinued as described in Product Information.

❖ **Severe myalgia and creatine phosphokinase (CPK) elevation**
- Myalgia or musculoskeletal pain was reported in patients in pivotal trials with Alecensa®, including Grade 3 events.
- Elevations of CPK occurred in pivotal trials with Alecensa®, including Grade 3 events.
- The median time to Grade 3 CPK elevation was 14 days across clinical trials (NP28761, NP28673, BO28984).
- Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be assessed every two weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, Alecensa® should be withheld, then resumed, or the dose reduced.

❖ **Bradycardia**
- Symptomatic bradycardia can occur with Alecensa®. Heart rate and blood pressure should be monitored as clinically indicated. Dose modification is not required in the case of asymptomatic bradycardia.
- If patients experience symptomatic bradycardia or life-threatening events, concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products, should be evaluated and Alecensa® treatment should be adjusted as described in Product Information.

❖ **Haemolytic anaemia**

- Haemolytic anaemia has been reported with Alecensa®. If haemoglobin concentration is below 10 g/dL and haemolytic anaemia is suspected, Alecensa® should be withheld and appropriate laboratory testing should be initiated. If haemolytic anaemia is confirmed, Alecensa® should be resumed at a reduced dose upon resolution as described in Product Information.

❖ **Gastrointestinal perforation**
- Cases of gastrointestinal perforations have been reported in patients at increased risk (e.g., history of diverticulitis, metastases to the gastrointestinal tract, concomitant use of medicinal product with a recognised risk of gastrointestinal perforation) treated with alectinib.
- Discontinuation of Alecensa® in patients who develop gastrointestinal perforation should be considered. Patients should be informed of the signs and symptoms of gastrointestinal perforations and advised to consult rapidly in case of occurrence.

❖ **Photosensitivity**
- Photosensitivity to sunlight has been reported with Alecensa® administration. Patients should be advised to avoid prolonged sun exposure while taking Alecensa®, and for at least 7 days after discontinuation of treatment. Patients should also be advised to use a broad-spectrum Ultraviolet A/ Ultraviolet B sunscreen and lip balm (sun protection factor ≥50) to help protect against potential sunburn.

❖ **Women of child-bearing potential**
- Alecensa® may cause foetal harm when administered to a pregnant woman. Female patients of child-bearing potential receiving Alecensa®, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa®.

❖ **Lactose intolerance**
- This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, a congenital lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

❖ **Sodium content**
- This medicinal product contains 48 mg sodium per daily dose (1200 mg), equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Study characteristics [8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
ALINA NCT03456076	257 (1:1)	oral alectinib (600 mg twice daily) for 24 months	intravenous platinum-based chemotherapy in four 21-day cycles	disease-free survival	27.8 months vs. 28.4 months	**ongoing**[2], global, phase 3, open-label, randomised trial	ALK	F. Hoffmann–La Roche	ALINA trial [11]

Inclusion criteria[3]	Exclusion criteria	Patient characteristics at baseline (I vs. C, n=130 vs. n= 127)
❖ Age ≥ 18 years at the time of signing the Informed Consent Form ❖ Complete resection of histologically confirmed Stage IB (tumour≥ 4 cm) to Stage IIIA (T2-3 N0, T1-3 N1, T1-3 N2, T4 N0-1) NSCLC as per AJCC, 7th edition, with negative margins, at 4-12 weeks before enrolment. • Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy.	❖ Pregnant or breastfeeding, or intending to become pregnant during the study or within 90 days after the last dose of alectinib or according to local label for chemotherapy. ❖ Prior adjuvant radiotherapy for NSCLC. ❖ Radiotherapy in the neo-adjuvant setting is allowed and must be completed at least 4 weeks prior to initiation of study treatment. ❖ Prior exposure to systemic chemotherapy. ❖ Prior exposure to ALK inhibitors.	❖ Median age: 54 vs. 57 years ❖ <65 years: 79.2% vs. 73.2% ❖ ≥65 years: 20.8% vs. 26.8% ❖ Female sex: 57.7% vs. 46.5% ❖ Race[4]: • Asian: 55.4% vs. 55.9% • Black: 0.8% vs. 0% • White: 42.3% vs. 40.9% • Unknown: 1.5% vs. 3.1% ❖ ECOG PS score:

[2] The ALINA trial is currently ongoing; the estimated study completion date is 11/2026.
[3] For detailed in- and exclusion criteria, please see trial protocol.
[4] Of note, Black patients were underrepresented in the trial population.

- Resection by segmentectomy or wedge resection is not allowed.
- N3 disease is not allowed.

