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Comparative-Effectiveness Research/HTA

Matching-Adjusted Indirect Comparisons of Lorlatinib Versus Chemotherapy for Patients With Second-Line or Later Anaplastic Lymphoma Kinase–Positive Non–Small Cell Lung Cancer

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ABSTRACT

Objectives: This study aimed to compare the relative efficacy of lorlatinib, an anaplastic lymphoma kinase–tyrosine kinase inhibitor, with chemotherapy, for patients with second-line or later advanced anaplastic lymphoma kinase–positive non–small cell lung cancer. The endpoints of interest were overall survival (OS) and progression-free survival (PFS).

Methods: Evidence for lorlatinib was informed by the single-arm phase I/II trial B7461001. A systematic literature review (SLR) was performed to identify OS and PFS data for chemotherapy. Unanchored matching-adjusted indirect comparisons (MAICs) between lorlatinib and chemotherapy (pemetrexed/docetaxel, platinum-based, or systemic therapy) were performed.

Results: The SLR identified 3 relevant studies reporting PFS. Lorlatinib was associated with a significant decrease in the hazard of progression versus the 2 types of chemotherapy assessed. For PFS, the MAIC of lorlatinib versus the combined treatment arm of docetaxel or pemetrexed resulted in an adjusted hazard ratio (HR) of 0.22 (95% confidence interval [CI] 0.15-0.31). When lorlatinib was compared with platinum-based chemotherapy through an MAIC, the adjusted HR for PFS was 0.40 (95% CI 0.29-0.55). An exploratory comparison was performed for OS with evidence for systemic therapy (assumed equivalent to chemotherapy) not identified in the SLR. Lorlatinib provided a significant decrease in hazard of death (OS) versus systemic therapy, with HRs ranging from 0.12 (95% CI 0.05-0.27) to 0.43 (95% CI 0.27-0.60).

Conclusions: Lorlatinib demonstrated a significant improvement in PFS compared with chemotherapy, although limitations in the analyses were identified. The evidence informing OS comparisons was highly limited but suggested benefit of lorlatinib compared with systemic therapy.

Keywords: chemotherapy, indirect treatment comparison, lorlatinib, non–small cell lung cancer, ALK-positive.

VALUE HEALTH. 2023; 26(1):64–70

Introduction

Non–small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 80% to 85% of all lung cancers.[1-3] Approximately 3% to 5% of cases of NSCLC are histologically defined as anaplastic lymphoma kinase (ALK) positive (ALK+).[1,4,5] ALK+ NSCLCs are associated with advanced clinical stage at presentation and are more frequently observed in nonsmokers and younger patients compared with ALK-negative disease.[6]

The current standard first-line treatment for patients with advanced ALK+ NSCLC is a first- or second-generation ALK-tyrosine kinase inhibitor (TKI); nevertheless, many patients develop resistance to their initial and subsequent ALK-TKIs.[6,7] Lorlatinib is a third-generation ALK-TKI that in 2018 received accelerated approval from the US Food and Drug Administration to treat second- or third-line ALK+ metastatic NSCLC. In 2019, the European Medicines Agency granted conditional approval.[8] Preclinical data have shown that lorlatinib is capable of overcoming resistance to existing ALK inhibitors and can penetrate the blood–brain barrier in ALK-driven tumor models.[9] In particular, lorlatinib was well tolerated and had activity against all tested clinical resistance mutations in ALK. This supports the expectation that lorlatinib may address the high level of unmet need in ALK+ NSCLC, including in patients who have developed resistance. Previously, chemotherapy was the main treatment option for patients who developed resistance to their initial and subsequent ALK-TKIs.[10]

Lorlatinib is being investigated in the multicenter, open-label, single-arm phase I/II study B7461001 (ClinicalTrials.gov identifier: NCT01970865) for ALK+ or advanced ROS1-positive (ROS1+) NSCLC.[11] In phase II, eligible patients received the recommended phase I dose and were enrolled into several ALK+ expansion cohorts (EXP1 to EXP5) and one ROS1+ cohort (EXP6; Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002).

