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ORIGINAL ARTICLE

LOREALAUS: LOrlatinib REAL-World AUStralian Experience in Advanced ALK-Rearranged NSCLC

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ABSTRACT

Introduction: Over the past decade, ALK tyrosine kinase inhibitors have delivered unprecedented survival for individuals with *ALK*-positive (*ALK*+) lung cancers. Real-world data enhance the understanding of optimal drug sequencing and expectations for survival.

Methods: Multicenter real-world study of individuals with pretreated advanced *ALK*+ lung cancers managed on a lorlatinib access program between 2016 and 2020. Key outcomes were lorlatinib efficacy, tolerability, and treatment sequencing. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method among all individuals (PFSa and OSa), with at least 30 days (one-cycle) lorlatinib exposure (PFSb and OSb), and with good performance status (PFSc and OSc). Subgroups of interest were analyzed to assess signals of potential clinical applicability. Two OS index dates were analyzed, from lorlatinib initiation and advanced *ALK*+ diagnosis.

Results: The population (N = 38, 10 sites) was heavily pretreated (23 had ≥2 previous treatment lines) with a high disease burden (26 had 2–4 sites and 11 had >4 sites of metastatic disease, 19 had brain metastases). The overall response rate was 44% and the disease control rate was 81%. Lorlatinib dose reduction (18%), interruption (16%), and discontinuation (3%) were consistent with the trial experience. From advanced *ALK*+ diagnosis, the median OS for populations a, b, and c was 45.0 months, 69.9 months and 61.2 months respectively. From lorlatinib initiation, the median PFSa, PFSb and PFSc was 7.3 months, 13.2 months and 27.7 months and the median OSa, OSb and OSc was 19.9 months, 25.1 months and 27.7 months. The median PFSa with versus without brain metastases was 34.6 months versus 5.8 months ($p = 0.09$). The intracranial median PFS was 14.2 months. Previous good response versus poor response to the first *ALK*-directed therapy median PFSa was 27.7 months versus 4.7 months with a hazard ratio of 0.3 ($p = 0.01$).

Conclusions: Lorlatinib is a potent, highly active brain-penetrant third-generation ALK tyrosine kinase inhibitors with benefits for most individuals in the later-line setting in a real-world evaluation, consistent with clinical trial data.

Keywords: Lorlatinib; ALK; Anaplastic Lymphoma Kinase; Non–small cell lung cancer; NSCLC; Real-World

Introduction

ALK gene rearrangements are present in and molecularly define a distinct subset of NSCLCs, representing about 5% of NSCLCs. In Australia, lung cancer is the fourth most typically diagnosed cancer, and this corresponds to an incidence of approximately 620 new *ALK* NSCLC diagnoses per year among 13,810 new lung cancer diagnoses and 12,430 new NSCLC diagnoses (2021 data).[1,2] The most common recurring genomic alteration is the *EML4-ALK* gene fusion.[3,4] Since the discovery of *EML4-ALK* in NSCLC,[5] and the subsequent development of ALK-tyrosine kinase inhibitors (ALKi's), treatment and survival have been revolutionized for individuals with *ALK*-rearranged NSCLC.[6]

The first-in-class oral ALKi, crizotinib, was established as the standard of care in 2014, superseding platinum chemotherapy and surpassing expectations with mature overall survival (OS) at 57 months.[7] Second-generation ALKi's were next designed to be more potent to wild-type *ALK*, more brain-penetrant, and more active against *ALK* resistance mutations conferring crizotinib resistance—an eventuality for nearly all individuals either by on-target *ALK*-dependent, off-target *ALK*-independent resistance mechanisms or both.[8,9] Clinical trial data supporting efficacy for ceritinib, alectinib, brigatinib, and ensartinib followed in this order, with the latter three exhibiting superior frontline efficacy compared with crizotinib.[10–13]

Third-generation ALKi lorlatinib was then designed to overcome the common *ALK* kinase domain mutations conferring resistance to earlier generation ALKi's, notably *ALK* G1202R, and to be highly brain-penetrant. The phase 1/2 single arm data reported progression-free survival (PFS) after one line of second-generation ALKi at a modest 5.7 months, and in those treated with multiple lines of ALKi, 6.9 months. A strong signal was found in those with brain metastases with a central nervous system (CNS) overall response rate (ORR) 53% to 87% across cohorts. Highly positive frontline interim data for CROWN (First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer) present a landmark three-year PFS with more than 2/3 still on lorlatinib, and only one case of CNS recurrence.[14–17] Whilst detailed relapse performance and resistance mechanisms are awaited from CROWN, exploration of real-world ALKi sequencing provides novel data, not captured by means of the constraints of a clinical trial with every individual presenting a unique experience.

LOREALAUS details an Australian access program experience in a geographically and culturally diverse population, initiating lorlatinib from 2016 to 2020. The objectives of LOREALAUS were to provide novel real-world data to complement and further the previous multinational real-world data report by Zhu et al.,[18] and to provide the first mature OS sequencing data with later-line lorlatinib.

