Research Article

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US population-level model of clinical impact of lorlatinib treatment on ALK+ metastatic non-small cell lung cancer outcomes

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Aim: Lorlatinib and alectinib are next-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) approved for the treatment of ALK-positive (ALK+) advanced/metastatic non-small cell lung cancer (NSCLC) after demonstrating superior efficacy over crizotinib (first-generation ALK TKI) in the CROWN and ALEX trials, respectively. This analysis estimated the US population-level clinical impact of first-line (1L) lorlatinib versus alectinib treatment for ALK+ advanced/metastatic NSCLC. **Materials & methods:** We developed a decision-analytic model comparing lorlatinib versus alectinib use in 1L. We used a three-state partitioned survival model (pre-progression, post-progression and death) and tracked incidence of brain metastases (BMs). Lorlatinib-eligible population estimates were derived from published literature and market forecasts; treatment effectiveness for lorlatinib was derived from CROWN; alectinib comparative effectiveness was informed using a match-adjusted indirect comparison (CROWN vs ALEX). We assumed lorlatinib uptake of 38% in the base case; selected scenarios included different survival extrapolations, assuming 100% lorlatinib uptake and applying risk of BM post-discontinuation. **Results:** We estimated that 3096 patients in the US would be eligible for lorlatinib. Compared with 1L alectinib use only, our model projected that 1L lorlatinib treatment results in 1620–5170 and 1590–4880 more life-years and quality-adjusted life-years, respectively, over a 20-year time horizon across scenarios. Per-patient incidence of BM ranged from 0.14–0.18 and 0.21–0.40 for lorlatinib and alectinib, respectively, resulting in 68–256 fewer BMs. Separately, for every 5–15 patients treated with 1L lorlatinib instead of 1L alectinib, one BM would be avoided. **Conclusion:** This analysis projected that 1L lorlatinib treatment in the US could result in more LYs and quality-adjusted life-years and fewer BMs versus 1L alectinib in ALK+ advanced/metastatic NSCLC.

Plain language summary

Lorlatinib and alectinib are newer drugs approved for the first-line (1L) treatment of anaplastic lymphoma kinase-positive (ALK+) advanced/metastatic non-small cell lung cancer (NSCLC). Although both lorlatinib and alectinib have demonstrated better efficacy over crizotinib, an older drug in the same class, no head-to-head trials have been conducted to compare lorlatinib and alectinib to each other. While modeling studies have been conducted to compare these two drugs, the population-level clinical impact of adopting lorlatinib over alectinib has not been quantified.

This study estimated the US population-level clinical impact in terms of life years (LYs), quality-adjusted life years (QALYs) and incidence of brain metastases (BMs), of selecting 1L lorlatinib versus 1L alectinib in ALK+ advanced/metastatic NSCLC populations. QALYs are estimated by weighting time in each health state (progression-free, progressed disease) by the quality of life weight for each health state. Lorlatinib was associated with gains in LYs, QALYs, and reductions in BMs, compared with alectinib. Overall, lorlatinib availability was projected to yield meaningful population-level benefits under different modeled assumptions.

The findings provide quantitative evidence supporting lorlatinib as a 1L treatment for ALK+ advanced/metastatic NSCLC. With consistent gains in LYs and QALYs and a reduction in BMs, the results can help inform reimbursement decisions, clinical guideline updates and formulary considerations favoring broader access to lorlatinib.

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Lung cancer is among the most common and deadly cancers in both men and women in the USA, with an estimated 226,650 new cases and 124,730 deaths in 2025 [1]. Approximately 85% of lung cancers are non-small cell lung cancer (NSCLC), with 5-year survival rates ranging from 12% for cases diagnosed in advanced stages to 67% when diagnosed at a localized stage [1]. Brain metastases (BMs) are highly prevalent in advanced NSCLC, having been shown to present in up to 36% of patients over the course of the disease [2], which incur a clinical burden and decreased quality of life for patients [2].

Anaplastic lymphoma kinase (ALK) gene rearrangements are present in approximately 5% of NSCLC cases [3,4]. Current guidelines recommend that patients with untreated ALK-positive (ALK+) advanced/metastatic NSCLC receive a third generation ALK tyrosine kinase inhibitor (TKI) such as lorlatinib or a select second generation ALK TKI, such as alectinib, brigatinib or ensartinib [5]. Among the ALK+ population, the clinical burden of BMs remains prevalent. In a large US claims study of Medicare patients treated with a second-generation TKI, 28% had BMs at baseline. Among patients without BM at baseline, the 5-year cumulative incidence of developing a BM was 20%, and those who developed an incident BM had a 2.6-fold higher risk of mortality versus those who did not [6].

