Evaluating the Optimal TKI for Patients With ALK Positive Advanced Non-Small-Cell Lung Cancer (aNSCLC) in the First Line (1L) Setting: An Updated Systematic Literature Review (SLR) and Network Meta-Analysis (NMA)

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INTRODUCTION

This study investigates the comparative impact of lorlatinib versus other first-line (1L) tyrosine kinase inhibitors (TKIs) in patients with anaplastic lymphoma kinase-positive (ALK+) advanced non-small-cell lung cancer (aNSCLC). There were two primary objectives of this work:

- To update previously published network meta-analysis (NMA) utilizing the most recent data available[1]
- To provide a summary of other published NMAs conducted on ALK+ aNSCLC

BACKGROUND

Lorlatinib, a third-generation ALK TKI, demonstrated improved progression-free survival (PFS) when compared with crizotinib in the Phase III CROWN study (NCT03052608) for patients with previously untreated locally advanced or metastatic ALK+ NSCLC. Other treatments of interest, which were not evaluated in the CROWN study, include alectinib, brigatinib, ensartinib, envonalkib, iruplinalkib, and ceritinib. The NMA was updated, and a literature search was conducted to incorporate 10 additional independent published NMAs.

MATERIALS AND METHODS

Updated NMA data collection

The recent results from the 5-year CROWN data-cut were used and are presented in the abstract associated with this poster; note that overall survival (OS) data for CROWN were from the 18-month CROWN data-cut where data was immature.[2] NMAs have been updated to include recent papers for ALESIA, ALTA-1L, INSPIRE, Yang 2023 and J-ALEX.

For all relevant endpoints, data were extracted from the new papers and added to the previously identified data, which originated from a systematic literature review performed in 2021 plus a subsequent update in 2023. A feasibility assessment was then undertaken to assess the inclusion of new studies investigating envonalkib and iruplinalkib in the NMAs, due to emerging evidence.

NMA methods

NMA analyses were conducted using a Bayesian approach and the gemtc package in R. In the original NMA, both fixed effects and random effects models were fitted to the data, and model comparison methods were used to assess the goodness-of-fit. Fixed effects models were identified as the best-fitting models in the original analyses; therefore, only fixed effects models were run in subsequent updates to the NMA.

Summary of other published NMAs

One additional NMA was identified in this update (Zhao 2023), and results still showed consistent findings. Other NMAs only included 3Y data, and no other NMAs looked at data vs iruplinalkib. Key results of these NMAs, alongside the updated NMA, are summarized in Table 1.

RESULTS

Summary of 11 NMAs

- The 10 identified published NMAs included 17 randomized controlled trials (first and mixed treatment line). The results of these NMAs are summarized in Table 1, comparing lorlatinib versus alectinib 600 mg, brigatinib, ensartinib, envonalkib and irpulinalkib . Ou 2024 provides the results of the updated Pfizer-sponsored NMA
- Table 1 shows that lorlatinib consistently demonstrated a numerically or significantly better PFS (intention-to-treat [ITT]) versus alectinib, brigatinib, ensartinib, envonalkib and iruplinalkib across most NMAs where data was available. Wu 2021, Peng 2023, and Zhao 2023 did not indicate numerically better PFS; however, results were not statistically significant
- In the subgroup with brain metastasis at baseline, lorlatinib showed numerically better or comparable PFS versus alectinib and brigatinib. In the subgroup of patients without baseline brain metastasis, lorlatinib demonstrated better PFS versus brigatinib in five out of six NMAs, and numerically better PFS versus alectinib. Results for PFS with and without brain metastasis at baseline are available in the supplementary materials
- Time to intracranial/central nervous system progression was reported by only one NMA. This result was reasonably consistent with our NMA, showing numerically favourable results for lorlatinib versus both alectinib and brigatinib – although our NMA presented statistical significance
- Lorlatinib showed higher odds of Grade ≥ 3 AEs than alectinib, and numerically higher odds than brigatinib and ensartinib. The number of adverse events leading to treatment discontinuation (AEDCs) of lorlatinib appeared numerically lower versus brigatinib and versus ensartinib in the two NMAs that investigated this outcome; however, results versus alectinib were not consistent across the NMAs

Table 1: Key updated NMA results and review of 10 other independently published NMAs