Materials and Methods

Cohort Selection

Eligibility criteria included advanced *ALK*-positive (*ALK*+) NSCLC (immunohistochemistry (IHC)-screened, fluorescence in situ hybridization (FISH)–diagnosed), previous ALKi failure, disease progression or intolerance, and treatment with lorlatinib on a region-specific, Pfizer-sponsored, early access program between October 2016 and August 2020.

Design

This multicenter investigator-initiated study (IIS) was conducted through the AUstralian Registry and biObank of thoRacic cAncers (AURORA) (ethics approval number HREC/17/PMCC/42). The AURORA platform facilitates a coordinated approach to the collection of diagnostic, treatment, and clinical outcomes data for Australians diagnosed with thoracic cancers. Individuals may be enrolled in AURORA by providing informed consent for prospective follow-up, or through an ethics-approved waiver of consent for retrospective data capture. A total of 10 AURORA sites having enrolled people onto the lorlatinib access program contributed patients into LOREALAUS. Deidentified multisite data were extracted from the AURORA database with analyses performed according to a prespecified study-specific statistical analysis plan. Pfizer provided deidentified access program registration information to support case identification and contributed funding to support this analysis. Pfizer had no input into the design, analysis, or interpretation of the results or content of this IIS.

Interventions

As part of the access program, all individuals commenced lorlatinib at the registered dose of 100 mg daily. All clinical management was at the discretion of the treating clinician including dose reductions and delays, imaging modality and frequency, and use of local therapies for oligoprogressive disease. Computed tomography (CT) staging imaging on an 8- to 12-weekly basis was common practice, with the addition of fluorodeoxyglucose–positron emission tomography (FDG-PET) increasingly used during the recruitment period, intermingled with CT, or to validate findings on CT imaging. CNS imaging was performed by means of at least CT, with brain magnetic resonance imaging (MRI-B) increasingly intermingled and replacing CT during the recruitment period depending on local access. Rebiopsy strategies and molecular profiling were as per local standard practice at the time of recruitment. Treating clinicians were required to report serious and unexpected adverse events separately and directly to the access program sponsor (Pfizer) in real time.

Objectives and End Points

Key objectives were to report lorlatinib efficacy and tolerability, treatment sequencing and patterns of progression, patterns of care with respect to the use of local therapies and rebiopsy, and *ALK* variant and resistance profiling if and when available.

Real-world PFS[19] was calculated as the time from lorlatinib treatment initiation to the first occurring event of clinician-reported disease progression, initiation of local therapy, or death. OS was calculated both from advanced *ALK* diagnosis (commencement of first-line therapy for advanced *ALK*+ NSCLC) and from lorlatinib initiation, to death by any cause. Three PFS and OS populations of clinical interest were analyzed: (1) whole population (PFSa and OSa); (2) 30 days or longer (one-cycle) lorlatinib exposure (PFSb and OSb); and (3) baseline Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (PFSc and OSc). Intracranial PFS was calculated as the time from lorlatinib initiation to the first occurring event of clinician-reported intracranial progression, initiation of intracranial therapy, or death. Real-world response and progression were defined by clinician-reported events according to the standard of care imaging as complete response (CR), partial response (PR), stable disease, and progressive disease (PD). Real-world ORR and disease control rate (DCR) were defined respectively as the proportion of individuals with CR or PR and CR, PR or stable disease among individuals with available response assessments guided by the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 definitions.[20] The intracranial ORR and DCR were similarly reported, with the denominator being individuals with the intracranial disease at lorlatinib initiation and available intracranial response assessment (CT-brain or MRI-B imaging accepted on the basis of local practice).

Adverse event data were limited because of the nature of retrospective data collection. Two clinically meaningful surrogate end points indicating drug tolerability were reported: (1) dose reduction, delay, and toxicity-related discontinuation; and (2) hospitalization for adverse events attributed by the treating clinician to study the drug (serious adverse events).