❖ Systematic mediastinal lymph node sampling, at a minimum, for patients for whom mediastinoscopy was not performed preoperatively.
- Systematic sampling is defined as removal of at least one representative lymph node at specified levels.
- Complete mediastinal lymph node dissection (MLND) is preferred. MLND entails resection of all lymph nodes at those same levels.
- For patients who have undergone a right thoracotomy, sampling or MLND is required at Levels 4 and 7; for those who have undergone a left thoracotomy, sampling or MLND is required at Levels 5 and/or 6 and 7.
- If the preoperative staging imaging results (contrast CT and PET scans) do not suggest evidence of disease in the mediastinum, the patient may be considered eligible even if the investigator deems N2 nodal sampling unnecessary.

❖ Documented ALK-positive disease according to an FDA-approved test.

❖ Eligible to receive a platinum-based chemotherapy regimen according to the local labels.

❖ ECOG PS of Grade 0 or 1.

❖ Adequate hematologic function, defined by the following laboratory test results, obtained within 3 days prior to initiation of study treatment:
- Platelet count ≥ 100 x 10^9/L
- ANC ≥ 1500/μL
- Haemoglobin ≥ 9 g/dL

❖ Adequate renal function, defined by the following laboratory test results, obtained within 3 days prior to initiation of study treatment:
- Serum creatinine ≥ 1.5 x ULN and CrCl ≥ 60 mL/min

❖ For women of childbearing potential: agreement to remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of alectinib or according to local label for chemotherapy.

❖ Known sensitivity to any component of the study drug (alectinib or planned chemotherapy) to which the patient may be randomised.

❖ Malignancies other than NSCLC within 5 years prior to enrollment, except for curatively treated basal cell carcinoma of the skin, early gastrointestinal GI cancer by endoscopic resection, in situ carcinoma of the cervix, ductal carcinoma in situ, papillary thyroid cancer, or any cured cancer that is considered to have no impact on DFS or OS for the current NSCLC.

❖ Any GI disorder that may affect absorption of oral medications.

❖ Liver disease is characterised by any of the following:
- ALT and AST ≥ 3 x ULN or
- Impaired excretory function or, synthetic function or other conditions of decompensated liver disease or
- Acute viral or active autoimmune, alcoholic, or other types of acute hepatitis.

❖ Japanese patients participating in the serial/intensive PK sample collection only: administration of strong/potent CYP450 3A inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib up to Week 3.

❖ Any exclusion criteria based on the local labels of the chemotherapy regimen.

❖ Patients with symptomatic bradycardia.

❖ History of organ transplant.

❖ Known HIV positivity or AIDS-related illness.

❖ Any clinically significant concomitant disease or condition that could interfere with - or for which the treatment might interfere with - the conduct of the study or the absorption of oral medications or that would pose an unacceptable risk to the patients in this study, in the opinion of the Principal Investigator.

❖ Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures.

- 0: 55.4% vs. 51.2%
- 1: 44.6% vs. 48.8%

❖ Smoking status:
- Never smoked: 64.6% vs. 55.1%
- Previous smoker: 31.5% vs. 42.5%
- Current smoker: 3.8% vs. 2.4%

❖ Disease stage at initial diagnosis:
- IB: 10.8% vs. 9.4%
- II: 36.2% vs. 35.4%
- IIIA: 53.1% vs. 55.1%

❖ Regional lymph-node stage:
- N0: 16.2% vs. 14.2%
- N1: 34.6% vs. 33.9%
- N2: 49.2% vs. 52.0%

❖ Nodal assessment:
- MLND: 83.1% vs. 82.7%
- Lymph-node sampling: 14.6% vs. 11.8%
- MLND and lymph-node sampling not performed: 2.3% vs. 5.5%

❖ Histologic type:
- Squamous: 4.6% vs. 2.4%
- Nonsquamous: 95.4% vs. 97.6%

❖ Surgical procedure for lung cancer:
- Lobectomy: 96.9% vs. 92.1%
- Sleeve lobectomy 0 vs. 0.8%
- Bilobectomy: 1.5% vs. 3.9%
- Pneumonectomy: 1.5% vs. 3.1%

❖ For men: agreement to remain abstinent or use contraceptive measures, and agreement to refrain from donating sperm. ❖ Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures		

