

Lorlatinib as First-Line Treatment for Locally Advanced ALK-Positive NSCLC: A Real-World Multicenter Observational Study

Q. Chu¹, J. Wang¹, Y. Hu², Y. Chen³, X. Song⁴, W. Wang³, W. Liu²

¹Tongji Hospital of Tongji Medical College, Huazhong University of Science & Technology, Wuhan,Hubei/CN ,²The Second Xiangya Hospital of Central South University, Changsha/CN ,³Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan Province/CN ,⁴The first College of Clinical Medicine science, China Three Gorges University,Yichang Central People’s Hospital, Yichang/CN

INTRODUCTION

- Although lorlatinib has exhibited superior clinical efficacy in advanced NSCLC. However, its role as an induction therapy for locally advanced (stage III) disease remains poorly defined due to limited clinical evidence.
- Herein, we report preliminary results of a real-world, multicenter observational study evaluating lorlatinib as first-line therapy for locally advanced ALK-positive NSCLC.

RESULTS

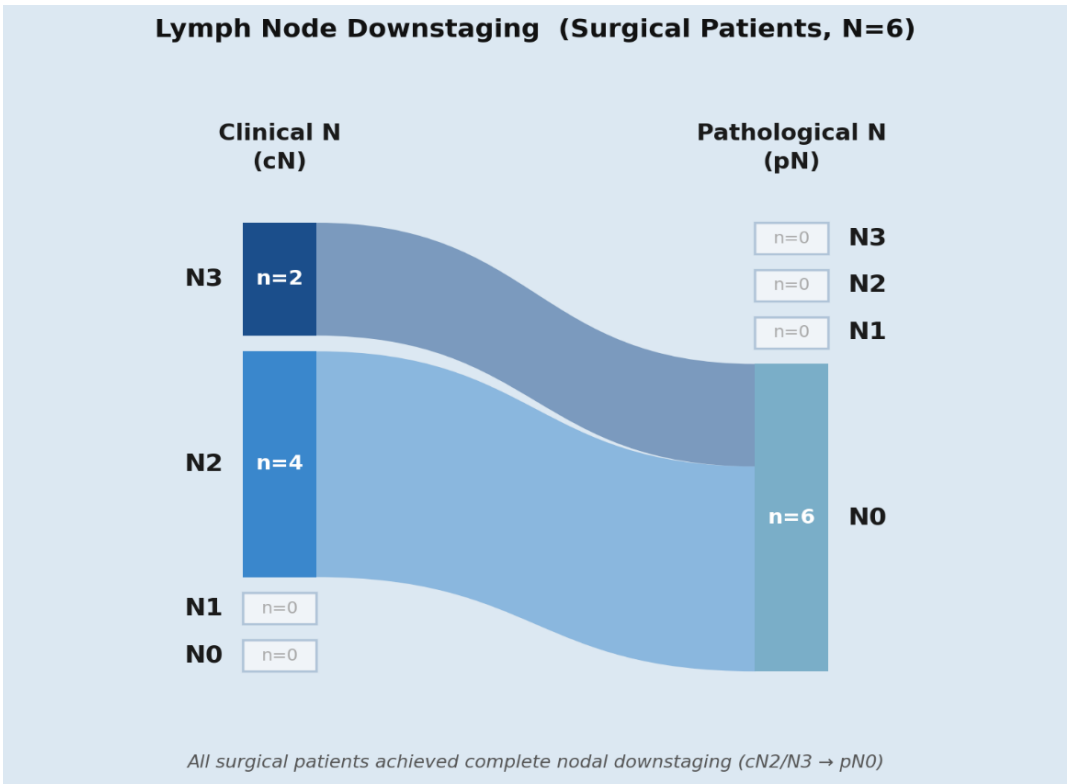
- Between November 2022 and September 2025, 18 patients were enrolled across four centers (**Figure 1**).
- In all patients, the median age 53.5 years; 61.1% female; 61.1% never-smokers, TNM stages were IIIA (27.8%), IIIB (55.6%), and IIIC (16.6%); Lymph node staging included N1 (5.6%) , N2 (38.9%) and N3 (55.6%) (**Table 1**).
- The confirmed objective response rate (ORR) was 77.8%, No primary progressive disease was observed. Six patients (33.3%) underwent R0 surgical resection following a median induction period of 131 days (range: 48–193). Notably, 5/6 surgical patients (83.3% of resected; 27.8% of total) achieved major pathological response (MPR), including 3 (16.7% of total) pathological complete responses (pCR)(**Table 2**).
- All 6 surgical patients (100%) achieved complete lymph node downstaging to pN0(**Figure 2**).
- With a median follow-up of 319 days, the median progression-free survival (PFS) was not reached; the 6-month and 12-month PFS rates were both 100%. One patient experienced relapse post-surgery and was successfully re-treated with lorlatinib (**Figure 3**).
- Treatment-related adverse events (TRAEs) were consistent with the known safety profile of lorlatinib. No treatment-related deaths occurred(**Table 3**).