In the Phase III ALEX trial in 2017, alectinib in the first-line (1L) setting showed significant improvement in progression-free survival (PFS) versus crizotinib (34.8 vs 10.9 months) and improved 12-month cumulative incidence of CNS progression (9.4% vs 41.4%) [7]. Lorlatinib was later approved, on 3 March 2021, to treat 1L ALK+ advanced/metastatic NSCLC [8] following positive read-out from the CROWN Phase III trial in 2020 [9]. In the 5-year CROWN update, median PFS was not reached (NR [95% CI: 64.3 to NR]) in the lorlatinib arm, versus 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]) [10]. Median time to intracranial progression was NR with lorlatinib (95% CI: NR to NR) and was 16.4 months (95% CI: 12.7 to 21.9) with crizotinib (HR 0.06 [95% CI: 0.03 to 0.12]) [10].

Although no head-to-head studies have been conducted, a match-adjusted indirect comparison (MAIC) was recently published comparing lorlatinib (using PFS reported from the CROWN study at 5 years) and alectinib (using PFS reported from the ALEX trial at 4 years) [11]. While MAIC estimates remain susceptible to residual confounding from unmeasured differences between trial populations, in this analysis, lorlatinib was estimated to significantly improve PFS versus alectinib (HR: 0.55 [95% CI: 0.34, 0.88]) [11].

Adopting lorlatinib as the standard 1L treatment option in ALK+ advanced/metastatic NSCLC can potentially improve population-level outcomes substantially given its strong clinical efficacy, but this impact has yet to be quantified. The objective of this study was to estimate the clinical impact of 1L lorlatinib treatment versus 1L alectinib treatment at the US population level.

Materials & methods

Model structure & approach

We developed a decision model to estimate the long-term clinical outcomes in a cohort of ALK+ NSCLC patients eligible for 1L treatment with lorlatinib over 20 years, ensuring that long-term survival benefits are captured. We compared the clinical outcomes in scenarios where eligible patients in the US had access or no access to 1L lorlatinib treatment. The model structure is presented in Figure 1 and contains two components: a population model and a treatment model. The main outcomes of interest included total life years (LYs), quality-adjusted life years (QALYs) and incidence of BMs. We additionally captured the number needed to treat (NNT) for the incidence of BMs on a per-patient level. We used monthly cycles and a 20-year time horizon to estimate long-term clinical outcomes. The model was developed using Microsoft Excel®.

We used published data from real-world epidemiology studies and cancer databases to estimate the eligible patient population; clinical inputs for each treatment were informed by the CROWN trial [7] and the recently