Table 1. Patient Diagnostic and Treatment Information

Characteristics	N = 38	%[a]
Age at diagnosis of NSCLC, median (range), y	50 (35-82)	
Age at lorlatinib initiation, median (range), y	53 (35-89)	
Sex, % female	25	65.8
Ethnicity		
White	25	67.5
Asian	12	32.4
Other/unknown	1	2.6
ECOG Performance Status		
0-1	19	76.0
≥2	6	24.0
UNK	13	34.2
Comorbidities[b]		
0	19	50.0
1	12	31.6
≥2	7	18.4
Smoking history		
Never smoked	27	75.0
Ever smoked	9	25.0
Histology		
Adenocarcinoma	38	100.0
PD-L1 expression		
Tested	12	31.6
>50%, among tested	5	41.7
Previously treated early-stage disease	8	21.1
Clinical trial enrolment throughout diagnosis	11	28.9
Brain imaging before starting lorlatinib		
CT and MRI	17	44.7
CT	11	28.9
None	4	10.5
CNS metastasis at NSCLC diagnosis	10	26.3
CNS metastasis at lorlatinib initiation	19	50.0
Number of different organ sites with metastatic disease at lorlatinib initiation		
1	6	15.8
2-4	26	68.4
≥4	11	28.9
Most common sites (n > 10) of metastatic disease at lorlatinib initiation		
Brain	19	50.0
Bone	15	39.5
Lung	15	39.5
Lymph node/skin	13	34.2
Lines of therapy before lorlatinib		
1 line	15	39.5
2 lines	13	34.2
≥3 lines	10	26.3
Exposure to ALKi before lorlatinib		
First and second-generation ALKi	16	42.1
Second-generation ALKi only	22	57.9
First-line therapy advanced disease		
First-generation ALKi	12	31.6
Second-generation ALKi	20	52.6
Platinum doublet	5	13.2
Other[c]	1	2.6
Radiotherapy during lorlatinib	2	5.3
Lines of therapy after lorlatinib		
0	25	65.8
1	8	21.1
≥2	5	13.2

[a]Proportions expressed among known categories (i.e., unknown excluded from denominator).
[b]Comorbidity assessment as per Colinet (31): cardiovascular, respiratory, neoplastic, renal, diabetes, alcoholism, and tobacco consumption.
[c]Patient received erlotinib as the first line of empirical treatment overseas before ALK testing/diagnosis on arrival in Australia.
ALKi, ALK-tyrosine kinase inhibitor; CNS, central nervous system; CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging.

Statistical Analysis

Institutions that recruited two or more individuals to the nationwide lorlatinib access program were invited to join AURORA and contribute to LOREALAUS to derive a pragmatic sample. Site and investigator participation in LOREALAUS was voluntary. Median and range (continuous variables), and frequency and percentage (categorical variables) were used to describe individuals and their clinical characteristics. Follow-up time was estimated using the reverse Kaplan-Meier method; OS and PFS were estimated using the Kaplan-Meier method and differences were compared using the log-rank test. Association between patient and treatment factors and OS and PFS were analyzed using univariate Cox proportional hazards regression. Exploratory comparative analyses were performed according to sex, ethnicity (White versus Asian), previous lines of therapy, and presence or absence of brain metastasis. Two-sided p values were set at a 0.05 significance level. Hazard ratio (HR) and 95% confidence intervals (CIs) were reported. Systemic treatment lines are visualized using a using swimmer plot. Analyses and swimmer plot generation were performed using Stata version 15.0 software (StataCorp, College Station, TX).[21]

Results

Individuals and Patterns of Disease

LOREALAUS included 38 individuals from 10 Australian sites who commenced lorlatinib between October 2016 and August 2020. The last follow-up was completed in June 2022 with 24 individuals (63%) deceased and median follow-up from lorlatinib initiation 32.5 months (95% CI: 28.3 months–57.6 months). Follow-up from *ALK* diagnosis was 87.6 months (95% CI: 58.3 mo–112.6 months), and longer among those who received first-line crizotinib compared with those who received a second-generation ALKi first-line (median = 99.7 months versus 54.2 months).