Table 2:Surgical outcomes & ORR

Surgical outcomes (N=18)	
Days from last lorlatinib to surgery, median (range) (n=6)	131 (48-193)
Resection, n(%) R0 resection/ No resection	6 (33.3%)/ 12 (66.7%)
Pathological response (N=18)	
Non-MPR*	13 (72.2%)
MPR	5 (27.8%)
pCR	3 (16.7%)
Radiographic response (N=18)	
ORR	77.8%
CR	1 (5.6%)
PR	13 (72.2%)
SD	3 (16.7%)
NE	1 (5.6%)

* 12 patients did not undergo surgery, 1 patient undergoing surgery Non-MPR

Figure 2: Nodal Downstaging



METHODS

- This real-world, multicenter observational study enrolled treatment-naïve patients with histologically or cytologically confirmed unresectable Stage III (IIIA–IIIC, AJCC 8th edition) ALK-positive NSCLC, verified by local IHC or NGS. Patients received first-line lorlatinib (100 mg QD).
- Following induction, those deemed resectable by a multidisciplinary team (MDT) underwent surgery.
- The primary endpoint was objective response rate (ORR).
- Secondary endpoints included major pathological response (MPR), pathological complete response (pCR), R0 resection rate, lymph node downstaging, progression-free survival (PFS) and safety.
- Date cutoff: March 19, 2026.