NMA	Ou 2024[a]	Ando 2021[3]	Chuang 2021[4]	Zhao 2021[5]	Ma 2021[6]	Peng 2021[7]	Wang 2021[8]	Wen 2022[9]	Wu 2021[10]	Peng 2023[11]	Zhao 2023[12]
PFS INV ITT HR (95% CrI) [b]											
Lorlatinib vs alectinib 600 mg	**0.49 (0.32 to 0.75)**	0.74 (0.47, 1.18)	0.68 (0.42, 1.08)	0.53 (0.21, 1.35)	0.68 (0.23, 2.12)	0.82 (0.26, 2.98)	**0.59 (0.39, 0.94)**	0.66 (0.41, 1.04)	1.16 (0.61, 2.22)[c]	0.68 (0.43, 1.1)	0.63 (0.39, 1.00)
Lorlatinib vs brigatinib	**0.44 (0.27 to 0.72)**	**0.57 (0.33, 0.997)**	**0.57 (0.34, 0.95)**	0.44 (0.15, 1.35)	0.57 (0.16, 2.05)	0.57 (0.13, 2.58)	**0.54 (0.31, 0.94)**	**0.58 (0.35, 0.96)**	1.23 (0.57, 2.70)[c]	0.59 (0.36, 1.0)	**0.56 (0.35, 0.91)**
Lorlatinib vs ensartinib	**0.42 (0.25 to 0.70)**	NR	**0.54 (0.22, 0.92)**	NR	0.58 (0.16, 2.08)	0.63 (0.14, 2.78)	NR	0.62 (0.36, 1.08)	1.47 (0.69, 3.13)[c]	0.63 (0.36, 1.08	**0.54 (0.33, 0.88)**
Lorlatinib vs envonalkib	**0.45 (0.28 to 0.74)**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lorlatinib vs iruplinalkib	**0.48 (0.29 to 0.77)**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Time to intracranial/CNS progression HR (95% CrI)[d]											
Lorlatinib vs alectinib 600 mg	**0.39 (0.17 to 0.89)**	NR	NR	NR	NR	0.35 (0.09, 1.82)	NR	NR	NR	NR	**NR**
Lorlatinib vs brigatinib	**0.2 (0.07 to 0.54)**	NR	NR	NR	NR	0.2 (0.03, 1.34)	NR	NR	NR	NR	NR
Lorlatinib vs ensartinib	NR	NR	NR	NR	NR	0.18 (0.03, 1.28)	NR	NR	NR	NR	NR
Grade ≥ 3 or 3/4 AEs OR or RR (95% CrI)											
Lorlatinib vs alectinib 600 mg	**3.16 (1.69 to 5.94)[e]**	**RR: 1.92 (1.49, 2.48)**	**RR: 1.62 (1.24, 2.12)**	NR	OR: 3.46 (0.35, 38.24)	**OR: 4.26 (1.22, 15.53)**	NR	**OR: 3.39 (1.84, 6.30)**	NR	NR	**NR**
Lorlatinib vs brigatinib	1.42 (0.69 to 2.9)[e]	RR: 1.18 (0.90, 1.55)	RR: 1.07 (0.84, 1.37)	NR	OR: 1.67 (0.12, 24.25)	OR: 1.69 (0.36, 9.91)	NR	OR: 1.24 (0.62, 3.26)	NR	NR	NR
Lorlatinib vs ensartinib	1.71 (0.86 to 3.43)[e]	NR	NR	NR	OR: 1.53 (0.10, 21.26)	NR	NR	OR: 1.64 (0.83, 3.26)	NR	NR	NR
Lorlatinib vs envonalkib	1.8 (0.89 to 3.67)[e]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lorlatinib vs iruplinalkib	1.89 (0.94 to 3.79)[e]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
AEDC OR (95% CrI)											
Lorlatinib vs alectinib 600 mg	1.13 (0.45 to 2.83)	NR	NR	NR	NR	NR	NR	0.77 (0.27, 2.13)	NR	NR	**NR**
Lorlatinib vs brigatinib	0.63 (0.21 to 1.88)	NR	NR	NR	NR	NR	NR	0.44 (0.13, 1.41)	NR	NR	NR
Lorlatinib vs ensartinib	0.74 (0.23 to 2.32)	NR	NR	NR	NR	NR	NR	0.51 (0.15, 1.75)	NR	NR	NR
Lorlatinib vs envonalkib	0.59 (0.14 to 2.35)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lorlatinib vs iruplinalkib	0.84 (0.23 to 3.12)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Key: AE, adverse event; AEDC, adverse event leading to discontinuation; CNS, central nervous system; CrI, credible interval; HR, hazard ratio; INV, investigator-assessed; ITT, intention-to-treat; NMA, network meta-analysis; NR, not reported; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk.
Notes: [a] Fixed effects models are presented as these provided the best fitting models. [b] PFS NMA reported uses INV-assessed PFS. [c] Wu 2021 only included subgroup of Asian patients in all analyses. [d] No data was reported for envonalkib or iruplinalkib for IC-TTP. [e] The updated NMA included Grade 3/4 AEs, while other NMAs included Grade ≥ 3 AEs. **Bold data in the table indicate results with significant differences.**
Additional comparators were included in Ou 2024 but were not treatments of interest and so are not reported in this poster: alectinib 300mg (PFS INV, IC-TTP, Grade ≥ 3 AEs, AEDC), chemotherapy (IC-TTP, Grade ≥ 3 AEs, AEDC), Ceritinib 450mg (AEDC) and ceritinib 750mg (Grade ≥ 3 AEs, AEDC).