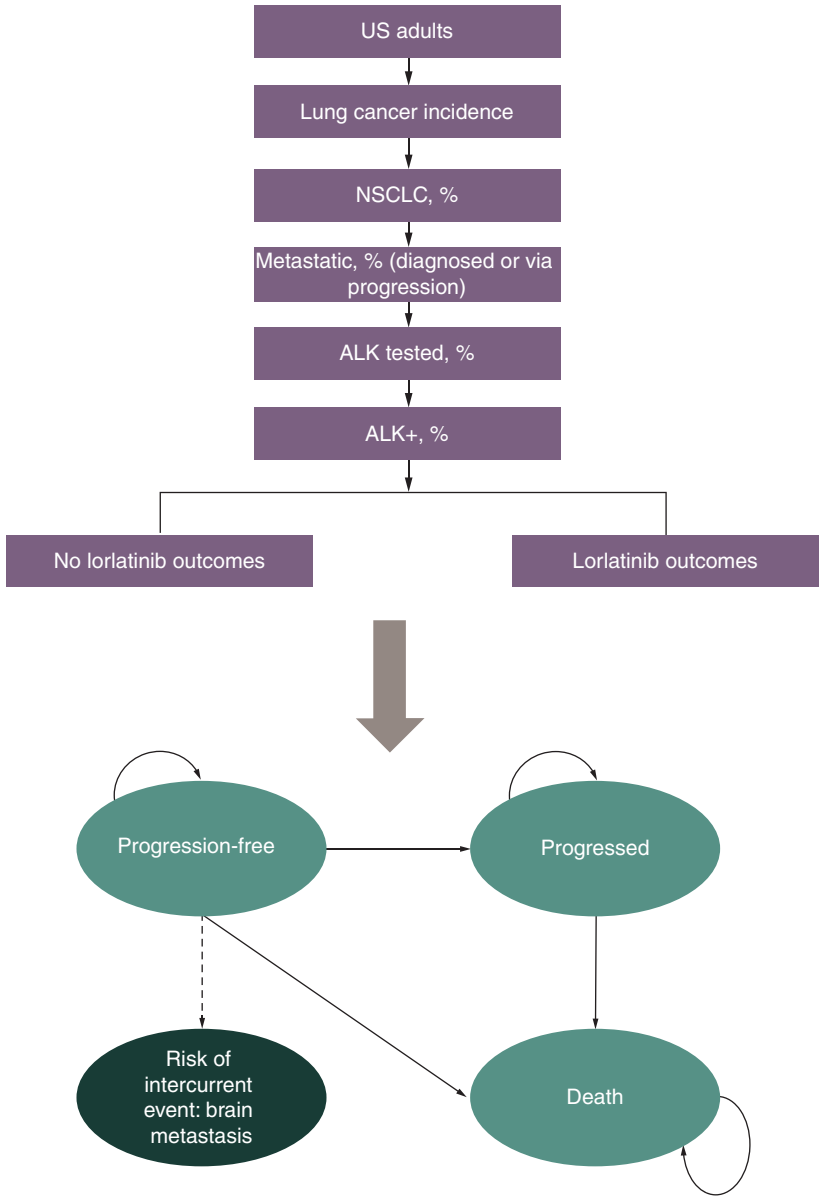

Figure 1. Model structure.
ALK+: Anaplastic lymphoma kinase positive; NSCLC: Non-small cell lung cancer.

published 5-year MAIC comparing lorlatinib and alectinib. Alectinib was available for use in both scenarios with an assumed 100% uptake in the scenario without lorlatinib. We used alectinib as the comparator of interest given that it was shown to have a >95% utilization rate among patients treated with a second-generation ALK TKI in this population in a recent claims analysis [12].

Population model inputs

Patient population eligibility inputs are presented in Table 1. To estimate the annual number of patients eligible for treatment, we first derived the number of adults in the US using the proportion of the population aged ≥18 years from US Census Bureau [13], applied to the total US population [14]. Annual lung cancer incidence (49.0/100,000) in 2025 was collected from the Surveillance, Epidemiology and End Results (SEER) [15] website and applied to the US adult population, and the proportion of incident lung cancers that are NSCLC (85.0%) was informed by the American Cancer Society [16]. We used SEER [17] to inform the distribution of lung cancer stages at diagnosis, assuming that localized was equivalent to stage I–II, regional was equivalent to stage III, and distant was equivalent

Table 1. Model input parameters.

Parameter	Base case value	OWSA/Scenario analysis values	PSA distribution	Source, year	Ref.
Population inputs					
US population size	341,554,233	N/A	N/A	US Census Bureau	[14]
Proportion adults	78.0%	N/A	N/A	US Census Bureau	[13]
Lung cancer incidence	49.0/100,000	±10%	N/A	SEER	[15]
NSCLC among lung cancer	85.0%	±10%	N/A	American Cancer Society	[1]
Stage I–IIIA at diagnosis	32.7%	±10%	N/A	SEER; Hansen *et al.*, 2020	[17,20]
Progression to Stage IIIB–IV	19.9%	±10%	N/A	Sasaki *et al.*, 2014	[18]
Proportion with ALK test	70.0%	±10%	N/A	Shah-Manek *et al.*, 2018	[19]
ALK+	5.4%	3–7%	N/A	Lovly *et al.*, 2018	[3]
Clinical inputs					
Lorlatinib PFS model	Gamma	Exponential, Weibull, Log-logistic	Multivariate normal	CROWN 5-year data	[10]
Lorlatinib OS model	Log-logistic	Gompertz, Log-normal	Multivariate normal	CROWN 18-month data	[21]
Exponential rate of developing BM	0.0015	0.0008–0.0029	Normal	CROWN 5-year data	[10]
Lorlatinib PFS HR vs alectinib	0.55	95% CI: 0.34–0.88	Log-normal	5-year MAIC	[11]
Lorlatinib intracranial progression HR vs alectinib	0.38	95% CI: 0.10–1.37	Log-normal	5-year MAIC	[11]
2L chemotherapy exponential monthly mortality rate†	0.084	0.077–0.092	Log-normal (SE: 0.048)	PROFILE 1001/1005	[22]
2L lorlatinib exponential monthly mortality rate†	0.016	0.014–0.018	Log-normal (SE: 0.067)	Study 1001	[23]
2L chemotherapy utilization after progression on 1L alectinib†	12.0%	±10%	Beta	Assumption based on Bauman *et al.*, 2024	[12]
2L lorlatinib utilization after progression on 1L alectinib†	88.0%	±10%	Beta	Assumption based on subsequent TKI utilization in Bauman *et al.*, 2024	[12]
Utility Inputs					
Progression-free	0.81	±10%	Beta	Derived using mixed-model from ALEX EQ-5D data in NICE TA536	[24]
Progressed disease	0.73				
BM multiplier	75%	±10%	Beta	Roughley *et al.*, 2014	[25]