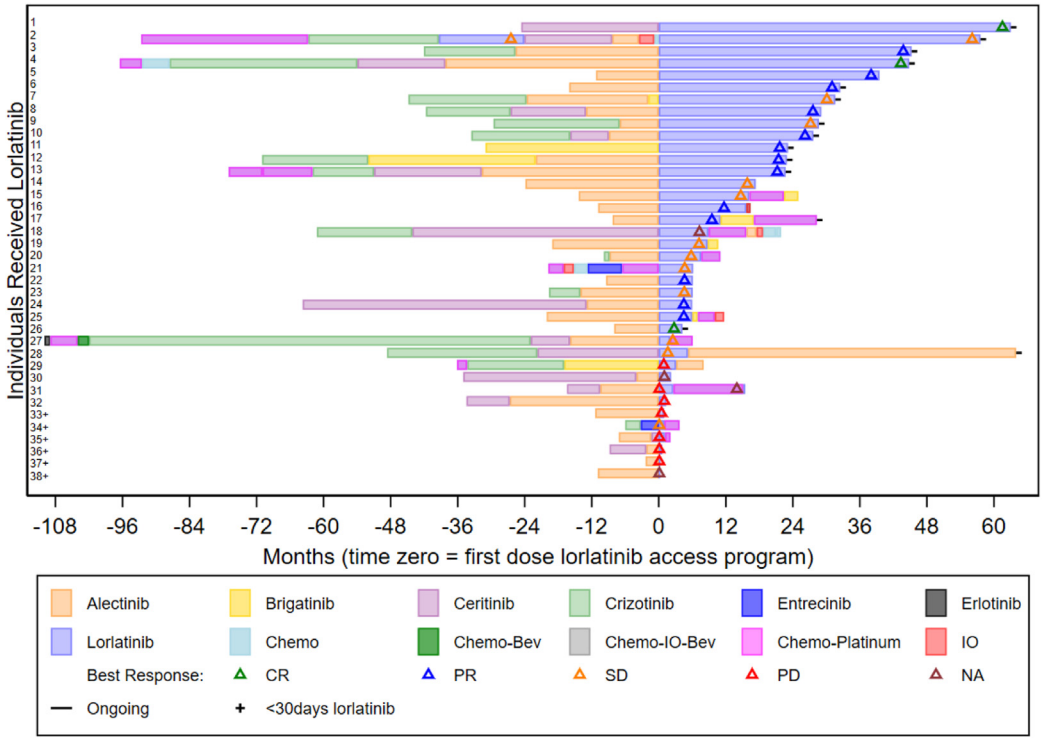

Figure 1. Swimmer plot displaying treatment sequences from diagnosis of advanced or metastatic NSCLC, the best response to lorlatinib, duration of benefit on lorlatinib, and current mortality status, with time zero reflecting the initiation of lorlatinib on the drug access program. Patient 2 received lorlatinib initially on clinical trial before reexposure on the access program and their lorlatinib PFS has been included as their PFS2 on lorlatinib under the study protocol analyzing patients' performance on lorlatinib under the compassionate access program. Chemo, nonplatinum cytotoxic chemotherapy; Chemo-Bev, bevacizumab/carboplatin/paclitaxel; Chemo-IO-Bev, atezolizumab/bevacizumab/carboplatin/paclitaxel, Chemo-Platinum, carboplatin with pemetrexed, paclitaxel or gemcitabine; IO, immunotherapy; CR, complete response; PR partial response; SD, stable disease; PD, progressive disease; NA, not assessed/not assessable; PFS, progression-free survival.

Demographics, disease characteristics, and treatment pathways are presented in Table 1.

Treatment Sequencing

Before lorlatinib treatment, eight individuals (21%) experienced recurrent advanced disease after initially undergoing curative intent treatments for early or locally advanced stage diagnoses. Lines of systemic treatment in the advanced metastatic setting are summarized in aggregate (Table 1) and for individuals (Fig. 1). Most received first-generation (n = 12, 32%) or second-generation (n = 20, 53%) ALKi's as first-line therapy. Lorlatinib was given in the second line (n = 15, 40%), third (n = 13, 34%), fourth (n = 5, 13%), and later lines (n = 5, 13%) of therapy—a median of two previous lines (third line), maximum of eight previous lines (ninth line). Local treatment for oligoprogressive disease was used for two individuals (6%) while on lorlatinib and four individuals (11%) after discontinuation of lorlatinib (all radiotherapy). In the advanced/ metastatic treatment setting, 11 individuals (29%) were treated on at least one clinical trial.

A total of 13 individuals (34%) received at least one line of systemic therapy after lorlatinib, including seven, subsequently treated with second-generation ALKi's and two rechallenged with lorlatinib on the access program with previous exposure on a clinical trial. Rechallenge after suspected lorlatinib-related bilateral hearing loss (patient 1 on Swimmer plot) was successful with the patient remaining on treatment after 18.3 months (additional to initial treatment period of 14.5 months). Rechallenge after progression (patient 3 on swimmer plot) occurred in the fifth line setting with limited lorlatinib exposure (11 days) before death.

Lorlatinib Duration of Therapy

At the data cutoff, 12 (32%) remained on lorlatinib with an overall median duration of 14.8 months (range: 5 days–5.3 years). Six individuals received less than 30 days lorlatinib including two less than 14 days; five of six (83%) were ECOG 2 at lorlatinib initiation and four of six (67%) received lorlatinib as third-line treatment.

Lorlatinib Disease Response Rates

Response evaluations were available for 95% of individuals (n = 36 of 38). The ORR was 44% (n = 16 of 36) and the DCR was 81% (n = 29 of 36), including CR (n = 3),

