ALK+ Non-Small Cell Lung Cancer
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO002

Description
Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena) are orally administered anaplastic lymphoma kinase positive (ALK+) tyrosine kinase inhibitors (TKI).

Length of Authorization
- Initial: Six months; first three months split fill for lorlatinib (Lorbrena), crizotinib (Xalkori), ceritinib (Zykadia), and brigatinib (Alunbrig).
- Renewal: 12 months
    i. Up to a maximum duration of 2 years for alectinib (Alecensa) for adjuvant treatment of NSCLC

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
crizotinib (Xalkori)	200 mg capsules	ALK+ NSCLC, metastatic; ROS1+ NSCLC, metastatic; ALK+ IMT, unresectable, recurrent, refractory	60 capsules/30 days
	250 mg capsules		60 capsules/30 days
	200 mg capsules	ALK+ systemic ALCL, relapsed/refractory; ALK+ IMT, unresectable, recurrent, refractory	120 capsules/30 days
	250 mg capsules		120 capsules/30 days
alectinib (Alecensa)	150 mg capsules	ALK+ NSCLC, adjuvant treatment, metastatic	240 capsules/30 days
ceritinib (Zykadia)	150 mg capsules	ALK+ NSCLC, metastatic	84 capsules/28 days
	150 mg tablets		84 tablets/28 days
brigatinib (Alunbrig)	30 mg tablets		180 tablets/30 days
	90 mg tablets		30 tablets/30 days
	90 mg and 180 mg tablet titration pack		30 tablets/30 days
	180 mg tablets		30 tablets/30 days
lorlatinib (Lorbrena)	25 mg tablets		90 tablets/30 days
	100 mg tablets		30 tablets/30 days

Initial Evaluation

I. **Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena)** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. The medication will not be used in combination with other agents and will be used as monotherapy for the diagnosis submitted; **AND**
   C. A diagnosis of **Non-Small Cell Lung Cancer (NCSLC); AND**
   D. Meets one of the following:
      1. Request is for the **adjuvant treatment** following complete tumor resection; **AND**
         i. Member has completely resected stage II–IIIA or stage IIIB (T3, N2) NSCLC or tumors are ≥ 4 cm or node positive; **AND**
         ii. Disease is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test; **OR**
      2. Member has **recurrent, advanced or metastatic (stage IV)** disease; **AND**
         i. Disease is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test; **AND**
            a. The request is for alectinib (Alecensa); **AND**
               i. The member has not progressed on any other agent listed in this policy; **OR**
               ii. The member has progressed on or after use of crizotinib (Xalkori); **OR**
            b. The request is for crizotinib (Xalkori); **AND**
               i. The member has not progressed on any other agent listed in this policy; **OR**
            c. The request is for ceritinib (Zykadia); **AND**
               i. The member has not progressed on any other therapy listed in this policy; **OR**
               ii. The member has progressed on crizotinib (Xalkori); **OR**
            d. The request is for brigatinib (Alunbrig); **AND**
               i. The member has not progressed on any other therapy listed in this policy; **OR**
               ii. The member has progressed on crizotinib (Xalkori); **OR**
            e. The request is for lorlatinib (Lorbrena); **OR**
         ii. **Disease is ROS1+ as detected by an FDA-approved test**; **AND**
            a. The request is for crizotinib (Xalkori); **OR**
            b. The request is for ceritinib (Zykadia)

II. Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena) are considered investigational when used for all other conditions, including but not limited to:
   A. ALK+ systemic Anaplastic Large Cell Lymphoma (ALCL) in patients one year of age and older
   B. Inflammatory myofibroblastic tumors (IMT)
   C. NSCLC outside of the ROS1+ or ALK mutation (e.g., RET-rearranged NSCLC)
   D. Erdheim-Chester Disease (ECD) with ALK fusion
   E. Large B-Cell Lymphoma (LBCL)
   F. NSCLC in combination with other therapies
   G. Thyroid cancer
   H. Melanoma
   I. Gastrointestinal cancer
   J. Prostate cancer
   K. Leukemias or lymphomas
   L. Urothelial cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will not be used in combination with another ALK+ or ROS1+ NSCLC drug (e.g. Alectinib (Alecensa), brigatinb (Alunbrig), ceritinib (Zykadia), crizotinib (Xalcori)); **AND**
IV. There is documentation of disease response with treatment, defined by stabilization of disease, decrease in tumor size, or tumor spread.