†2L treatment utilization and mortality rate were used to define post-progression survival for those who progressed and were still alive after 1L alectinib.
1L: First-line; 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; OWSA: One-way sensitivity analysis; PFS: Progression-free survival; PSA: Probabilistic sensitivity analysis; SE: Standard error; TKI: Tyrosine kinase inhibitor.

to stage IV. Stage IIIB–IV patients were followed through the rest of the funnel; we applied an annual progression rate to stage I–IIIA patients from Sasaki *et al.* [18] to include patients who were not initially diagnosed at an advanced/metastatic stage who eventually progress. We assumed 70% [19] of advanced/metastatic NSCLC would receive an ALK test; of those 5.4% [3] were ALK+, resulting in 3096 total patients eligible for treatment with lorlatinib.

In the scenario where lorlatinib is not available in 1L, we assumed that 100% of patients would receive alectinib. In the scenario with 1L lorlatinib, we assumed a base case uptake of 37.7%, based on a forecasted estimate among patients receiving 1L treatment for ALK+ NSCLC. Given the high level of uncertainty in this uptake assumption, we ran several alternative scenario analyses with varying levels of uptake.

Treatment model approach & inputs

Input estimates for clinical outcomes, including LYs, QALYs and incidence of BMs, can be found in Table 1. We utilized a partitioned survival model (PSM) with progression-free, progressed and dead health states to derive clinical outcomes for each arm. PSMs are a commonly used method in oncology to project long-term outcomes in cost-effectiveness analysis and health technology assessment [26]. In the model, all patients start in the progression-

free state and can remain progression-free, progress or die. Patients whose disease has progressed can remain alive with progressed disease or die; death is an absorbing state.

Parametric curves were fit to PFS and overall survival (OS) patient-level data from the CROWN [10,21] study to extrapolate outcomes beyond the observed trial period for lorlatinib. Standard parametric models were fit in line with health technology assessment guidance [27]. We selected the gamma PFS model (estimated median: 87.7 months) and log-logistic OS (estimated median: 98.6 months) model in our base case; these selections were based on a combination of long-term model plausibility, statistical fit to the data based on Akaike information criteria and visual inspection. Extrapolation of all PFS models, OS models and their corresponding Akaike information criteria and Bayesian information criteria values are presented in the Supplementary Figures A1 & A2 & Supplementary Tables A1 & A2.

For modeling the incidence of BM, we used the patient-level data from CROWN to fit curves to intracranial time to progression, which captures time from randomization to the development of BM for those without BM at baseline or intracranial progression for those with BM at baseline. Given that intracranial progression data was immature (at 5 years, 92% were without progression in the lorlatinib arm), we modeled CNS progression as an intercurrent event, as was conducted and recommended by clinical experts in the recent National Institute for Health and Care Excellence (NICE) assessment for lorlatinib [28]. As a simplifying assumption, we used the constant, monthly rate of intracranial time to progression (0.15%) from the exponential model and applied this to all patients alive and progression-free. In a separate scenario, we applied the risk of BM to all patients alive, including those in the progressed disease health state, for the population impact and NNT analysis.

We used a recently published long-term MAIC [11] to inform comparative effectiveness estimates of PFS and incidence of BM for alectinib versus lorlatinib. Given that the ALEX trial only reported 4-year PFS estimates and no long-term outcomes on intracranial events [7], an MAIC was necessary to compare the treatments over the extended follow-up period from CROWN. Effectiveness estimates in the MAIC were informed by CROWN [7] for lorlatinib and the ALEX trial [7] for alectinib. In this analysis, the HR for investigator-assessed PFS of lorlatinib versus alectinib was 0.55 (95% CI [0.34, 0.88]); the HR for development of BMs was 0.38 (95% CI [0.10, 1.37]). Since results of this analysis used alectinib as the reference arm, we used the reciprocal of the MAIC HRs and applied these to the lorlatinib-derived PFS and BM estimates described above for alectinib.

In the ALEX trial [7,29], a small proportion of progressed patients received subsequent lorlatinib or another TKI, likely biasing post-progression survival relative to CROWN where access to second-generation TKIs was more common. To reduce time-varying confounding introduced by use of subsequent TKIs, we used a semi-PSM approach for alectinib, where we defined OS as the sum of PFS and post-progression survival, rather than the traditional PSM approach where post-progression survival is defined by the difference in OS and PFS. This approach, rather than using OS from ALEX, was also preferred in the original NICE assessment for lorlatinib [30], since it more accurately reflects treatment options utilized in clinical practice post-progression versus what was seen in the ALEX study [7,29]. Similarly in the US context, most second-line (2L) treatments used after 1L alectinib are lorlatinib and other TKIs as was shown in Bauman *et al.* [12], which evaluated treatment patterns using electronic health record data in Flatiron.