To date, we are not aware of any published comparisons of lorlatinib with chemotherapy as second-line or later treatment in patients with ALK+ NSCLC. The objective of our research was to estimate the relative efficacy of lorlatinib versus chemotherapy in this population with respect to the endpoints of overall survival (OS) and progression-free survival (PFS). Therefore, both EXP1 and EXP6 expansion cohorts in B7461001 were not relevant. A further subset of the cohorts of interest for our research were expansion cohorts EXP3B, EXP4, and EXP5, where all patients were previously treated with an ALK-TKI (other than crizotinib if only 1 previous ALK-TKI was received), given that this population is consistent with the labeling of lorlatinib in the European Union. Because lorlatinib was investigated in a single-arm trial, we used matching-adjusted indirect comparison (MAIC) methods to estimate relative effects.

Methods

Evidence Base

The phase II individual-patient data (IPD) from B7461001 were used in this study to demonstrate the efficacy of lorlatinib. OS was defined as the time from first dose to date of death from any cause. PFS was defined as the time from first dose to first documentation of objective disease progression or death because of any cause, based on independent review.

A systematic literature review (SLR), originally performed in February 2017 and then updated in June 2018, April 2019, and February 2020, examined the clinical evidence for the treatment of advanced ALK+ NSCLC with chemotherapy. The February 2020 update expanded the searches to include studies investigating platinum-based chemotherapy. Electronic databases searched were Embase®, MEDLINE®, MEDLINE In-Process, and the Cochrane Library. Given the comparator of interest, explicit inclusion and exclusion criteria were subsequently applied to the literature search results to identify evidence for chemotherapy that included patients already treated with one or more ALK inhibitors and results that also reported OS or PFS Kaplan-Meier curves. See Appendix Section A; Appendix Tables 1 to 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002 for more details.

Indirect Treatment Comparisons

Given that the efficacy of lorlatinib was investigated in a single-arm trial, anchored comparisons that require a common comparator could not be performed. Therefore, we used unanchored MAIC methods to estimate the comparative efficacy of lorlatinib with chemotherapy.[12,13] These methods can be used to form treatment comparisons without a common comparator and adjust for between-trial differences in baseline patient characteristics in the absence of randomization. An unanchored MAIC assumes that differences between absolute outcomes from different studies are entirely explained by imbalances in prognostic factors and treatment effect modifiers.

The baseline patient characteristics included in the matching were based on those identified as either important prognostic factors, treatment effect modifiers or both. These were identified through a combination of research of published literature, clinical input, and exploratory analyses of the lorlatinib data. The research of published literature primarily focused on National Institute for Health and Care Excellence single technology appraisals in the same indication. The exploratory analyses consisted of fitting both univariate and multivariable Cox proportional hazards models to the OS and PFS data. The patient characteristics explored were sex, age, ethnicity, Eastern Cooperative Oncology Group performance status (ECOG PS), presence of brain metastases, adenocarcinoma, weight, and body mass index. Exploratory P values of $< .1$ were used as indicative that a characteristic was prognostic. The cutoff of 0.1 was chosen arbitrarily to capture potentially important characteristics while also acknowledging the data were not collected with the statistical power of these tests in mind. Clinical input was sought to understand whether the characteristics identified made clinical sense and which were most important. The characteristics included in the matching were limited to those available in the comparator evidence. If a characteristic was well balanced across studies and clinical input did not highlight the characteristics to be important, then it was not included in the matching. Characteristics were considered well balanced if the mean (and variance where available) of the characteristics was similar between groups (based on $\leq$ 10% difference).

The lorlatinib patient cohorts used in the analyses were chosen based on how closely they matched the previous treatment received by patients in the comparator evidence (Appendix Section B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002). If the previous treatment in the comparator evidence did not align with that in the combined lorlatinib patient cohorts EXP-3B, EXP-4, and EXP-5, a sensitivity analysis was performed using these cohorts. Collectively, these cohorts included patients previously treated with one ALK inhibitor other than crizotinib with or without chemotherapy or with 2 to 3 previous ALK inhibitors with or without chemotherapy; this aligns with the labeling of lorlatinib in the European Union.

Where multiple chemotherapy evidence sources were available and if the studies were considered similar enough in terms of study design, baseline characteristics, inclusion/exclusion criteria, and endpoint definitions, data were pooled from these studies to allow one overall comparison. Average baseline characteristics for the pooled population were based on combined characteristics from the individual studies, weighted by the individual sample sizes. Moreover, where the definition of chemotherapy differed across studies, comparisons were performed between lorlatinib and each of the different chemotherapy types.

