CO258

US Population-Level Clinical Impact of Lorlatinib Treatment on ALK+ Metastatic Non-small Cell Lung Cancer

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Objectives

- Adopting lorlatinib as the standard first-line treatment in ALK+ advanced/metastatic NSCLC can potentially improve population-level clinical outcomes.
- The objective of this study was to estimate the clinical impact of lorlatinib treatment vs alectinib treatment on the US population level.

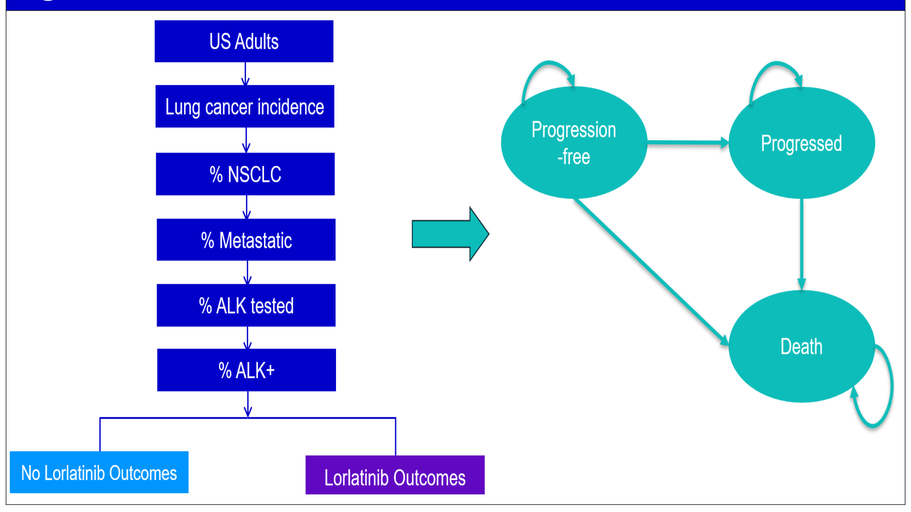
Background

- Current guidelines recommend that patients with untreated anaplastic lymphoma kinase-positive (ALK+) advanced/metastatic non-small cell lunger cancer (NSCLC) receive a next generation ALK tyrosine kinase inhibitor (TKI) such as alectinib, brigatinib, lorlatinib or ensartinib.[1]
- Lorlatinib, a 3rd generation ALK TKI, was approved to treat first-line (1L) ALK+ advanced/metastatic NSCLC[2] based on the CROWN phase III trial.[3] In the 5-year trial update, median progression-free survival (PFS) was not reached (NR [95% CI, 64.3 to NR]) in the lorlatinb arm, vs 9.1 months (95% CI, 7.4 to 10.9) in the crizotinib arm (hazard ratio [HR] 0.19 [95% CI, 0.13 to 0.27]).[4] Median time to intracranial progression was NR with lorlatinib (95% CI, NR to NR)[4]
- Adopting lorlatinib as the standard 1L treatment in ALK+ advanced/metastatic NSCLC can potentially improve population-level outcomes substantially. The objective of this study was to estimate the clinical impact of lorlatinib treatment vs alectinib treatment on the US population level in the 1L setting.

Methods

- We developed a decision model in Microsoft Excel® to estimate the long-term clinical outcomes in a cohort eligible for 1L treatment with lorlatinib in the US over 20 years. We compared the clinical outcomes in scenarios where eligible patients had access or no access to lorlatinib 1L treatment.
- The model contains a population model and a treatment model (**Figure 1**). The main outcomes of interest were total life years (LYs), quality-adjusted life years (QALYs), and incidence of brain metastases (BMs). We also estimated the number needed to treat (NNT) to avoid an incident BM.
- QALYs and LYs were estimated using a partitioned survival model (PSM) with progression-free, progressed and death health states.[5] Clinical inputs for each treatment were informed by the CROWN trial[4] and a recently published MAIC comparing lorlatinib and alectinib (**Figure 2**).
- In the scenario where lorlatinib is not available, we assumed that 100% of patients would receive alectinib. In the scenario with 1L lorlatinib, we estimated lorlatinib uptake of 37.7% based on internal market research.
- Post-progression survival for alectinib was informed by published second-line (2L) ALK+ NSCLC studies[6,7] given the limited use of 2L TKIs in the ALEX trial[8], which was the pivotal trial evaluating alectinib vs crizotinib in 1L ALK+ NSCLC.
  - In the ALEX trial[8], a small proportion of patients who progressed received subsequent lorlatinib or another TKI, likely biasing post-progression survival relative to CROWN in which access to second-generation TKIs was more common; to reduce confounding effects introduced by subsequent TKIs, post-progression overall survival for alectinib was informed by published 2L lorlatinib and chemotherapy outcomes.[6,7,9]
- For PFS, OS and incidence of BM, we used data from CROWN to fit survival curves to project long-term outcomes.
- Health state utilities were informed by recent submissions to National Institute for Health and Care Excellence (NICE).[10] We used a multiplier based on the ratio of utilities in Roughley et al. 2014[11]; all inputs are presented in **Table 1.**