Given this, post-progression survival for alectinib was informed by Study 1001 [23], a Phase II study evaluating lorlatinib in the 2L ALK+ setting, and PROFILE 1001/1005 [31], a Phase II study evaluating crizotinib versus chemotherapy in the 2L ALK+ setting. We utilized a weighted average of OS outcomes from lorlatinib in Study 1001 and the chemotherapy arm in PROFILE 1001/1005 to derive an OS estimate for 1L alectinib. Weights of 2L lorlatinib and chemotherapy survival were based on US real-world subsequent treatment utilization following 1L alectinib reported in Bauman *et al.* [12]. In this study, 97% of patients received alectinib in 1L. Of those progressing to 2L treatment, 86% (n = 101) received an ALK TKI or ALK TKI in combination with chemotherapy, which we used to assume the weight of those receiving lorlatinib in 2L. We allocated 10% receiving chemotherapy or pembrolizumab regimens without a TKI (n = 12) to the weight of those receiving 2L chemotherapy. Since remaining 2L treatments received in this sample were a clinical study drug with uncertain impact on survival, they were excluded and we normalized the TKI and chemotherapy proportions to sum to 100% to weight survival. For lorlatinib 2L survival from Study 1001 [23], we used the OS estimations from the 3B–5 cohorts, which included patients receiving 2L lorlatinib following progression on a 1L TKI as representative of 2L lorlatinib following 1L alectinib. From both studies, a constant, monthly rate of mortality was derived assuming an exponential distribution (Table 1). The resulting weighted average rate of post-progression death per monthly cycle for alectinib was 2.4% and was applied to the proportion of patients in the progressed disease health state.

Table 2. Base case results over 20 years.

Treatment Scenario	Patients on Treatment	Total LYs	Total QALYs	Total Incident BM
Patient level				
Lorlatinib	Per patient	10.14	8.12	0.14
Alectinib	Per patient	8.47	6.55	0.21
Population level (US)				
Lorlatinib	1168†	11,838	9486	164
Alectinib	1928‡	16,328	12,632	403
Total with lorlatinib	3096	28,166	22,118	566
Total without lorlatinib	3096	26,217	20,282	647
Population impact		+1949	+1836	-81

†Based on 37.7% uptake among total population of 3096. Estimates may not sum due to rounding.
‡Based on 62.3% uptake among total population of 3096. Estimates may not sum due to rounding.
BM: Brain metastasis; LY: life year; QALY: Quality-adjusted life year.

We used utilities over the duration patients spent in each health state to estimate QALYs over the time horizon. We applied health state utilities for patients in the progression-free and progressed health states and estimated a one-time QALY loss for patients with incident BM. Health state utilities were informed using the mixed-model from ALEX EQ-5D data in NICE technology appraisal 536 [24]. These utilities were applied by health state to both treatments. Additionally, in the first cycle, we applied a disutility based on grade 3+ adverse events observed in CROWN and ALEX in at least 5% of patients; this resulted in a one-time QALY loss of 0.1907 and 0.0002 for lorlatinib and alectinib, respectively. Adverse event incidence, duration, and disutility are presented in Supplementary Table A4 and were based on inputs and approaches used in the NICE submission [28]. For BM events, we used a multiplier based on the ratio of utilities in Roughley *et al.* [25], which was incurred for the assumed duration of a BM (24 months). Utility values are presented in Table 1.

Sensitivity analyses

We ran a one-way sensitivity analysis (OWSA), probabilistic sensitivity analysis (PSA) and several scenario analyses to test how robust our model's results were to alternate assumptions and parameter ranges. We ran an OWSA to explore uncertainty around all key model parameters and presented the outcome using a tornado diagram of the top 10 parameters. OWSA ranges for each parameter are presented in Table 1.

The PSA jointly varied all clinical parameters by their chosen distribution based on available uncertainty information like standard errors, or where unavailable, confidence intervals which were used to derive standard errors. Scenario analyses included varying the time horizon, selection of different survival models, applying different levels of lorlatinib uptake, and applying treatment effect of developing incident BM beyond 1L treatment.

Results

Base case results

We estimated that 3096 patients in the US would be eligible for treatment with 1L lorlatinib or alectinib in 2025. Based on treatment uptake forecasting estimates, we assumed that 1168 (38%) patients would receive lorlatinib and 1928 (62%) patients would receive alectinib in the scenario where lorlatinib was available.