To make an adjusted comparison between selected lorlatinib cohorts and the comparative evidence source, individual patients treated with lorlatinib were assigned statistical weights that adjusted for their over or underrepresentation, relative to that observed in the comparative evidence source. Given that IPD were not available for the identified comparative evidence sources, reported Kaplan-Meier curves were digitized using GetData Graph Digitizer to create pseudo-IPD using the Guyot algorithm.[14,15] The patients in the pseudo-IPD were each assigned weights of 1 and combined with the relevant weighted IPD from the phase II portion of the lorlatinib trial in one data set for analysis. For both OS and PFS, unweighted and weighted Kaplan-Meier curves for lorlatinib were generated and compared with the chemotherapy Kaplan-Meier curves. Hazard ratios (HRs) comparing the relevant lorlatinib cohorts and the chemotherapy evidence were estimated using weighted Cox proportional hazards models, and the corresponding 95% confidence intervals (CIs) were calculated using bootstrapping to account for the within-subject correlation induced by the weights. The robustness of the analyses was also considered by approximating the effective sample size (ESS) and producing histograms of the weights (see Appendix Figs. 3 to 8 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002). The ESS is the number of independent nonweighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. A small ESS, relative to the original sample size, indicates that the weights are

Table 1. Baseline patient characteristics across studies.

Population	n	ECOG PS $^1/_2$ (%)	Brain metastases present (%)	Asian (%)	Male (%)	Median age (range)
Lorlatinib population (EXP2 and EXP3A)	59	52.5	62.7	28.8	33.9	54 (30-85)
Lorlatinib population (EXP3B, EXP4, and EXP5)	139	56.1	62.6	38.1	43.9	52 (29-83)
ALUR	35	68.6	25.7	20	48.6	59 (37-80)
ASCEND-5	116	56	59	33	47	54 (47-64)
Pooled ALUR and ASCEND-5 patients who received pemetrexed/docetaxel	151	58.9*	62.9	29.8	47.7	57† (37-80)
Lin et al[20] patients who received platinum-based chemotherapy	32	NR	47	19	28	45 (26-70)
Ou et al[21] patients who received systemic therapy	37	75.7	27.0	56.8	40.5	54 (28-71)

Note. Further details of patient characteristics in the lorlatinib populations have been presented in Appendix Table 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002.
ECOG PS indicates Eastern Cooperative Oncology Group performance status; EXP, expansion cohort; n, total number of patients assigned to study treatment per population; NR, not reported.
*ASCEND-5 reported performance status as per the World Health Organization criteria, which was assumed equivalent to the ECOG PS.
†Median age was 59 years in ALUR and 54 years in ASCEND-5.

highly variable because of a lack in population overlap and that the estimate may be unstable.[13]

All analyses were performed in R[16] using code based on example code provided in the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 18 Appendix D (see Appendix Section C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002).[17]

Results

Evidence Base

In the original SLR conducted in 2017, we identified 2 relevant studies investigating chemotherapy treatments and reporting PFS by independent review committee data (ALUR, investigating alectinib vs pemetrexed or docetaxel; ASCEND-5, investigating ceritinib vs pemetrexed or docetaxel).[18,19] No OS Kaplan-Meier data were identified for chemotherapy. Although the first update to the SLR (conducted in 2018) did not identify any new studies, it did identify more evidence for the ALUR study. The most recent update to the SLR (February 2020) identified a retrospective study reporting PFS data for platinum-based chemotherapy (Lin et al[20]). Given the lack of OS chemotherapy evidence, we sourced information outside of that directly identified in the SLR from a retrospective study (Ou et al[21]) that reported OS for systemic therapy after crizotinib (a linked article in the SLR). No further details were reported on the exact treatments received as part of systemic therapy. At the time of the Ou et al[21] study, there were no approved subsequent therapies to crizotinib, and therefore, we assumed that most patients would receive a type of chemotherapy and that systemic therapy was therefore representative of chemotherapy in this study. For more details of the evidence base, see Appendix Section B; Figs. 1 and 2 and Appendix Tables 5 to 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002.