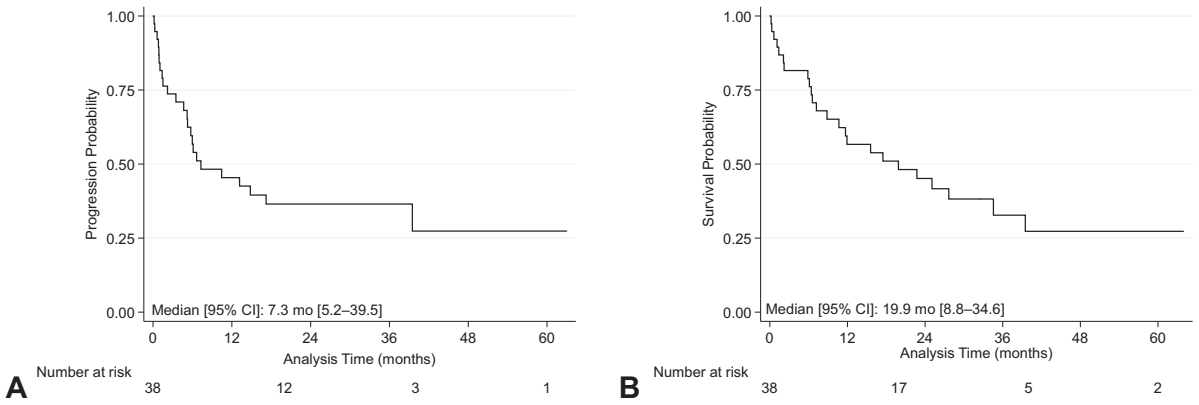

Figure 2. Real-world progression-free survival (*A*) and overall survival (*B*) from initiation of lorlatinib. ALKi, ALK-tyrosine kinase inhibitor.

PR (n = 13), stable disease (n = 13), PD (n = 7), and not applicable (n = 2, died, assumed PD). Therefore, PD as the best response was encountered in 24% (n = 9 of 38).

Progression-Free Survival

The median PFSa was 7.3 months (95% CI: 4.7–27.7) (Fig. 2*A*). The median PFSb was 13.2 months (95% CI: 6.0– not reported [NR]) including only individuals with 30 or more days lorlatinib exposure treatment and median PFSc was 27.7 months (95% CI: 4.7–39.5) including only individuals with baseline ECOG 0 to 1. The median PFS for the first subsequent therapy after lorlatinib was 4.9 months (95% CI: 1.3–6.8) among 13 individuals and for the second subsequent therapy was 2.0 months (95% CI: 0.4–NR) among 6 individuals.

The PFS according to previous ALKi exposure (Fig. 3) and response (Fig. 4) and among individuals with versus without brain metastasis (Fig. 5) are illustrated. By subgroups, median PFSa was 34.6 months (95% CI: 4.7–NR) with more than one previous ALKi, which included crizotinib (group 1); 10.5 months (95% CI: 3.1–39.5) with one previous second-generation ALKi (group 2; HR = 1.7, $p = 0.16$ versus group 1), and 1.1 months (95% CI: 0.6–NR) in the small group (n = 6) treated with multiple previous second-generation ALKi (group 3; HR = 4.3, $p < 0.01$ versus group 1) (Fig. 3*A*). The median PFS was 27.7 months (95% CI: 6.0–NR) compared with 4.7 months (95% CI: 0.9–10.5) among individuals with previous good versus poor response (defined as PFS above versus below the median of 14.3 months) to first *ALK*-directed therapy (first- or second-generation ALKi) (HR = 0.3, $p = 0.01$) (Fig. 4*A*). A similar trend was observed in the subgroup of individuals who only received one line of *ALK*-directed therapy being a second-generation ALKi before lorlatinib (PFS above versus below the median of 10.5 months) (Fig. 4*A*. Acknowledging small numbers, no obvious differences in PFS were observed according to ethnicity (White versus Asian), sex, or previous chemotherapy exposure and lorlatinib efficacy.

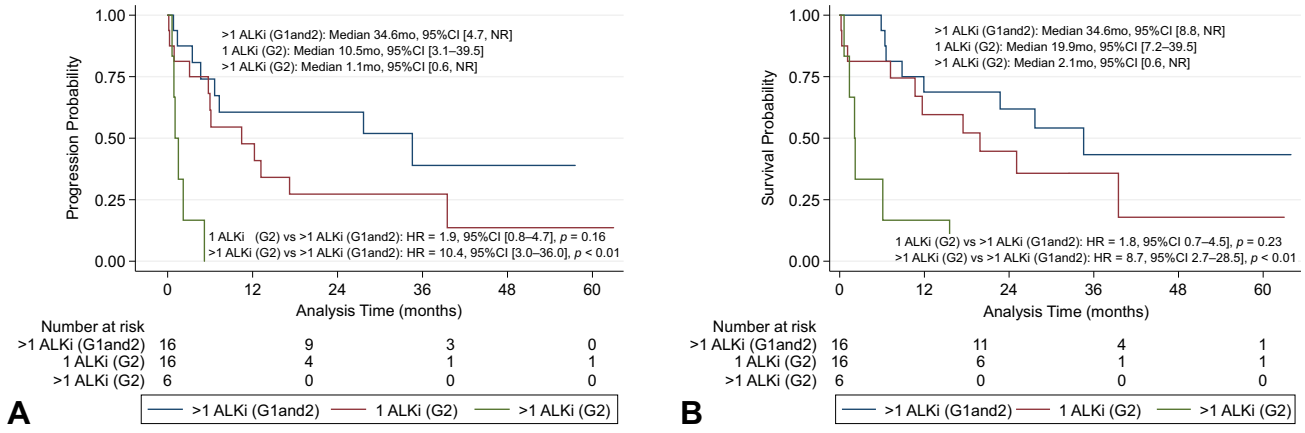

Figure 3. Real-world progression-free survival (*A*) and overall survival (*B*) from initiation of lorlatinib according to previous exposure to ALKi. Treatment group classification according to ALKi only; patients may have received chemotherapy and/or immunotherapy. ALKi, ALK-tyrosine kinase inhibitor; G1, first-generation ALKi; G2, second-generation ALKi.