Figure 1. Model Structure



ALK+, anaplastic lymphoma kinase positive; NSCLC, non-small cell lung cancer.

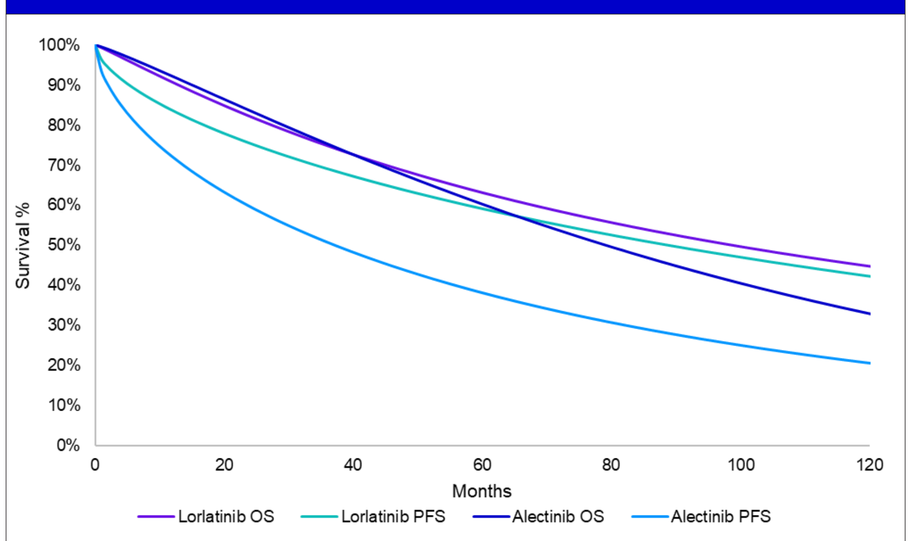
Table 1: Input Parameters

Parameter	Base Case	Sensitivity Analysis	Source
Population size	341,554,233	N/A	12
% Adults	78.0%	N/A	13
Lung cancer incidence	49.0/100,000	+/- 10%	14
% NSCLC	85.0%	+/- 10%	15
% Stage I-IIIA at diagnosis	32.7%	+/- 10%	16,17
% Progression to Stage IIIB-IV	19.9%	+/- 10%	18
% Stage IIIB-IV at diagnosis	67.3%	+/- 10%	16
Proportion with ALK test	70.0%	+/- 10%	19
ALK+	5.4%	3% - 7%	20
Lorlatinib PFS model	Gamma	Exponential, Weibull, Log-logistic	4
Lorlatinib OS model	Log-logistic	Gompertz, Log-normal	4
Exponential rate of developing BM	0.15%	Normal distribution (0.08%–0.29%)	4
Lorlatinib PFS HR vs alectinib	0.55	95% CI: 0.34–0.87	21
Lorlatinib BM HR vs alectinib	0.38	95% CI: 0.10–1.37	22
2L chemotherapy exponential monthly mortality rate*	8.4% (SE: 0.048)	Normal distribution (7.7%–9.2%)	23
2L lorlatinib exponential monthly mortality rate*	1.6% (SE: 0.067)	Normal distribution (1.4%–1.8%)	7
Progression-free utility	0.81	+/- 10%	10
Progressed utility	0.73	+/- 10%	10
BM utility multiplier	75%	+/- 10%	11

*2L treatment utilization and mortality rate were used to define post-progression survival for those who progressed and were still alive after 1L alectinib. Chemotherapy (12%) and lorlatinib (88%) utilization informed by Bauman et al. 2024[9]

2L, second-line; ALK+ anaplastic lymphoma kinase positive; BM, brain metastasis; HR, hazard ratio; MAIC, match-adjusted indirect comparison; NSCLC, non-small cell lung cancer; OS overall survival; PFS, progression-free survival; SE, standard error; TKI, tyrosine kinase inhibitor.