RESULTS

Updated NMA using 5-year CROWN data-cut

Following a feasibility assessment of the available data for additional endpoints of interest:

- NMAs were deemed unfeasible due to limited data for intracranial time to progression for the subgroups with and without brain metastasis
- NMAs for PFS (investigator-assessed) for the ITT population and subgroups with and without brain metastasis were updated, along with intracranial time to progression (IC-TTP), Grade ≥ 3 or 3/4 adverse events (AEs) and AEDCs

Results for PFS assessed by the investigator in the ITT population are presented in Figure 1. Key results are presented in Table 1 under the column Ou 2024. Updated results for PFS show a statistically significant reduced hazard of progression or death for lorlatinib versus all key comparators.

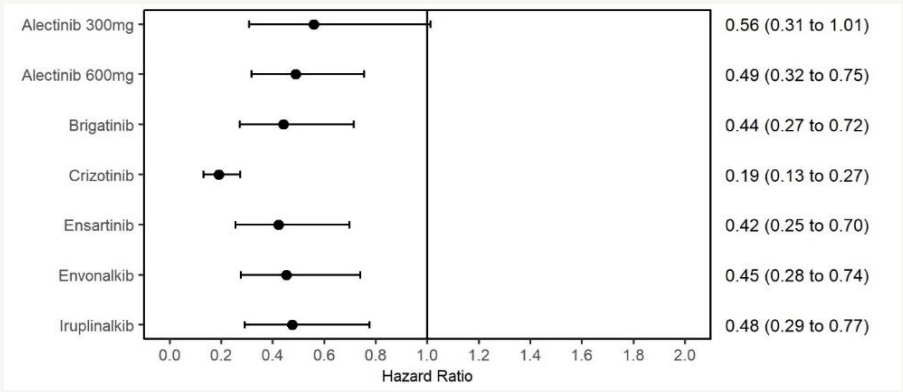
Lorlatinib showed a statistically significant improvement in IC-TTP versus both alectinib 600mg and brigatinib.

In the subgroup of patients with brain metastasis at baseline, lorlatinib showed a statistically significant improvement in PFS versus alectinib 600mg and brigatinib (HR [95% CrI]): 0.28 [0.11, 0.7] and 0.33 [0.11, 0.97], respectively). Results were consistent in the subgroup of patients without brain metastasis at baseline versus alectinib 600mg and brigatinib (HR [95% CrI]: 0.53 [0.32, 0.86] and 0.42 [0.24, 0.74]), respectively).

Updated NMA data for AEs is similar to previous data showing higher odds of grade ≥3 AEs than alectinib, and numerically higher odds than other TKIs. However, the AEDC remained either similar vs alectinib and numerically lower vs. other TKIs, indicating that AEs are manageable.

OS analysis is ongoing.

Figure 1. Relative effect of lorlatinib vs comparators for PFS ITT (investigator-assessed) in updated NMA (Ou 2024)



Key: ITT, intention to treat; NMA, network meta-analysis; PFS, progression-free survival.

LIMITATIONS

- Limited data were reported for certain endpoints
- Fixed effects models alone were used for the updated NMAs
- No adjustments were made for differences in characteristics between studies. However, the studies were assessed and deemed feasible to use in NMA
- OS data were not updated in the 5-year CROWN data-cut and were immature

CONCLUSIONS

- With the unprecedented CROWN 5-year data (Solomon et al., JCO 2024), the relative effect of 1L lorlatinib is significantly improved vs. other 1L second-generation ALK TKIs
- Totality of evidence across 11 available NMAs consistently support lorlatinib as preferred 1L treatment of choice for ALK+ aNSCLC patients

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Poster presented at the 2024 ISPOR Europe; 17-20 November 2024; Barcelona, Spain.