Indirect Treatment Comparisons

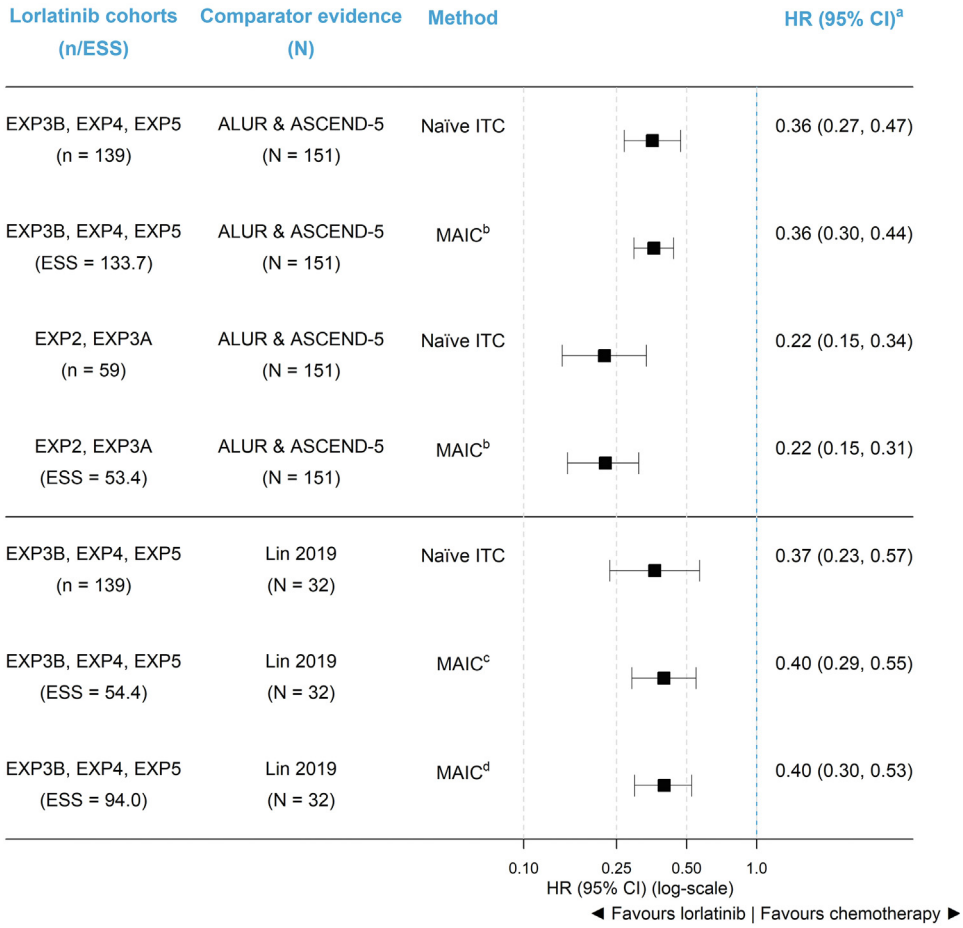
Based on the evidence, we made 3 distinct comparisons: (1) lorlatinib versus pemetrexed/docetaxel (informed by pooled data from ALUR and ASCEND-5) for PFS, (2) lorlatinib versus platinum-based chemotherapy (informed by the Lin et al[20] study) for PFS, and (3) an exploratory comparison of lorlatinib versus systemic therapy (informed by the Ou et al[21] study) for OS.