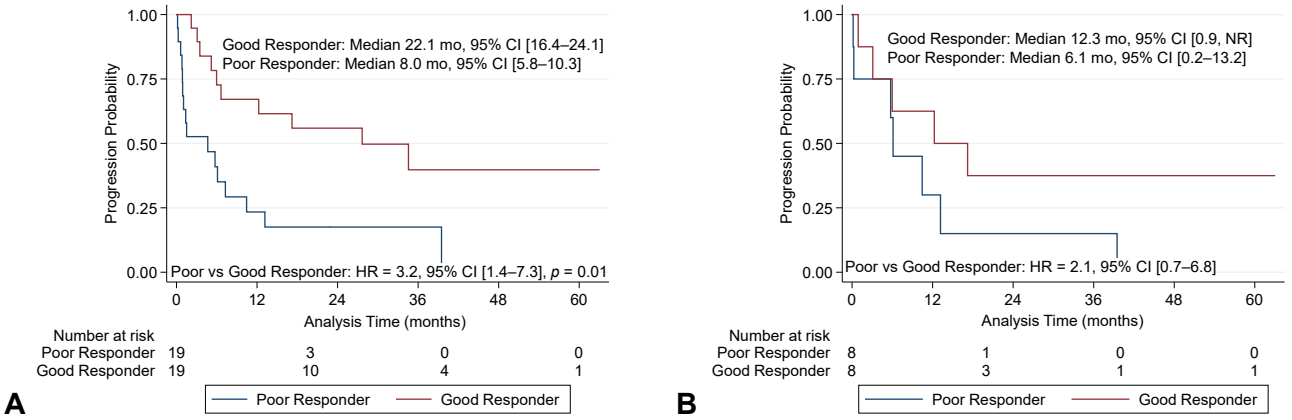

Figure 4. Real-world progression-free survival from initiation of lorlatinib according to previous responses to first ALKi among all comers (*A*), and among the subgroup who received only one second-generation ALKi before lorlatinib (*B*). Groups classified according to PFS to first ALK-directed therapy with individuals having PFS less than the median grouped as "poor responders" and greater than the median grouped as "good responders." Figure *A* includes all patients regardless of first systemic treatment line (some individuals had chemotherapy and/or immunotherapy before first ALKi) and regardless of first ALKi generation (first or second-generation ALKi). Figure *B* includes the subgroup that received only first-line second-generation ALKi followed by second-line lorlatinib. ALKi, ALK-tyrosine kinase inhibitor; PFS, progression-free survival.

Among 20 individuals with documented disease progression before death, patterns of progression varied: local (n = 2), regional (n = 2), local and regional (n = 3), distant with local or regional (n = 6), and distant (n = 7). Biopsy at lorlatinib discontinuation was not performed in any individuals; thus, histopathologic and molecular resistance mechanism data are unavailable.

OS, Advanced ALK Diagnosis

The median OS from advanced *ALK* diagnosis was 45.0 months (95% CI: 31.8–84.0) (Fig. 6). the median OSb was 70.0 months (95% CI: 39.4–NR) including only individuals with at least 30 days lorlatinib exposure, and median OSc was 61.3 months (95% CI: 28.4–NR) including only individuals with baseline ECOG 0 to 1.

By subgroups, the median OS was 116.3 months (95% CI: 45.0–NR) for individuals with more than one previous ALKi including crizotinib (group 1), 39.4 months (95% CI: 27.0–50.8) in those receiving only one previous ALKi line being a second-generation ALKi (group 2; HR = 3.3, $p = 0.02$ versus group 1), and 32.0 months (95% CI: 9.3–NR) in the small group (n = 6) treated with multiple previous second-generation ALKi's (group 3; HR = 5.7, $p < 0.01$ versus group 1). In the population treated with only second-generation ALKi before lorlatinib (groups 2 and 3 combined), the median OS was 35.8 months.

OS, Lorlatinib Initiation

The median OSa from lorlatinib initiation was 19.9 months (95% CI: 8.8–34.6) (Fig. 2*B*). The median OSb was 25.1 months (95% CI: 11.9–NR) including only individuals with at least 30 days lorlatinib exposure, and the median OSc was 27.7 months (95% CI: 8.8–39.5) including only individuals with baseline ECOG 0 to 1.