Supporting Evidence

I. There is currently no evidence for safety and efficacy of any of these agents in combination with another ALK inhibitor, or in combination with any other therapies for the treatment of non-small-cell lung cancer (NSCLC). Any open prior authorizations for other ALK-inhibitors will be closed if coverage is approved for an agent in this policy. These agents have only been studied for the adjuvant treatment, metastatic, and adult populations with NSCLC in clinical trials.
II. Alectinib (Alecensa) is indicated as 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. Alectinib (Alecensa) was evaluated in the international, open-label, phase 3 ALINA trial which assessed the efficacy and safety of 24 months of adjuvant alectinib vs. platinum-based chemotherapy in 257 patients with completely resected stage IB to IIIA ALK-positive NSCLC. The primary endpoint was disease-free

survival (DFS). Patients were randomized to receive oral alectinib (600 mg twice daily) for 24 months or chemotherapy (cisplatin and vinorelbine, gemcitabine, or pemetrexed) for four 21-day cycles. Treatment with alectinib reduced the risk of recurrence or death by 76% (HR, 0.24; 95% CI, 0.13–0.45; P<0.001) compared with adjuvant chemotherapy alone. The alectinib group also had a 78% improvement in central nervous system DFS (HR, 0.22; 95% CI, 0.08–0.58). Alectinib was well tolerated with no new safety signals. Therapy with alectinib (Alecensa) for two years is recommended as a category 1 treatment for patients with completely resected stage and positive for ALK rearrangements.

III. Alectinib (Alecensa) has been evaluated in the first-line setting for metastatic ALK+ NSCLC, or after progression on crizotinib (Xalkori). A class review was done in 2018 which revealed advantages with alectinib (Alecensa) including superior head-to-head progression-free survival (PFS), intracranial response compared to crizotinib, and a more favorable safety profile via indirect comparison. As of September 2024, NCCN guideline for NSCLC list the following as first line therapy for ALK-positive NSCLC when ALK rearrangement is discovered prior to first line systemic therapy (all category 1): alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena) are preferred, ceritinib (Zykadia) is marked as “other recommended treatment,” and crizotinib ((Xalkori) marked useful in certain circumstances for performance status 0-4.

IV. A review of clinical data indicates that all ALK+ tyrosine kinase inhibitors indicated in the first-line treatment setting have comparable evidence with no agent standing out as superior to others (based on efficacy analysis supported by improvement in PFS, comparable toxicity profiles, and no clear survival advantage reported for any of the agents). Alectinib was recommended as the preferred first-line therapy of ALK-positive NSCLC by National Comprehensive Cancer Network (NCCN) NSCLC panel (V9.2024) (based on clinical trial data from ALEX and J-ALEX trials). As of September 2024, this recommendation remains unchanged. Additionally, alectinib (Alecensa) has been evaluated after progression on crizotinib (Xalkori) or lorlatinib (Lorbrena); however, safety and efficacy after progression on ceritinib (Zykadia) and/or brigatinib (Alunbrig) are unknown.

V. Patients typically have disease progression after first-line therapy with alectinib, brigatinib, ceritinib, crizotinib, or lorlatinib; subsequent therapy recommendations are described in the algorithm and often include continuing the first-line targeted therapies, depending on the type of progression. In the second line setting, several agents have been evaluated after progression on crizotinib (Xalkori). Lorlatinib (Lorbrena) is the only agent at this time that has been evaluated in the third line setting following progression on crizotinib (Xalkori) and one other ALK+ TKI for NSCLC.

VI. Lorlatinib (Lorbrena) received its FDA-approval for second or greater line therapy in the metastatic setting of NSCLC. In March 2021, lorlatinib (Lorbrena) received expanded approval in the first-line setting for metastatic ALK+ NSCLC based on the data from a phase 3, open-label, randomized clinical trial (CROWN study). In 296 previously untreated patients with advanced metastatic ALK+ NSCLC, lorlatinib (Lorbrena) showed higher efficacy as compared to crizotinib (Xalkori) based on a 12 month PFS rate of 78% (95% CI; 70, 84) versus that of 39% (95% CI, 30 to 48) in crizotinib arm [HR 0.28; (95% CI, 0.19 to 0.41) *; P*<0.001]. Median PFS for lorlatinib (Lorbrena) was not reached while that for crizotinib (Xalkori) was 9.3 months (95% CI; 7.6, 11.1).