The research of published literature identified the following potentially important prognostic factors and/or treatment effect modifiers for ALK+ NSCLC: sex, age, ethnicity, ECOG PS, smoking status, presence of brain metastases, and presence of adenocarcinoma.[22,23] ECOG PS, presence of brain metastases, and ethnicity were identified as the most important factors based on clinical feedback. Exploratory analyses with the lorlatinib IPD further confirmed ECOG PS to be an important prognostic factor (see Appendix Section D; Appendix Tables 8 and 9 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002). Given that data regarding smoking status were not collected in B7461001, it was not possible to include this characteristic in the matching. *ALK* translocation occurs almost exclusively in adenocarcinoma NSCLCs; given that the percentage of patients with adenocarcinoma was expected to be high across all studies, this was not considered for matching. Therefore, the set of characteristics to potentially include in the matching were the following: ECOG PS, presence of brain metastases, ethnicity, sex, and age. These characteristics are summarized in Table 1 for the distinct populations of interest. Across all populations, the median age was relatively balanced (45-57); the lorlatinib population had a median age most similar to the Ou et al[21] population. The proportion of Asian patients was relatively similar across lorlatinib, ALUR, and ASCEND-5 populations; nevertheless, in Lin et al[20] the proportion of Asian patients was lower (19%), whereas in Ou et al[21] the Asian population was higher at 56.8%. Brain metastases at baseline were also similar across lorlatinib cohorts, ALUR, and ASCEND-5 (62.6%-62.9%); in Lin et al[20] and Ou et al,[21] the brain metastases were lower at 47% and 27%, respectively. The previous treatment received in the EXP2 and EXP3A cohorts most closely aligned with the previous treatment received by patients in ALUR, in ASCEND-5, and in Ou et al.[21] The previous treatment received in EXP3B, EXP4, and EXP5 most closely aligned with the previous treatment received by patients in Lin et al.[20] Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002 includes more information on previous treatment across studies.

Lorlatinib versus pemetrexed/docetaxel (PFS)

The ALUR and ASCEND-5 studies most closely matched the lorlatinib cohort EXP3A, given that all patients in these 2 trials had received previous crizotinib and previous chemotherapy. Nevertheless, both EXP2 and EXP3A were used in the analyses because these 2 cohorts were considered reasonably similar. Including the

Figure 1. Indirect treatment comparison results for PFS.



Notes: [a]bootstrapped 95% CI for the MAICs; [b]matching was performed on ECOG PS, ethnicity, sex, and presence of brain metastases; [c]matching was performed on ethnicity, sex, presence of brain metastases, and age; [d]matching was performed on ethnicity, sex, and presence of brain metastases. CI indicates confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; EXP, expansion cohort; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; n, total number of patients in the subpopulation of the lorlatinib trial; N, total number of patients assigned to study treatment; PFS, progression-free survival.

2 EXP cohorts also ensured that the sample size on which the matching was conducted was larger. Therefore, 2 comparisons were made between lorlatinib and pemetrexed/docetaxel: (1) lorlatinib (EXP2 and EXP3A) versus pemetrexed/docetaxel (pooled ASCEND-5 and ALUR arms) and (2) lorlatinib (EXP3B, EXP4, and EXP5) versus pemetrexed/docetaxel (pooled ASCEND-5 and ALUR arms). The former allowed for the most robust comparison, whereas the latter was investigated as a scenario using the population that aligns with the European Medicines Agency's indication of lorlatinib.

The matching characteristics used for these 2 comparisons were ECOG PS (1-2 vs 0), ethnicity (Asian vs not Asian), sex (male vs female), and presence of brain metastases (yes vs no). We considered age to be relatively balanced across ALUR, ASCEND-5, and the lorlatinib populations and, therefore, did not use this variable for matching. In each case, the matching procedure resulted in weighted average baseline characteristics for the lorlatinib populations that were the same (to 1 decimal place) as the average baseline characteristics in the pooled ASCEND-5 and ALUR population (based on the matching characteristics; see Appendix Table 10 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002).

