Lorlatinib in Advanced *ALK*-Rearranged NSCLC: Real-World Experience in a UK Population

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Summary

Purpose

To understand the efficacy, side effect profile, and tolerability of lorlatinib, a third-generation TKI, in NSCLC. Analysing data from several sites across London and the South East, representing a multi-ethnic UK-based population.

Methodology

This multi-centre retrospective observational real-world study accrued data from 13 NHS trusts across London and the South East, totalling 81 patients receiving lorlatinib with pre-treated *ALK*-positive advanced NSCLC.

Key Findings/Concluding Statement

Lorlatinib was typically given second-line (63%). Median PFS for all patients was 7.5 months and overall survival 17.2 months. Amongst those receiving lorlatinib third-line, a proportion appeared to have a heightened response, likely due to unknown benefits of *ALK*-targeted TKIs secondary to variations in tumour biology.
Only 3% of patients developed first brain metastases during or after treatment, suggesting promising impact upon CNS disease control.
Toxicity was predominantly low-grade, most commonly due to hypercholesterolaemia, hyperlipidaemia, fatigue, and peripheral oedema. Toxicity-related discontinuations of lorlatinib was minimal (4%).

Context

- Lorlatinib is a third-generation tyrosine kinase inhibitor (TKI) used for the treatment of anaplastic lymphoma kinase (*ALK*) rearranged non-small cell lung cancer (NSCLC). It provides an additional, highly-potent, treatment option following the development of resistance with first-line TKIs, typically second-generation[1,2].
- The recent CROWN study demonstrated good efficacy in the first-line setting, although not currently reimbursed in the UK[3]. The expanding promise of lorlatinib's effectiveness in treating such patients highlights the need for an enhanced understanding of its real-world efficacy and toxicity profile, of which is currently unclear.
- Lorlatinib has a unique safety profile compared to other TKIs, with a majority of its grade 3/4 toxicity burden secondary to derangements in lipid, triglyceride levels, and weight gain[4]. This has been reflected in the outcomes of the likes of the CROWN study and early phase trials[3,4].
- Real-world data will reinforce our ability to manage these toxicities, reducing discontinuation rates, improving time spent on treatment, and therefore response with lorlatinib.

Aims

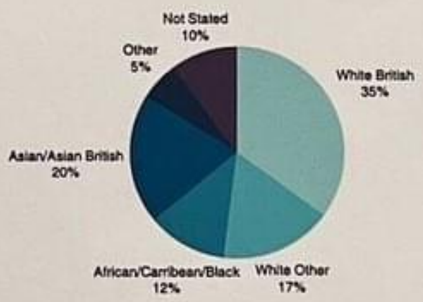
- To analyse real-world data from a multi-ethnic UK population receiving lorlatinib for advanced NSCLC and assess efficacy plus better understanding its side effect profile.
- To recognise current trends in treatment approaches to lorlatinib-related adverse effects and rates of therapy delay or discontinuation.

Methodology

- This multi-centre retrospective observational real-world study included pre-treated *ALK*-positive metastatic NSCLC patients, from 13 NHS trusts across London and SE England.
- Patient had to have commenced lorlatinib during the period September 2016 to January 2024 and have completed one cycle of treatment at the point of data retrieval.
- Clinical and demographic data were collected from electronic medical records. Key outcomes included best response, progression free (PFS) and overall survival (mOS) calculated using Kaplan-Meier method.