Figure 1: The Trial Design

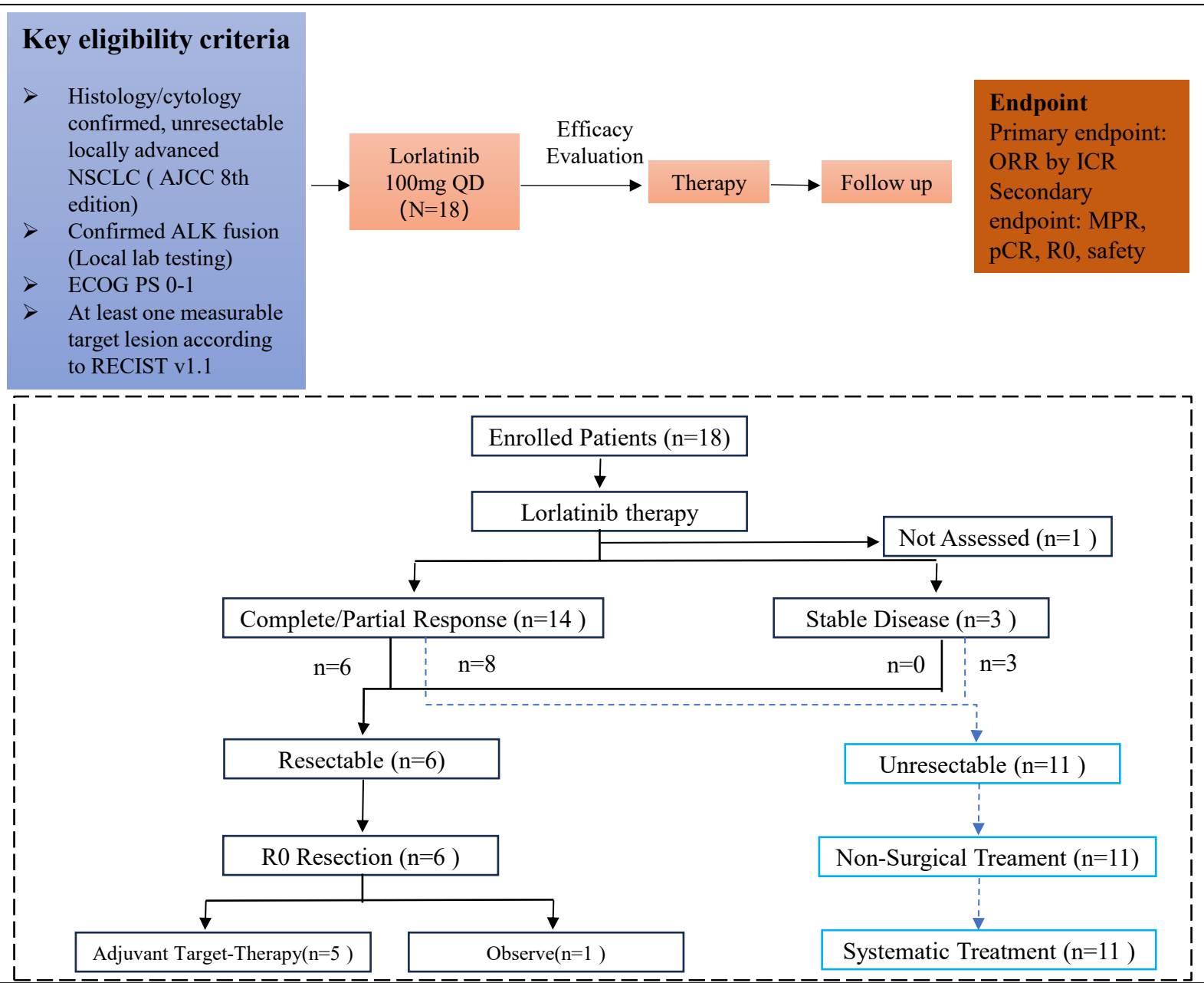


Table 1: Patients characteristics

Baseline characteristics n(%)	N=18
Sex, n (%)	
Male	7 (38.9%)
Female	11 (61.1%)
Median age, years (range)	53.5 (30.0–70.0)
Tabacco use, n (%)	
Never	11 (61.1%)
Curret/former	5 (27.8%)
Unkown	2 (11.1%)
TNM stage, n (%)	
IIIA	5 (27.8%)
IIIB	10 (55.6%)
IIIC	3 (16.6%)
Lymph node stage at diagnosis n (%)	
N1	1 (5.6%)
N2	7 (38.9%)
N3	10 (55.6%)
ALK testing, n (%)	
IHC	3 (16.6%)
NGS	14 (77.8%)
pCR	1 (5.6%)
Surgery, n (%)	6 (33.3%)

Figure 3: Progression-free Survival

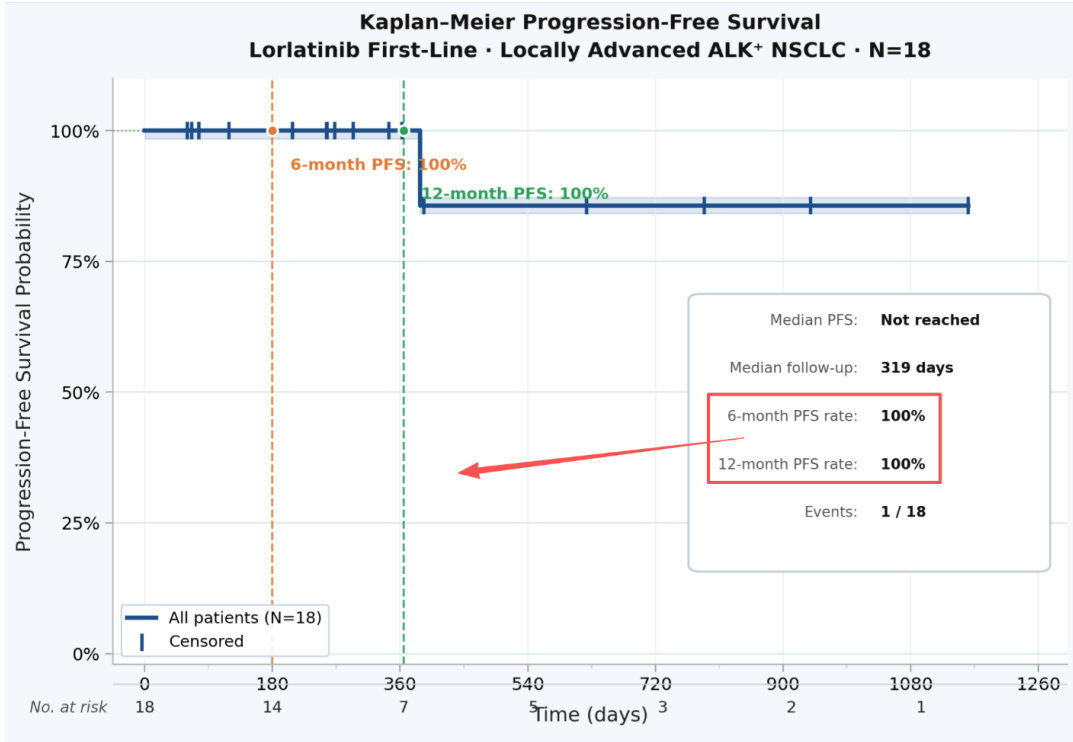


Table 3: TRAEs in all patients

Adverse Events N=18	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Hypercholesterolemia	5 (28)	4 (22)	3 (16)	0
Hypertriglyceridemia	2 (11)	2 (11)	3 (16)	2 (11)
Edema	2 (11)	5 (28)	0	0
Peripheral neuropathy	2 (11)	2 (11)	0	0
Diarrhoea	1 (6)	0	0	0
ALT increased	1 (6)	0	0	0
Cognitive effects	1 (6)	0	0	0
Weight increased	1 (6)	0	0	0

CONCLUSIONS

- First-line lorlatinib demonstrates remarkable efficacy a manageable safety profile in patients with unresectable Stage III ALK-positive NSCLC.
- The high objective response rate (77.8%), coupled with a 100% R0 resection rate and universal complete lymph node downstaging (pN0) among surgical candidates, underscores the potent cytoreductive capacity of induction lorlatinib. Furthermore, the 12-month PFS rate of 100% in the overall cohort is notable given the advanced stage at presentation.
- These preliminary real-world findings strongly support the further prospective validation of lorlatinib-based induction strategies as a multimodal treatment approach for locally advanced ALK-positive NSCLC.