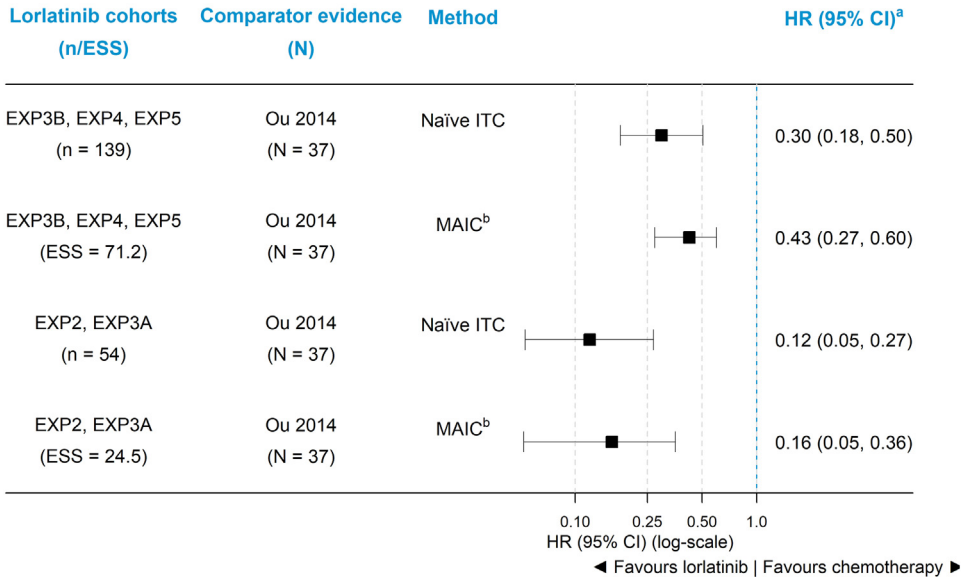
The matching had very little effect on the results. The difference between the HRs from the naive and matched indirect treatment comparisons was minimal. Following the matching procedure, the ESSs did not considerably reduce and were similar to the original sample sizes. The weighted lorlatinib Kaplan-Meier curve aligned closely with the original unadjusted Kaplan-Meier curve (see Appendix Section E; Appendix Figs. 9 and 10 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002).

Across the 4 different comparisons that assessed the impact of lorlatinib on PFS versus pemetrexed or docetaxel, lorlatinib was consistently associated with a significant decrease in the hazard of progression or death (Fig. 1). When making a comparison with the most closely aligned lorlatinib cohorts (EXP2 and EXP3A), the HR from the MAIC was 0.22 (95% bootstrapped CI 0.15-0.31).

Lorlatinib versus platinum-based chemotherapy (PFS)

The lorlatinib cohorts EXP3B, EXP4, and EXP5 were identified as corresponding most closely with the patient population described in Lin et al.[20] The 32 patients in the Lin et al[20] study who received platinum-based chemotherapy had previously received 1,

Figure 2. Indirect treatment comparison results for OS.



Notes: [a]bootstrapped 95% CI for the MAICs; [b]matching was performed on ECOG PS, ethnicity, sex, and presence of brain metastases. CI indicates confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; EXP, expansion cohort; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; n, total number of patients in the subpopulation of the lorlatinib trial; N, total number of patients assigned to study treatment; OS, overall survival.

2, or 3 or more previous ALK inhibitors—and for those patients who had received only one previous ALK inhibitor, the ALK inhibitor was not crizotinib.

The matching variables used for this comparison were ethnicity, sex, presence of brain metastases, and age (mean). Because ECOG PS was not reported in Lin et al,[20] this characteristic could not be included in the matching. We considered age to be imbalanced between the relevant lorlatinib cohorts (EXP3B, EXP4, and EXP5) and the Lin et al[20] population and therefore included it in the matching. The median age of the Lin et al[20] population was assumed equal to the mean for the purposes of the matching. A sensitivity analysis without age in the matching was performed for consistency with the comparisons made with pemetrexed and docetaxel.

The matching procedure resulted in weighted average baseline characteristics for the lorlatinib population that were the same as the average baseline characteristics reported for the Lin et al[20] population (see Appendix Table 10 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002). Matching on age led to a notably lower ESS for lorlatinib than that for the original sample size (ESS was 40% of the original sample size), suggesting further uncertainty associated with this comparison. The weighted lorlatinib Kaplan-Meier curve is less closely aligned with the original unadjusted Kaplan-Meier curve when age is included in the matching (see Appendix Section E; Appendix Figs. 11 and 12 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002).

Across the naive comparison and both MAICs, lorlatinib was consistently associated with a significant decrease in the hazard of progression or death versus platinum-based chemotherapy (Fig. 1). The MAIC with age included in the matching resulted in an HR of 0.40 (95% bootstrapped CI 0.29-0.55).

Lorlatinib versus systemic therapy (OS)

We identified the lorlatinib cohorts of EXP2 and EXP3A as corresponding most closely to the Ou et al[21] population, given that all patients in this population had received previous crizotinib. Therefore, we made 2 comparisons with systemic therapy: (1) lorlatinib (EXP2 and EXP3A) versus systemic therapy (Ou et al[21]) and (2) lorlatinib (EXP3B, EXP4, and EXP5) versus systemic therapy (Ou et al[21]).