Projecting over a 20-year time horizon, on a per patient basis, the lorlatinib and alectinib arms accrued 10.14 and 8.47 LYs, 8.12 and 6.55 QALYs and 0.14 and 0.21 incident BMs, respectively (Table 2). Compared with a scenario where only alectinib is available, we estimated a gain of 1949 LYs and 1836 QALYs in the scenario with a 38% uptake of lorlatinib. Lorlatinib availability also resulted in 81 fewer incident BMs (Table 2).

Lorlatinib and alectinib accrued 0.14 and 0.21 incident BMs per patient, respectively. The NNT for avoiding a BM on a per-patient level was 15.

Sensitivity & scenario analyses results

The OWSA identified OS curve parameters and the PFS HR for lorlatinib versus alectinib as the most influential parameters on the change in QALYs for the base case population impact analysis. Results ranged from a loss in QALYs of 1493 to a gain of 3837 QALYs; QALY gains remained within a positive range across most, but not all key parameters (Figure 2). Over 1000 PSA iterations, the likelihood that lorlatinib resulted in a positive LY and

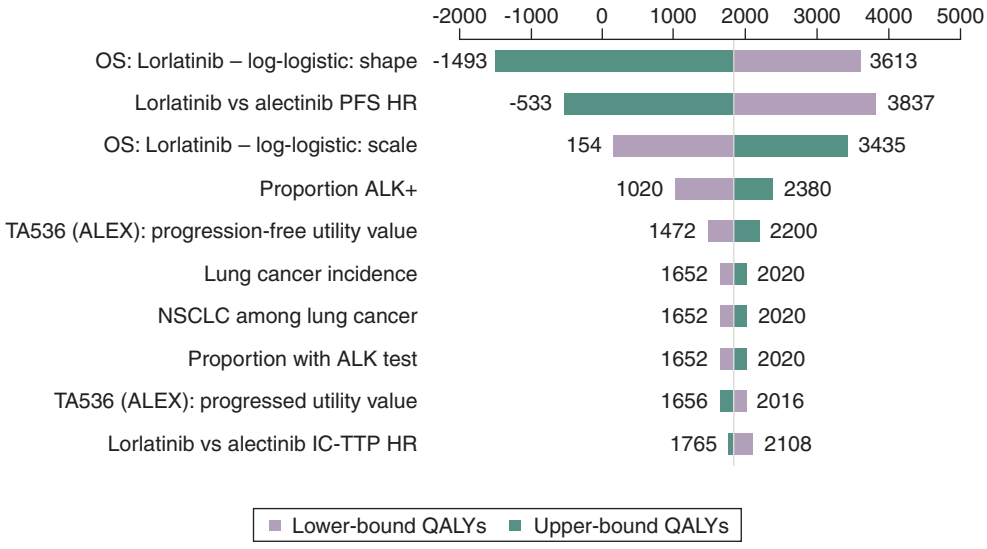

Figure 2. OWSA results on gain in quality-adjusted life-years*.
*Negative values represent QALY loss relative to the scenario without lorlatinib.
ALK: Anaplastic lymphoma kinase-positive; HR: Hazard ratio; IC-TTP: Intracranial time to progression; NSCLC: Non-small cell lung cancer; OS: Overall survival; OWSA: One-way sensitivity analysis; PFS: Progression-free survival; QALY: Quality-adjusted life-year; TA: Technology assessment.

QALY gain and prevented BMs on a population level was 81%, 84% and 72%, respectively. The LY and QALY scatterplot for the PSA is presented in Supplementary Figure A3.

Across scenario analyses, we observed a population-level clinical benefit with lorlatinib. Compared with the base case time horizon of 20 years, the population impact on incremental QALYs and LYs increased with the time horizon, while incremental BMs decreased marginally. This was because, under our base case assumption, risk of BM is only applied to those in progression-free, and under shorter time horizons, a greater proportion of patients in the lorlatinib arm remain progression-free compared with alectinib. Additionally, using different OS and PFS parametric models demonstrated a maintained clinical impact of lorlatinib. The most substantial difference versus base case result was under the assumption of full lorlatinib uptake versus alectinib; this resulted in a gain of 5167 and 4867 LYs and QALYs, respectively, with 215 BMs avoided. Additionally, when we applied the risk of BM to patients in the progression-free and progressed health state, the number of BMs avoided was 256. This translated into an NNT of 5 to avoid a BM on a per-patient level. Scenario analysis results are presented in Table 3.