In an updated analysis from the CROWN study, after 5 years of follow-up, lorlatinib continued to show superior efficacy over crizotinib in patients with ALK+ NSCLC, with at a median follow-up of 60.2 months, median PFS was still NR with lorlatinib. Most (76%) PFS events occurred in the first 2 years with lorlatinib in the CROWN study, with only six additional PFS events occurring between 3 years and 5 years. At the time of this analysis in May 2024, the required number of OS events for a protocol-specified second interim analysis was not met. Overall survival (OS) follow-up is currently ongoing in the CROWN study.

VII. ROS1 gene rearrangements occur in an estimated 1% - 2% of patients with NSCLC. The NCCN guidelines recommend crizotinib, entrectinib, or ceritinib as first-line monotherapy options for patients with ROS1+ metastatic NSCLC. Ceritinib (Zykadia) is an "other recommended" first-line therapy option for patients with ROS1+ metastatic NSCLC and provides a cost-effective treatment option. Crizotinib (Xalkori) is currently FDA-approved for ROS1+ NSCLC and ALK+ systemic ALCL.

VIII. Brigatinib (Alunbrig) was evaluated in an open-label, Phase 3, randomized trial against crizotinib (Xalkori) in metastatic ALK+ NSCLC. The study included 275 subjects, and those receiving brigatinib (Alunbrig) had a greater PFS (12-month PFS was 67% versus 43%; HR 0.49, $p<0.001$). The intracranial response was 78% for brigatinib (Alunbrig) and 29% for crizotinib (Xalkori). The data is not considered of high quality due to open label trial design, and lack of clinically significant outcomes such as overall survival and quality of life parameters.

IX. There is currently no evidence that ALK-inhibitors improve clinical outcomes (e.g., overall survival, quality of life) in patients with NSCLC. Quality of life parameter improvements were reported in CROWN study for lorlatinib (Lorbrena). However, this improvement was not clinically significant. Although PFS data is promising, PFS is a surrogate endpoint in NSCLC that has not been correlated with improved outcomes.

X. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

XI. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/CompanionDiagnostics

Investigational or Not Medically Necessary Uses

I. The agents in this policy have not been sufficiently evaluated in the following settings. There may be NCCN recommendations or low-quality data available; however, safety and efficacy have not been established for:
   A. ALK+ systemic Anaplastic Large Cell Lymphoma (ALCL) in patients one year of age and older

i. In January 2021, crizotinib (Xalkori) received expanded approval in patients aged one and older with ALK+ relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) based on a phase 2, open-label, single-arm study in 26 patients aged one to ≤ 21 years with ALK+ ALCL. All enrolled patients were refractory to systemic chemotherapy, two patients were refractory to a monoclonal antibody, and one patient was refractory to brentuximab. Primary outcome studied was objective response rate (ORR), which was 88% [95% CI 71-96]. There were 21 (81%) and 2 (8%) of patients who achieved complete response (CR) and partial response (PR), respectively. The median time to first response was 3.9 weeks (range: 3.5-9.1 weeks). Progression free survival and overall survival were not evaluated.

ii. The NCCN guidelines for peripheral T-cell lymphoma version 4.2024 recommend ALK+ Inhibitors (alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib) as other recommended regimens for the treatment ALK+ ALCL. Enrollment in clinical trial remains the preferred regimen for ALCL. There is currently no evidence that crizotinib (Xalkori) or other ALK inhibitors improves clinically meaningful outcomes (e.g., overall survival, quality of life) in patients with ALCL. Improvement in ORR has not been correlated with improved clinically meaningful outcomes. While Alectinib is approved for relapsed/refractory ALCL in Japan, crizotinib (Xalkori) and remaining ALK inhibitors remain an investigational treatment in all patients with ALCL.