Efficacy (I vs. C), interim analysis data	**Safety** (I vs. C, n=128 vs. n=120), interim analysis data
Data-cutoff date: June 26 2023; median duration of follow-up for survival was 27.8 months; median time from surgery to randomisation was 1.7 months **Disease-free survival among patients with stage II or IIIA disease at 2 years**: 93.8% vs. 63.0% **Disease-free survival among patients with stage II or IIIA disease at 3 years**: 88.3% vs. 53.3% **HR for disease recurrence or death**: 0.24 (95% CI, 0.13-0.45; p<0.001) **Disease-free survival in the ITT population[5] at 2 years**: 93.6% vs. 63.7% **Disease-free survival in the ITT population at 3 years**: 88.7% vs. 54.0% **HR for disease recurrence or death**: 0.24 (95% CI, 0.13 to 0.43; p<0.001) **Disease recurrence**: 11.5% vs. 38.6% **HR for CNS disease recurrence or death**: 0.22 (95% CI, 0.08 to 0.58) **OS data:** immature at the data-cutoff date, with a 2.3% event–patient ratio	**Any AE of any grade**: 98.4% vs. 93.3% **Any AE grade 3 or 4**: 29.7% vs. 30.8% **AEs of any grade that were considered by the investigator to be related to treatment**: 93.8% vs. 89.2% **AE of grade 3 or that were considered by the investigator to be related to treatment**: 18.0% vs. 27.5% **Serious AEs**: 13.3% vs. 8.3% **AEs leading to dose discontinuation**: 5.5% vs. 12.5%

Patient-reported outcomes

According to the trial protocol, the evaluation of patient-reported outcomes is planned. To date, results are not available.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	adjuvant	1	-	30.8% (+29.9% in ITT pop.) DFS at 2 years	0.24 (0.13-0.43)	Improvements in DFS alone (HR <0.65) in studies without mature survival data	A	-	-	-	A
Adapted	adjuvant	1	-	30.8% (+29.9% in ITT pop.) DFS at 2 years	0.24 (0.13-0.43)	Improvements in DFS alone (HR <0.65) in studies without mature survival data	A	-	-	-	A

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no high risk	unclear[6] unclear risk	yes[7] high risk	unclear

Ongoing trials [14]

NCT number/trial name	Description	Estimated study completion date
NCT03456076 / ALINA	Please see above.	11/2026

Available assessments

❖ In October 2023, NIHR published a Health Technology Briefing "Alectinib adjuvant therapy for ALK-positive non-small cell lung cancer" [15].

[5] The ITT population included 257 patients: 130 in the alectinib group and 127 in the chemotherapy group.
[6] The ALINA trial is ongoing; currently, only interim analysis data is available.
[7] The sponsor provided the trial drugs, and collaborated with the academic authors on the collection, analysis, and interpretation of the data. Medical writing assistance, under the direction of the authors, was funded by the sponsor.

- No assessments were identified via NICE, CDA-AMC, ICER and G-BA.

Other aspects and conclusions

- In April 2024, the CHMP adopted a new indication for Alecensa® as monotherapy for the adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence. Also, in April 2024, the FDA approved Alecensa® for the adjuvant treatment following tumour resection in patients with ALK-positive NSCLC (tumours ≥ 4 cm or node-positive), as detected by an FDA-approved test.
- **ALINA** (NCT03456076) is an **ongoing**, randomised, open-label, **phase 3 trial** investigating the efficacy and safety of adjuvant alectinib compared to standard chemotherapy in patients with resected ALK-positive NSCLC.
- The primary endpoint was **disease-free survival** among patients with stage II or IIIA disease and in the ITT population. The percentage of patients who were alive and disease-free at 2 years was 93.8% vs. 63.0% in the chemotherapy group among patients with stage II or IIIA disease (HR for disease recurrence or death, 0.24; 95% CI, 0.13-0.45; p<0.001) and 93.6% vs. 63.7%, respectively, in the ITT population (HR, 0.24; 95% CI, 0.13-0.43; p<0.001).
- Evaluating **patient-reported outcomes** is planned; however, no results are available yet.
- The original and adapted ESMO-MCBS were applied, resulting in a magnitude of clinical benefit **grade A** each.
- The **risk of bias was considered unclear** due to the ongoing status of the ALINA trial. However, it is increased by the open-label design and the sponsor's involvement in collecting, analysing, and interpreting trial data.
- Besides the ALINA trial, no further ongoing phase 3 trial assesses the alectinib for the adjuvant treatment following complete tumour resection in patients with NSCLC.
- Final analysis data from the ALINA trial and further robust phase 3 data, including patient-reported outcomes, are required to further assess the efficacy and safety of alectinib as adjuvant therapy in patients with resected ALK-positive NSCLC.

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Abbreviations: AE=adverse event, AIDS=acquired immunodeficiency syndrome, AJ=adjustment, AJCC=American Joint Committee on Cancer ALK=anaplastic lymphoma kinase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, C=comparator, CDA-AMC=Canada's Drug Agency (formerly CADTH), CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPK=creatine phosphokinase, CrCl=Creatinine clearance, CT=computed tomography, DFS=disease-free survival, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GI=gastrointestinal, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, ILD=interstitial lung disease; Int.=intention, ITT=intention-to-treat, MG=median gain, MLND=mediastinal lymph node dissection, n=number of patients, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, OS=overall survival, PE=primary endpoint, PET=positron emission tomography, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RET=rearranged during transfection, SAE=serious adverse event, ST=standard treatment, ULN= upper limit of normal

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