By subgroups, the median OS was 34.6 months (95% CI: 8.8–NR) with more than one previous ALKi including crizotinib (group 1), 19.9 months (95% CI: 7.2–39.5) with one previous second-generation ALKi (group 2; HR = 1.8, $p = 0.23$ versus group 1), and 2.1 months (group 3; 95% CI: 0.6–NR) in the six patients treated with multiple previous second-generation ALKi (group 3; HR = 8.7, $p < 0.01$ versus group 1) (Fig. 3*B*). In the population treated with only second-generation ALKi before lorlatinib (groups 2 and 3 combined), the median OS was 11.7 months. Acknowledging small numbers, no obvious difference was observed in OS according to ethnicity (white versus Asian), sex, or previous chemotherapy exposure.

CNS Outcomes

Response evaluations were available for 89% (n = 17 of 19) of individuals with intracranial disease at lorlatinib initiation. The intracranial ORR was 35% (n = 6 of 17) and the DCR was 77% (n = 13 of 17) including CR (n = 2), PR (n = 4), stable disease (n = 7), and PD (n = 4). More than 1/3 with brain metastases at study entry had received CNS radiotherapy before commencing lorlatinib (n = 7, 37%). One individual received radiotherapy for CNS disease during and one after the discontinuation of lorlatinib. The intracranial median PFS was 14.2 months (95% CI: 6.6–34.6) (Fig. 4*A*). One individual (3%) developed a new brain metastasis while receiving lorlatinib with normal baseline CNS imaging. Among individuals with brain metastases at the

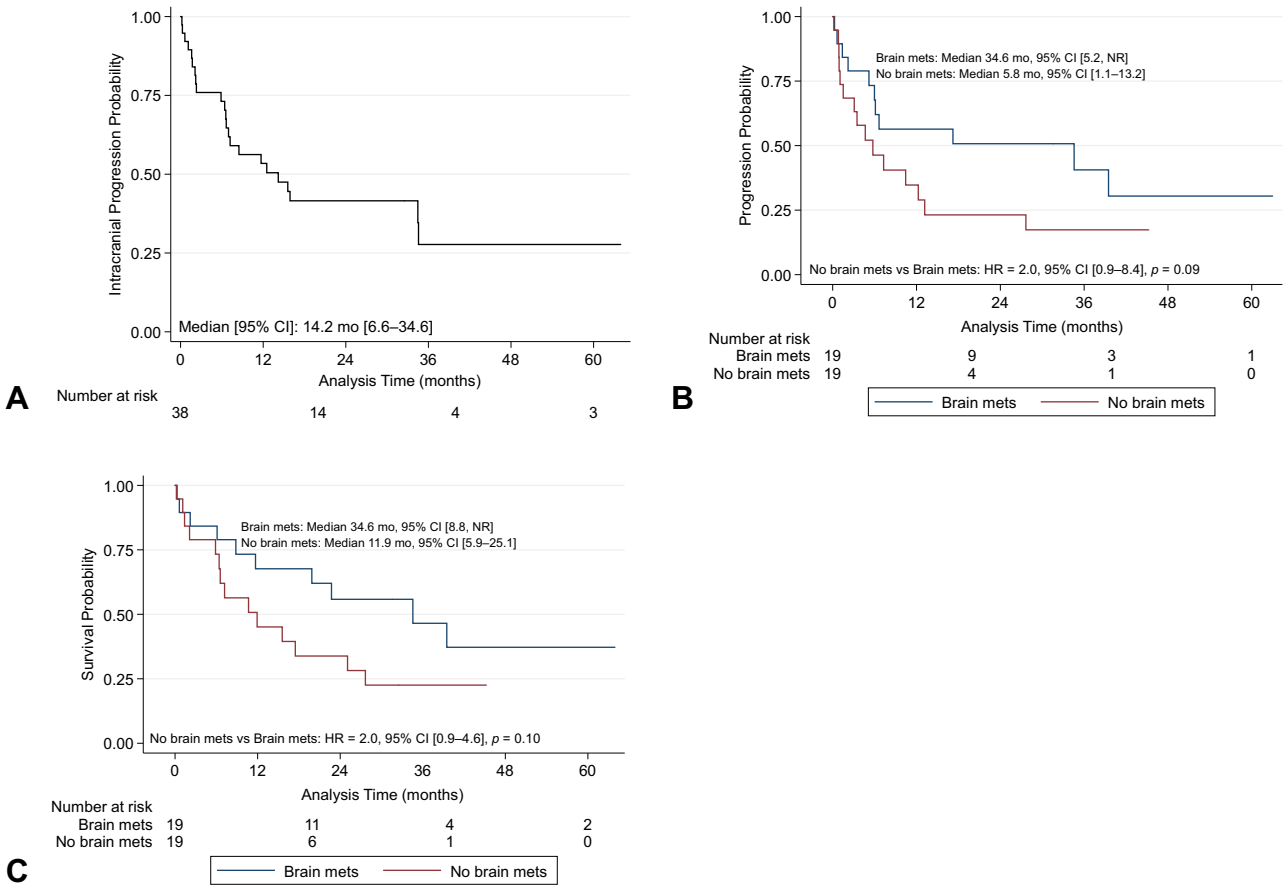

Figure 5. CNS outcomes. CNS progression-free survival from initiation of lorlatinib in the whole population (*A*) and progression-free survival (*B*) and overall survival (*C*) according to the presence of brain metastasis at the initiation of lorlatinib. CI, confidence interval; CNS, central nervous system; mets, metastasis; NR, not reported.