The matching characteristics used in this comparison were ECOG PS, ethnicity, presence of brain metastases, and sex. Again, we considered age to be relatively balanced across Ou et al and the lorlatinib populations (median age was 54 years in both Ou et al[21] and the lorlatinib cohorts of EXP2 and EXP3A and 52 years in the lorlatinib cohorts of EXP3B, EXP4, and EXP5) and as such did not use this variable for matching. One patient in Ou et al[21] had ECOG PS 3 and was grouped with patients who had ECOG PS 1 or 2 for the purposes of the matching.

The matching procedure resulted in weighted average baseline characteristics for the lorlatinib populations that were the same as the average baseline characteristics of the Ou et al population (see Appendix Table 10 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002). For the 2 comparisons, the ESS was approximately 50% of the original sample size, suggesting increased uncertainty associated with these results compared with the PFS results. There was a bigger difference in the weighted lorlatinib Kaplan-Meier curve than the original unadjusted Kaplan-Meier curve when the lorlatinib cohorts of EXP3B, EXP4, and EXP5 were used in the analyses (see Appendix Section E; Appendix Figs. 13 and 14 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.002).

Overall, lorlatinib was consistently associated with a significant decrease in the hazard of death compared with systemic therapy (Fig. 2). When making a comparison between the most closely aligned lorlatinib cohorts (EXP2 and EXP3A) and the Ou et al[21] population, the HR from the MAIC was 0.16 (95% bootstrapped CI 0.05-0.36).

Discussion

This research aimed to estimate the effect of lorlatinib versus that of chemotherapy for the treatment of second-line or later

ALK+ NSCLC, specifically for the endpoints of OS and PFS. Additional complexity was introduced into this comparison, given that there were no randomized controlled trials comparing the 2 treatments and that lorlatinib was investigated in a single-arm trial. Therefore, we used MAIC methods to compare lorlatinib, investigated in B7461001, with chemotherapy, using the available evidence sourced from an SLR.

Our analyses showed that lorlatinib was associated with a significant decrease in the hazard of progression compared with chemotherapy (defined as pemetrexed/docetaxel or platinum-based chemotherapy). The 7 different analyses for PFS—which varied based on the evidence sources used to represent chemotherapy, the expansion cohorts used to represent lorlatinib, the method used to make the comparison (naive vs MAIC), and the patient characteristics used in the MAIC—resulted in HRs between 0.22 and 0.40, with all CIs excluding 1. The exploratory analysis comparing lorlatinib with systemic therapy (assumed approximately equivalent to chemotherapy) suggested a decrease in the hazard of death. The 4 different analyses for OS, which varied based on the expansion cohorts used to represent lorlatinib and the method used to make the comparison (naive vs MAIC), resulted in HRs between 0.12 and 0.43; again, all CIs excluded 1. These results show a strong improvement in outcomes when treated with lorlatinib compared with chemotherapy and therefore support the expectation that lorlatinib may address the high level of unmet need in ALK+ NSCLC, including in patients who have developed resistance to crizotinib.

This research encountered some challenges. The SLR was updated twice to capture the available evidence for chemotherapy, and the most recent update identified further evidence for platinum-based chemotherapy. Despite the addition of the Lin et al[20] study, the evidence base for chemotherapy remained limited.

The SLR did not identify any relevant chemotherapy evidence for OS. To fill the gap in OS evidence, Ou et al[21] was identified, despite not meeting the SLR criteria for evidence of chemotherapy, from linked evidence supporting the PROFILE 1007 trial that investigated crizotinib. The comparability of the study to the lorlatinib cohorts was limited by several factors, including the fact that Ou et al was a retrospective study and that the sample size of relevant patients treated with systemic therapy after crizotinib was small (37 patients). After matching, there was a noteworthy difference between the lorlatinib-treated population sample size and the ESS, highlighting the uncertainty with this comparison. Importantly, we also assumed that systemic therapy was suitable to represent the outcomes for chemotherapy, whereas there was no description of what the systemic therapy arm of this study included. Nevertheless, given that our SLR results did not provide any evidence for OS for this comparator, we considered it necessary to include this publication.