Discussion

The goal of this study was to estimate the US population-level clinical impact of using lorlatinib versus alectinib as a 1L treatment for ALK+ advanced/metastatic NSCLC. On a per-patient basis, lorlatinib was projected to be associated with higher LYs (10.14 vs 8.47), higher QALYs (8.12 vs 6.55) and fewer incident BMs (0.14 vs 0.21) than alectinib. At the US population level in 2025, we estimated that access to lorlatinib would yield a gain of 1949 LYs, 1836 QALYs and 81 fewer BMs compared with a scenario where only alectinib was available in an annual cohort.

The modeled gains in survival and QALYs, along with reduced BMs, suggest that lorlatinib as a 1L option could meaningfully improve long-term outcomes for patients with ALK+ advanced/metastatic NSCLC. The NNT of 15 to prevent one brain metastasis (and as low as 5 when including post-progression benefit) highlights a clinically relevant reduction in neurologic complications that are often morbid, resource-intensive and costly to manage. These findings support prioritizing lorlatinib among next-generation ALK TKIs for appropriate patients, particularly where intracranial control and prolonged PFS are key goals. The modeled gains in LYs and QALYs and reductions in BMs provide quantitative evidence that can inform reimbursement decisions and guideline updates favoring access to lorlatinib as standard 1L therapy.

As with any health economic analysis, our model relies on assumptions and input parameters that carry considerable uncertainty. A key limitation of this study is the absence of a head-to-head randomized trial directly comparing

Table 3. Sensitivity analyses results.

Scenario	Difference in LYs	Difference in QALYs	Difference in BMs[†]
Base case	+1949	+1836	-81
Time horizon set to 10 years	+208	+376	-87
Time horizon set to 30 years	+3632	+3188	-71
Time horizon set to 40 years	+4165	+3618	-68
OS model – Gompertz	+2161	+1989	-81
OS model – Log-normal	+3407	+2893	-81
PFS model – Exponential	+2708	+2318	-77
PFS model – Weibull	+1809	+1745	-83
PFS model – Log-logistic	+1627	+1589	-87
20% lorlatinib uptake	+1033	+973	-43
30% lorlatinib uptake	+1550	+1460	-65
50% lorlatinib uptake	+2584	+2434	-108
100% lorlatinib uptake	+5167	+4867	-215
Apply risk of BM to all alive patients	+1949	+1906	-256

[†]Negative difference denotes an avoidance of BMs.
BM: Brain metastasis; LY: Life year; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life year.

lorlatinib and alectinib; instead, we relied on MAIC-based estimates to align patient characteristics across studies, which are still subject to unmeasured differences across clinical trials. Additionally, we extrapolated long-term PFS, OS and intracranial progression outcomes in CROWN beyond the observed trial period [10]. We assessed both of these limitations by evaluating multiple parametric survival models in scenario analyses. Across alternative PFS and OS models, we observed a consistent increase in LYs and QALYs, and decrease in patients developing a BM. Uncertainty was also introduced when estimating OS for alectinib using the semi-partitioned survival approach rather than directly observed OS data as was done with lorlatinib. This approach was taken since using an indirect comparison with lorlatinib OS outcomes would introduce bias, given that there was higher use of later-line ALK TKI in the control arm of CROWN [9] versus ALEX [7] that could impact OS outcomes. That said, under our approach, we projected a median OS of 81.8 months, which was nearly equal to the final, recently published alectinib OS in the ALEX trial of 81.1 months [32]. In addition, input assumptions about lorlatinib uptake, 2L therapy use, and epidemiologic inputs may not fully capture regional practice variation or future changes in standards of care. Despite these limitations, clinical impact remained robust when varying these inputs in OWSA and PSA.

This is the first study to evaluate the population-level clinical impact of lorlatinib in 1L ALK+ advanced/metastatic NSCLC. Mudumba and colleagues [33] estimated the cost-effectiveness of lorlatinib, alectinib and brigatinib in the US. Over a 5-year time horizon, they estimated 2.88 and 2.85 QALYs for lorlatinib and alectinib, respectively, per patient. Additionally, He *et al.* [34]. evaluated the cost-effectiveness of lorlatinib versus alectinib in China and estimated that lorlatinib increased lifetime QALYs (5.28 vs 3.90) compared with alectinib. Naik *et al.* [35] and Presa *et al.* [36] developed cost-effectiveness analyses for lorlatinib versus alectinib in Sweden and Spain, respectively. Their analyses found that lorlatinib produced increased LYs (+1.13 and +0.70) and QALYs (+1.22 and +1.42), respectively, consistent with our findings on a per patient level. While the designs of these studies are not directly comparable to ours in terms of time horizon and incorporation of discounting, their findings support increased LYs and QALYs for lorlatinib in this indication, supporting one of our key findings. Luo *et al.* [37] and Zhang *et al.* [38] both evaluated the cost-effectiveness of all 6 ALK TKIs in China, and found that treatment with alectinib had a marginal QALY gain versus lorlatinib (+0.03 and +0.04, respectively). It should be noted that both models were published before the CROWN 5-year update and therefore rely on less mature data than our analysis. This can be seen with the PFS HR applied in Luo 2022 [37] versus crizotinib of 0.28, whereas the reported CROWN 5-year PFS HR versus crizotinib was 0.19. Additionally, Zhang *et al.* [38] fit survival curves to trial data directly rather than using formal indirect comparison methods to account for cross-trial differences versus alectinib.