Figure 2. Base Case Survival Curves



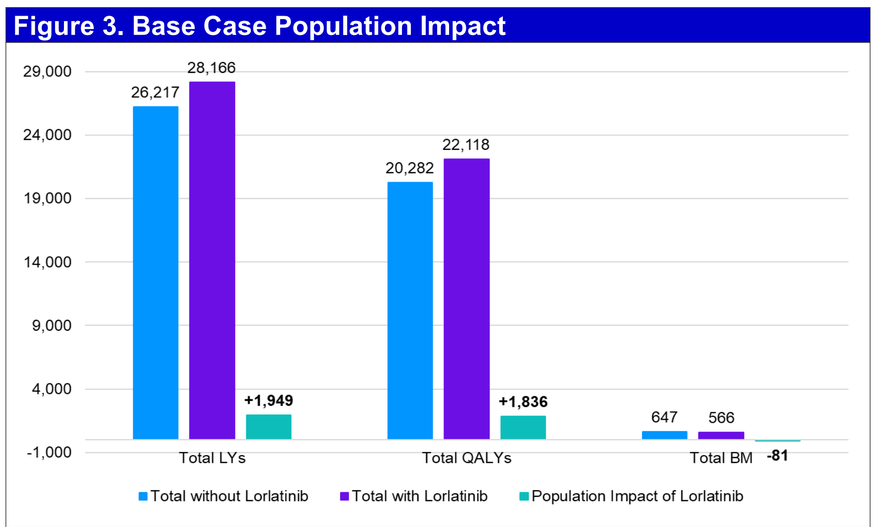
OS for alectinib derived using PFS plus a weighted average of post-progression survival from second-line clinical studies of lorlatinib and chemotherapy.

OS overall survival; PFS, progression-free survival.

Base Case Results

- We estimated 3,096 patients were eligible for treatment and assumed 1,168 would receive lorlatinib vs 1,928 with alectinib.
- On a per-patient basis, lorlatinib treatment resulted in 10.14 LYs, 8.12 QALYs, and 0.14 incident BMs, respectively; alectinib treatment resulted in 8.47 LYs, 6.55 QALYs, and 0.21 incident BMs, respectively.
- Compared with a scenario where only alectinib is available, we observe a gain of 1,949 and 1,836 LYs and QALYs, respectively, and 81 fewer BMs (**Figure 3**).
- Separately, the NNT for avoiding a BM for lorlatinib vs alectinib on a per-patient level was 14.4; when applying the lorlatinib treatment effect of developing a BM in post-progression as well as in progression-free health state, the NNT was 4.6.