The Lin et al[20] study had similar limitations to Ou et al,[21] given that it was also a retrospective study and included only 32 patients. These small sample sizes and MAIC procedures inevitably led to a reduction in the ESS, which in turn can lead to higher uncertainty in the results, which is reflected in the larger CIs. Lin et al[20] did not report any ECOG PS—which was highlighted across the desk review, clinical input, and exploratory analyses as being one of the most important prognostic factors—so this characteristic could not be included in the matching. The evaluation of disease progression and definition of PFS were also different in the Lin et al[20] study: follow-up was based on treatment schedule (compared with the other studies where follow-up occurred every 6 or 8 weeks) and progression was investigator defined rather than by an independent review committee (as in B7461001, ALUR, and ASCEND-5).

ALUR and ASCEND-5 were considered sufficiently similar that data from these studies could be pooled; this ensured there were ample patients contributing to the combined pemetrexed or docetaxel evidence. Nevertheless, we acknowledge the limitations of pooling data, because doing so effectively ignores any differences in population, intervention, outcomes, and study design.

We endeavored to perform comparisons with similar populations based on previous treatment by using the lorlatinib patient cohorts that most closely matched the previous treatment received by patients in the comparator evidence. This allowed for more like-for-like comparisons; nevertheless, it is acknowledged that there may still be differences in the extent of previous treatment that have not been accounted for.

The analyses are associated with the well-known limitations of unanchored MAICs, including the strong assumption required by this methodology that there are no prognostic factors or treatment effect modifiers in imbalance between the 2 populations after matching. We used 3 different methods to identify prognostic factors or treatment effect modifiers in the disease area (research of published literature, clinical input, and exploratory analyses of the lorlatinib data) and can therefore be confident that the most important prognostic factors were included in our analyses (where reported in the comparator evidence). Nevertheless, it is unlikely, and often deemed impossible, to include all prognostic factors or treatment effect modifiers. Given that lorlatinib was investigated in a single-arm trial, we could not identify treatment effect modifiers when exploring the lorlatinib data—only prognostic factors.

MAICs provide an insight into how lorlatinib and chemotherapy compare and have allowed for decision makers to assess the relative effectiveness in the context of health technology appraisals.[12,24] Nevertheless, given the limitations associated with MAIC methods, they cannot replace the robustness of comparing treatments in a randomized controlled trial. Therefore, in the absence of head-to-head trials comparing lorlatinib with chemotherapy in second-line or later ALK+ NSCLC or the ability to conduct phase III trials in this treatment setting, collecting real-world data that compare outcomes in these later lines of therapy is warranted to confirm the results from our research.

Conclusions

Our analyses suggested that lorlatinib significantly improved PFS compared with pemetrexed/docetaxel combination and with platinum-based chemotherapy for the treatment of second-line or later ALK+ NSCLC. The comparison with pemetrexed/docetaxel was more robust than that with platinum-based chemotherapy (evidence for the latter treatment included only 32 patients). The results also suggested that lorlatinib significantly improved OS versus systemic therapy (assumed approximately equivalent to chemotherapy); nevertheless, the evidence was highly limited and included only 37 patients, and the analyses considered exploratory only. Overall, results from the unanchored MAICs suggest lorlatinib is an effective treatment alternative for second-line or later treatment of ALK+ NSCLC compared with chemotherapy.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.07.002.

Article and Author Information

Accepted for Publication: July 7, 2022

Published Online: August 16, 2022

doi: https://doi.org/10.1016/j.jval.2022.07.002

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Statistical analysis: Smith and Cooper
Administrative, technical, or logistical support: Iadeluca

Conflict of Interest Disclosures: Mss Cooper and Smith are employees of BresMed, which was a paid consultant to Pfizer in connection with the statistical analyses reported and development of this manuscript. The authors did not receive direct payment as a result of this work outside of their normal salary payments. Drs Albuquerque de Almeida, Inês, and Iadeluca are employees of Pfizer Inc and hold Pfizer Inc stock. No other disclosures were reported.

Funding/Support: This study was sponsored by Pfizer Inc.

Role of the Funder/Sponsor: Pfizer employees were involved in the study design; the collection, analysis, and interpretation of data; the review of article; and the decision to submit for publication. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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