Beyond survival and BMs, it should be noted that lorlatinib and alectinib differ meaningfully in their toxicity profiles, which is relevant to individualized treatment selection. In the CROWN and ALEX trials, lorlatinib was associated with higher rates of metabolic and neurocognitive adverse events than alectinib, including hypertriglyceridemia, hypercholesterolemia, peripheral neuropathy and cognitive and mood effects, which can be seen

in Supplementary Table A4. Our model accounted for these differences by applying a first-cycle disutility derived from adverse events observed in each trial, yielding a larger one-time quality-of-life decrement for lorlatinib than for alectinib (0.1907 vs 0.0002 QALYs). Notably, lorlatinib retained a net per-patient gain of 1.57 QALYs even after this toxicity penalty, indicating that its efficacy advantage outweighed the modeled adverse-event burden.

This analysis found that 1L lorlatinib for ALK+ advanced/metastatic NSCLC in the US was projected to substantially increase LYs and QALYs while reducing the burden of BM compared with alectinib. Although population-level projections of clinical benefit are only one input to treatment recommendations and reimbursement decisions – which also depend on additional considerations, including safety, costs, patient preferences and budget impact – these results provide a compelling clinical rationale for adopting lorlatinib as a standard 1L treatment among the ALK+ advanced/metastatic NSCLC population.

Summary points

- This study is the first to quantify the US population-level clinical impact of first-line (1L) lorlatinib versus 1L alectinib in anaplastic lymphoma kinase-positive (ALK+) advanced/metastatic non-small cell lung cancer using a decision-analytic model.
- An estimated 3096 US patients were eligible for 1L lorlatinib or alectinib treatment in 2025, derived from published epidemiology sources.
- A three-state partitioned survival model (pre-progression, post-progression, death) was used to project life years (LYs) and quality-adjusted life years (QALYs) over a 20-year time horizon. Incidence of brain metastases (BMs) was modeled separately as an intercurrent event using published data on intracranial time to progression.
- Comparative effectiveness was informed by a recently published match-adjusted indirect comparison of the CROWN (lorlatinib) and ALEX (alectinib) trials, which estimated a progression-free survival hazard ratio of 0.55 (95% CI: 0.34–0.88) favoring lorlatinib.
- On a per-patient basis, lorlatinib was associated with 10.14 LYs versus 8.47 for alectinib, and 8.12 QALYs versus 6.55 for alectinib in the base case.
- At the population level (assuming 38% lorlatinib uptake), lorlatinib availability yielded an estimated 1949 additional LYs, 1836 additional QALYs and 81 fewer incident BMs compared with an alectinib-only scenario.
- The number needed-to-treat to prevent one brain metastasis ranged from 15 in the base case to as low as 5 when post-progression intracranial progression risk was included.
- Under a full (100%) lorlatinib uptake scenario, gains increased to 5167 LYs, 4867 QALYs and 215 fewer BMs over a 20-year time horizon.
- One-way sensitivity analysis, probabilistic sensitivity analysis, and scenario analyses, including varying survival extrapolation models, time horizons, utilities and uptake assumptions, demonstrated that the clinical benefit of lorlatinib was robust across a wide range of inputs.
- Results provide quantitative evidence to support reimbursement decisions, clinical guideline updates, and formulary considerations favoring broader 1L access to lorlatinib in ALK+ advanced/metastatic non-small cell lung cancer.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://becarispublishing.com/doi/epdf/10.57264/cer-2026-0096

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Competing interests disclosure

A Kasle and D Veenstra are employees of Curta, which was a paid consultant for Pfizer in connection with the study and the development of this manuscript. R Mak received honorarium from Pfizer in connection with the study and development of the manuscript. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Code of Ethics and ISPOR Good Practices for outcomes research.

Data sharing statement

Upon reasonable request and subject to review, Pfizer will provide the data that support the findings of this article. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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