



## Positive Quality Intervention: Lorlatinib (Lorbrena®) Clinical Management

**Description:** This document will help in the identification of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive and who may be good candidates for treatment with lorlatinib (Lorbrena®) as well as assist the care team in management strategies.

**Background:** Lorlatinib is indicated for the treatment of adult patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.<sup>1</sup> Lorlatinib is a potent, brain-penetrant, third-generation inhibitor of ALK and ROS1 tyrosine kinases with broad coverage of ALK mutations.<sup>2</sup> A phase 3 trial compared lorlatinib to crizotinib in patients with advanced ALK-positive NSCLC who had received no previous systemic therapy for metastatic disease. The primary end point was progression-free survival; secondary end points were objective response and intracranial response. At the interim analysis, 78% (95% confidence interval [CI], 70-84) in the lorlatinib group and 39% (95% CI, 30-48) in the crizotinib group (hazard ratio for disease progression or death, 0.28; 95% CI, 0.19 to 0.41; P<0.001) were alive without disease progression at 12 months.<sup>3</sup> The updated 5- year analysis of this study showed a median duration of follow-up for progression-free survival of 60.2 months (95% CI, 57.4 to 61.6) for lorlatinib and 55.1 months (95% CI, 36.8 to 62.5) for crizotinib. Median progression-free survival was not reached (NR, 95% CI, 64.3 to NR) for lorlatinib and was 9.1 months (95% CI, 7.4 to 10.9) for crizotinib (HR 0.19 [95% CI 0.13 to 0.27]). Five-year progression-free survival was 60% (95% CI, 51 to 68) in the lorlatinib group and 8% (95% CI, 3 to 14) in the crizotinib group. Median time to intracranial progression was NR (95% CI, NR to NR) for lorlatinib and 16.4 months (95% CI, 12.7 to 21.9) for crizotinib. Progression-free survival, objective response rate, intracranial objective response rate, time to intracranial progression, and duration of response were all improved with lorlatinib versus crizotinib.<sup>4</sup> Adverse events with lorlatinib were mostly mild to moderate in severity and deemed manageable by the study authors; all-causality hypercholesterolemia (72%), hypertriglyceridemia (66%), edema (57%), peripheral neuropathy (44%), and central nervous system (CNS) effects (42%) were among the most frequently reported.<sup>1-5</sup> Biomarker analyses using ctDNA collected at the end of lorlatinib treatment did not detect any new emerging ALK resistance mutations.<sup>4</sup>

### PQI Process:

- All patients with metastatic lung adenocarcinoma, large cell carcinoma, or NSCLC not otherwise specified should undergo broad molecular profiling, preferably with next-generation sequencing (NGS), to identify patients with ALK rearrangements/fusions; testing should be considered for patients with squamous histology<sup>6</sup>
  - Consider use of RNA-based NGS, if not already done, to maximize detection of fusion events, especially in patients with high likelihood of harboring a molecular driver (young, never smoked, adenocarcinoma histology);<sup>6</sup> FoundationOne CDx (tissue) and FoundationOne Liquid CDx<sup>7</sup>
  - Fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) are also acceptable means of detection;<sup>6</sup> Ventana ALK (D5F3) CDx and Vysis ALK Break Apart FISH Probe kit are alternatives<sup>7</sup>
  - The most common fusion partner for ALK is echinoderm microtubule-associated protein-like 4 (EML4) however other fusion partners have been identified and are likely to respond to oral ALK TKIs<sup>6</sup>
- Providers should identify patients who are candidates for lorlatinib by confirming ALK-positive status; lorlatinib may be used in the first-line setting as well as for subsequent treatment following progression on prior ALK TKI therapy, especially when lorlatinib-sensitive acquired resistance mutations such as G1202R are identified as a mechanism of resistance on a 1<sup>st</sup> or 2<sup>nd</sup> generation ALK TKI
- Lorlatinib is not restricted in dispensing and should be available through specialty pharmacies as well as some medically integrated pharmacies/dispensaries

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- Review all existing patient prescriptions for any necessary dose adjustments (Table 1) or alternative therapy<sup>1</sup>
- Once medication access is secured and an estimated start date is established, schedule patient for medication education session, ensure patient understands rationale for treatment, expected benefit, how to take medication, common and rare but serious side effects, and when to contact healthcare team

Table 1. Dosing considerations for lorlatinib<sup>1</sup>

|                                  |  |
|----------------------------------|--|
| Dosage form                      | 25 mg, 100 mg tablets  |
| Usual starting dose              | 100 mg po once daily, ± food   |
| Dose adjustments (renal/hepatic) | CrCl 15-30 mL/min: decrease dose from 100 mg to 75 mg/day  |
| Dose reductions for toxicity     | 75 mg once daily → 50 mg once daily → discontinue  |
| Drug Interactions                | Concurrent strong CYP3A inducers are contraindicated with lorlatinib   |
|                                  | Concurrent moderate CYP3A inducers should be avoided; if necessary to use, increase lorlatinib dose to 125 mg once daily   |
|                                  | Concurrent strong CYP3A inhibitors and fluconazole should be avoided; if necessary to use, decrease lorlatinib dose by one dose level  |
|                                  | Screen medication list for CYP3A substrates or P-gp substrates for which small concentration decreases could lead to therapeutic failure; lorlatinib is a moderate CYP3A inducer |