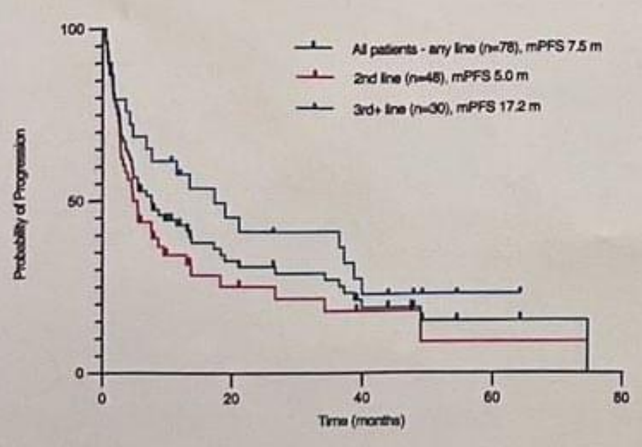
Results

- Eighty-one patients (median age 52, range 20 – 83 years; 62% female; 57% never-smoker) were included. **Ethnicity: White (52%), Asian (20%), and Black (12%).** Seventy-nine percent were PS 0-1 at initiation of lorlatinib.
- ALK testing was by IHC (37%), FISH (26%), or combination (23%).
- Brain metastases were present in 27% at diagnosis, 26% following diagnosis but prior to lorlatinib. **3% developed first brain metastases during/after lorlatinib therapy.**
- Lorlatinib was most commonly administered second-line (63%). Objective response rate was 44%, with a further 22% achieving best response of stable disease. **Median PFS for all patients was 7.5 months (m), 5.0m for second line, and 17.3 for third line; mOS was 17.2m for all patients, 12.2m for second line, and 28.9 for third (figure).**
- **Toxicities were predominantly low-grade, including hypercholesterolaemia (54%), fatigue (36%), peripheral oedema (23%). 8.6% experienced grade ≥3 psychosis or hallucinations.**

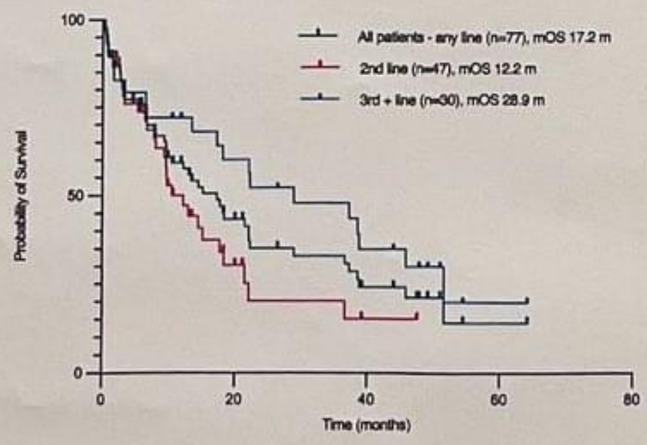


	mPFS	mOS
2nd Line (months)	5.0	12.2
3rd Line (months)	17.2	28.9
All Patients (months)	7.5	17.2

Toxicity	Grade 1-2 (CTCAE)	Grade > 3 (CTCAE)
Hypercholesterolaemia	34 (42%)	10 (12.3%)
Hyperlipidaemia	34 (42%)	0 (0%)
Fatigue	27 (33.3%)	1 (3%)
Oedema	18 (22.2%)	1 (1.2%)
Mood/Psychological	11 (13.6%)	7 (8.6%)
Weight Increase	13 (16%)	0 (0%)
Arthralgia	10 (12.3%)	1 (1.2%)
Peripheral Neuropathy	10 (12.3%)	0 (0%)
Cognitive Disturbance	6 (7.4%)	3 (3.7%)
Eye Disorders	5 (6.2%)	1 (1.2%)
Diarrhoea	6 (7.4%)	0 (0%)
Constipation	4 (5%)	0 (0%)



Progression free survival from initiation of lorlatinib



Overall survival from initiation of lorlatinib

Discussion

- This real-world study confirms reported clinical data for both efficacy and tolerability of lorlatinib in a multi-ethnic UK population. Whilst toxicities are common, they were predominantly of low grade and resulted in few discontinuations.
- Lorlatinib displayed good CNS impact with only 3% of patients developing first brain metastases on treatment.
- The longer median PFS and OS with lorlatinib use in later (3+) lines of therapy is likely due to the small number of 'excellent responders' with disease biology that is particularly sensitive to *ALK*-targeted therapy. This requires further evaluation in our planned national extension of this RWE study.
- We are now inviting collaborators from across the UK to join this study and hope to provide a more in-depth look at the real-world experience of lorlatinib in our population.

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Any queries, please contact us

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