Figure 3. Base Case Population Impact

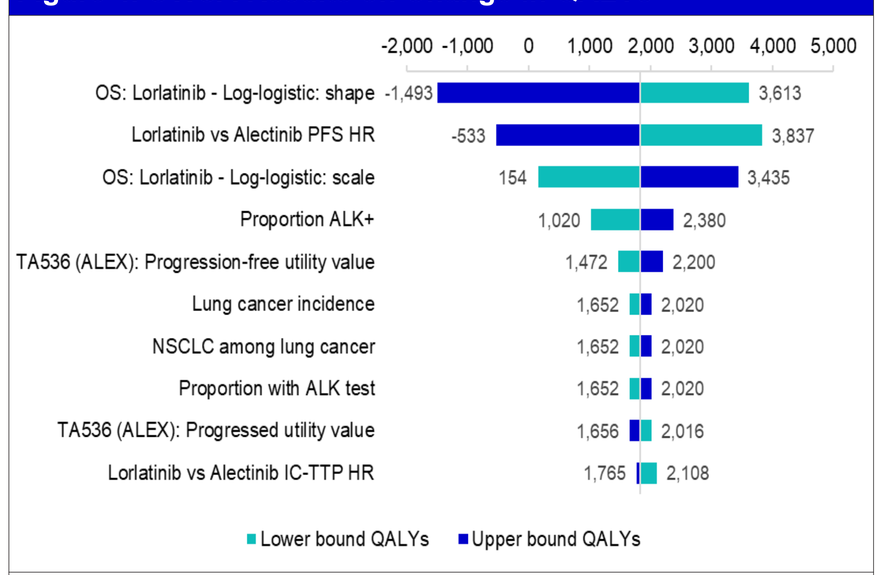


BMs, brain metastases; LYs, life years; QALYs, quality-adjusted life years.

Sensitivity Analysis

- Across several scenario analyses, there was a population-level clinical benefit for lorlatinib.
  - The most notable differences from the base case results were observed when using the log-normal OS model (+3,407 LYs, +2,893 QALYs, -81 BMs) and assuming 100% lorlatinib uptake (+5,167 LYs, +4,867 QALYs, -215 BMs).
- The most influential parameters on the OWSA for change in QALYs were lorlatinib OS curve parameters, PFS HR vs alectinib, and epidemiology parameters; across most parameters ranges we observe an increase in QALYs (**Figure 4**).

Figure 4. OWSA Results on Change in QALYs



ALK, anaplastic lymphoma kinase-positive; HR, hazard ratio; IC-TTP, intracranial time to progression; NSCLC, non-small cell lung cancer; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; QALY, quality-adjusted life-years; TA, technology assessment.

Limitations

- Lorlatinib and alectinib have never been evaluated directly in a RCT; our analysis relies on a MAIC to adjust for differences in patient characteristics.
- Though the analysis relies on long-term extrapolations beyond the CROWN study period which are uncertain, results were robust to several long-term survival scenarios and parameter ranges.

Conclusions

- We found that access to lorlatinib notably increases QALYs, LYs and decreases incident BMs compared to alectinib at a population level.
- For every 14.4 patients treated with lorlatinib vs. alectinib one BM would be avoided.
- Based on these findings, adopting lorlatinib as the standard 1L treatment in ALK+ advanced/metastatic NSCLC can improve population-level clinical outcomes.

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References: **1**. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.8.2025. ©2025 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed October 18, 2025. **2.** LORBRENA (lorlatinib). Prescribing Information. Pfizer; 2024. **3.** Shaw AT, et al. N Engl J Med. Nov 19 2020;383(21):2018-2029. **4.** Solomon BJ, Journal of Clinical Oncology. 2024;42(29):3400-3409. **5.** Latimer N. Accessed: April 22, 2025. **6.** Solomon BJ, et al. Lancet Oncol. Dec 2018;19(12):1654-1667**. 7.** Ou SHI, et al. Annals of Oncology. 2014;25(2):415-422. **8.** Mok T, et al. Annals of Oncology. 2020;31(8):1056-1064. **9.** Bauman JR, et al. Lung Cancer. Sep 2024;195:107919. **10**. NICE. Accessed: April 10, 2025. **11.** Roughly A, et al. Value Health. Nov 2014;17(7):A650. **12**. US Census Bureau. Accessed April 1, 2025. **13.** US Census Bureau. Accessed June 15, 2025. **14.** SEER. Accessed April 10, 2025. **15.** American Cancer Society. Accessed: July 29, 2025. **16.** National Cancer Institute. Accessed: April 10, 2025. **17**. Hansen et al. BMC Cancer. Apr 5 2020;20(1):276. **18.** Sazaki et al. Oncol Lett. Apr 2014;7(4):1300-1304. **19.** Shah, B et al. Journal of Clinical Oncology. 05/20 2018;36:e20515-e20515. **20.** Lovly - My Cancer Genome. Accessed: April 12, 2025. **21**. Pfizer Data on file. 2024. **22.** Garcia C, et al. Clin. Lung Cancer. Nov 2024;25(7):634-642. **23.** Blackhall F, et al. ESMO Open. 2017;2(3):e000219.

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