- Monitoring parameters<sup>1,5</sup>
  - Lipid panel (preferably fasting): baseline, 1-2 months after start, then periodically
  - Liver function tests (or as part of complete metabolic panel—CMP): baseline then periodically
  - Fasting serum glucose: at baseline then if elevated blood glucose on routine CMP
  - Body weight: baseline and periodically (such as with clinical exams/scans)
  - Complete blood count with differential: baseline and periodically
  - Blood pressure: baseline, 2 weeks, then monthly
  - Electrocardiogram (ECG): baseline then periodically
  - Signs/symptoms of interstitial lung disease/pneumonitis (new/worsening cough or shortness of breath)
  - CNS adverse effects (AE): seizures, changes in cognitive function, memory, mood (including suicidal ideation), speech, sleep, hallucinations, brain fog, slow speech, etc.
    - At first signs of CNS AEs consider dose hold/reduction; studies have shown no change in efficacy; CNS AEs should abate within a few days of dose interruption<sup>8,9</sup>

### Patient-Centered Activities:

- Provide [Oral Chemotherapy Education \(OCE\)](#) Sheet
- Lorlatinib is associated with a minimal to low emetic risk; routine prophylaxis is not required
- Counseling pearls<sup>1</sup>
  - Swallow tablet(s) whole; do not crush, chew or split
  - Take at the same time each day; if a dose is missed, take the missed dose unless next dose is due within 4 hours
  - If vomiting occurs, do not take an additional dose; continue with the next scheduled dose
  - Can cause fetal harm. Females of reproductive potential should use non-hormonal contraception during and for at least 6 months after final dose; males with female partners of reproductive potential should use effective contraception during and for 3 months after final dose
  - Hyperlipidemia is the most common AE reported; most patients will require additional drug therapy to control lipids within the first few months of treatment; see Table 2 below
  - Patients with brain metastases, prior brain radiation, comorbid psychiatric illness, or taking neurotropic medications may be at increased risk for CNS AEs and should report any signs and symptoms to their care team immediately<sup>8-10</sup>

## Supplemental Information:

Table 2. Management of Hyperlipidemia<sup>5</sup>

| Severity  | Lab Value                                     | Adjunctive Therapy  | Lorlatinib Dose  |
|---|---|---|--|
| Mild  | TChol ULN-300 mg/dL or<br>TG 150-300 mg/dL    | Start or modify lipid-lowering therapy*   | Continue current dose  |
| Moderate  | TChol 301-400 mg/dL or<br>TG 301-500 mg/dL    |   |  |
| Severe  | TChol 401-500 mg/dL or<br>TG > 500-1000 mg/dL | Start lipid-lowering therapy, increase dose of current agent, or change to new agent* | Continue current dose  |
| Life-threatening  | TChol > 500 mg/dL or<br>TG > 1000 mg/dL       |   | Hold until mild-moderate severity then rechallenge at same dose while maximizing therapy** |
| <p>*Preferred statins due to drug-drug-interactions with lorlatinib in order of increasing potency: pravastatin, pitavastatin, rosuvastatin. If additional TG lowering is required beyond statin dose optimization, consider fenofibrate, fish oil, or nicotinic acid. Ezetimibe is also an option if additional control is needed.</p> <p>**If severe hyperlipidemia recurs despite maximal therapy, reduce lorlatinib dose by one dose level.</p> |   |   |  |

## References:

1. [LORBRENA® \(lorlatinib\) Prescribing Information.](#)
2. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study [published correction appears in *Lancet Oncol.* 2019 Jan;20(1):e10]. *Lancet Oncol.* 2018;19(12):1654-1667. doi:10.1016/S1470-2045(18)30649-1.
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4. Solomon BJ, et al. Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. *J Clin Oncol.* 2024 May 31;JCO2400581. doi: 10.1200/JCO.24.00581. Epub ahead of print. PMID: 38819031.
5. Bauer TM, Felip E, Solomon BJ, Thurm H, Peltz G, Chioda MD, Shaw AT. Clinical Management of Adverse Events Associated with Lorlatinib. *Oncologist.* 2019 Aug;24(8):1103-1110. doi: 10.1634/theoncologist.2018-0380. Epub 2019 Mar 19. PMID: 30890623; PMCID: PMC6693708.
6. [National Comprehensive Cancer Network. Non-small cell lung cancer, ver 2.2024.](#)
7. [U.S. Food and Drug Administration. \(2023, Dec 21\). List of cleared or approved companion diagnostic devices \(in vitro and imaging tools\).](#)
8. Solomon BJ, et al. Post Hoc Analysis of Lorlatinib Intracranial Efficacy and Safety in Patients With ALK-Positive Advanced Non-Small-Cell Lung Cancer From the Phase III CROWN Study. *Journal of Clinical Oncology.* 2022;40(31):3593-3602. doi:https://doi.org/10.1200/jco.21.02278.
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