B. Inflammatory myofibroblastic tumors (IMT)

i. In July 2022, crizotinib (Xalkori) received FDA approval for the treatment of adult and pediatric patients one year and older with unresectable, recurrent, or refractory ALK+ IMT. The medication received the approval based on two clinical trials, one in the pediatric space and one in adults.

ii. The efficacy of crizotinib (Xalkori) in pediatrics was evaluated in a multicenter, single-arm, open-label Phase 2 study in fourteen patients aged 1 to 21 with unresectable, recurrent, or refractory ALK+ IMT. Twelve patients had undergone prior therapy, most commonly surgery, but also chemotherapy and radiation. Twelve of the fourteen patients received 280mg/m^2 twice daily until disease progression or unacceptable toxicity; two patients received a lower dose. The primary endpoint was objective response rate (ORR); five patients attained a complete response and seven had a partial response.

iii. The efficacy of crizotinib (Xalkori) in adults was evaluated in a multicenter, single-arm, open-label phase 1b study of seven patients with unresectable, recurrent, or refractory ALK+IMT. Patients received 250 mg twice daily in evaluation of the primary outcome of ORR. Of the seven patients, one patient had a complete response, five patients had a partial response, and the median duration of treatment was nearly three years in 67% of these patients.

iv. The NCCN soft tissue sarcoma version 2.2024 guidelines recommend ALK+ Inhibitors (alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib)) as preferred category 2A regimens for the treatment of IMT with ALK+ translocation.
v. Currently, there is no evidence that crizotinib (Xalkori) improves clinically meaningful outcomes (e.g., overall survival, quality of life) in patients with ALK+IMT. Improvement in ORR has not been correlated with improved clinically meaningful outcomes. ALK+ inhibitors remain an investigational treatment in all patients with ALK+IMT.

C. ROS1+ NSCLC for any agent in this policy except for crizotinib (Xalkori)
D. NSCLC outside of the ROS1+ or ALK mutation (e.g., RET-rearranged NSCLC)
E. Erdheim-Chester Disease (ECD) with ALK fusion
   i. The NCCN recommends the use of ALK+ inhibitors (alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib) for anaplastic lymphoma kinase (ALK)-fusion targeted symptomatic Erdheim-Chester Disease in certain circumstances. However their use in histiocytic neoplasms like ECD has not been evaluated for efficacy and safety in phase III clinical trials.
F. Large B-Cell Lymphoma (LBCL)
G. NSCLC in combination with other therapies
H. Thyroid cancer
I. Melanoma
J. Gastrointestinal cancer
K. Prostate cancer
L. Leukemias or lymphomas
M. Urothelial cancer

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
entrectinib (Rozlytrek)	ROS1+ metastatic NSCLC
repotrectinib (Augtyro)	ROS1+ metastatic NSCLC

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed step through alectinib as the preferred treatment option in advance/metastatic NSCLC. Added criteria for alectinib for adjuvant treatment of ALK+ NSCLC. Added certinib as a treatment option in ROS1+ NSCLC. Updated requirements for lorlatinib in ALK+ NSCLC. Removed oncologist specialist requirement in renewal. Updated supporting evidence, E/I, references, related policies.	09/2024
Added expanded indication for crizotinib (Xalkori) for ALK+ IMT as investigational and updated quantity limit table to include this indication	04/2023
Updated supporting evidence around alectinib being the preferred first-line therapy	11/2021
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Added expanded indication for lorlatinib (Lorbrena) in the first-line treatment setting; added indication of ALK+ systemic ALCL for crizotinib (Xalkori) as investigational, updated quantity level limits for crizotinib (Xalkori), updated the supporting evidence section to include crizotinib (Xalkori) in the setting of ALK+ systemic ALCL	04/2021
Criteria update: Transitioned prior authorization criteria to policy format and consolidated all agents into one policy. Brigatinib now allowed for first-line setting if member has CI or intolerance to preferred therapy. Quantity level limits updated to reflect currently available products and package sizes. Addition of Zykadia tablets that are available in addition to the capsules.	07/2019
Criteria updates: Crizotinib updated criteria to new format, moved new start versus continuation question up. Updated prescriber question to fit current format, updated and added a question regarding both of the FDA-approved indications. Added a question regarding other therapies tried and failed or contraindicated. Zykadia updated to new format, deleted try and fail crizotinib question as this agent can now be used first line, added try and fail alectinib question, as per class review this is Moda Health's preferred agent. Removed age question, removed LFT question, QT prolongation question, and placed new versus continuation question up front. Alecensa criteria updated criteria to new format, deleted try and fail	01/2018

crizotinib question as this agent can now be used first line, removed age question. Alunbrig criteria updated to add question regarding prescribed and preferred therapy.	
Past criteria reviews	12/2012, 09/2014, 12/2015, 06/2017
Criteria created	12/2011