initiation of lorlatinib, the median PFS was 34.6 months (95% CI: 5.2–NR) and 5.8 months in those without brain metastases (95% CI: 5.9–25.1) (Fig. 4*B*). The median OS was 34.6 months (95% CI: 8.8–NR) with and 11.9 months (95% CI: 5.9–25.1) without brain metastases (Fig. 4*C*).

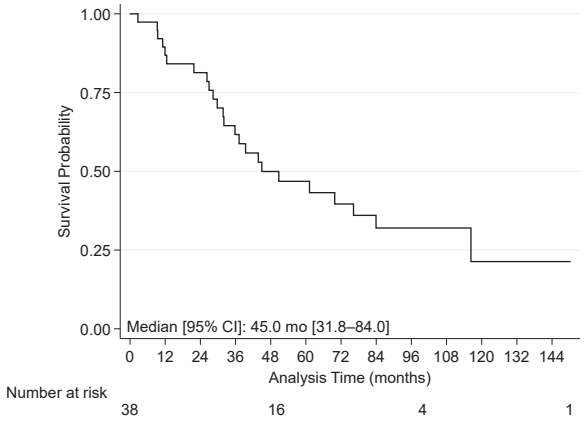

Figure 6. Overall survival from advanced *ALK* diagnosis.

Lorlatinib Safety and Tolerability

Six individuals were hospitalized while receiving lorlatinib with five disease-related events and one "potential" lorlatinib-related toxicity (blurred vision and hypotension). Dose reductions were required for seven individuals (18%) and delays for six individuals (16%)—two had both reductions and delays. Reasons for reductions and delays were not captured in this report. One individual (3%) discontinued the drug because of treatment-related toxicity on the lorlatinib access program (pneumonitis not requiring hospitalization; no rechallenge). Another individual had previously discontinued lorlatinib on clinical trial because of hearing loss, successfully rechallenged on the access program as previously described. Thromboembolic events were reviewed as an AE of special interest and reported among 23 individuals, with four (17%) individuals developing thrombotic events throughout their diagnosis (three white; one Asian). There was no difference in rates of dose modifications or hospitalizations according to ethnicity (white versus Asian).

Discussion

This multicenter multicultural real-world cohort presents a unique experience with longitudinal ALKi sequencing, including later-line lorlatinib in an *ALK*+ NSCLC population. LOREALAUS supports, compliments, and expands on the only previously published real-world report of this nature by Zhu et al.,[18] providing mature OS data in an ethnically diverse cohort and a further depth of understanding of this important population when sequencing multigeneration ALKi's.

In a small, yet meaningful cohort size respective to tumor rarity, individuals recruited were reflective of an *ALK* population. ALKi's were sequenced empirically, largely dictated by access, with molecular profiling not performed reflecting a lack of access in the region, lack of evidence to alter therapeutic care (at this time), and appreciating the temporality of disease at *ALK* progression may preclude rebiopsy. Although a shifting paradigm, disappointingly, at this time, there are no active recruiting biomarker-informed later-line therapeutic intervention clinical trials in *ALK*+ lung cancers internationally that the authors are aware of. This is despite a strong biological rationale supported by case reports and small series detailing heterogeneity in cases longitudinally and spatially.[22–24] A dynamic circulating tumor DNA (ctDNA) profiling clinical trial DYNAMALK (ALK+ NSCLC: an Australian DYNAMic ctDNA Profiling Study, ACTRN12623000226606p) will open in Australia in 2023, to inform ALKi and broader therapeutic selection, which may assist optimal sequencing including treatment-naive and pretreated lorlatinib arms. Similarly, a European study ALKALINE (Activity of Lorlatinib Based on ALK Resistance Mutations Detected on Blood in ALK Positive NSCLC Patients, NCT04127110) is undertaking longitudinal ctDNA profiling to define previously treated *ALK* populations that may benefit most from subsequent-line lorlatinib treatment on the basis of detected resistance mutations.[25]

In 2022, the international guidelines recommend frontline second-generation ALKi with lorlatinib as second-line.[26] A total of 16 individuals (40%) in LOREALAUS managed with this approach exhibited less favorable PFS and OS of 11 months and 20 months versus 35 months for both PFS and OS in those sequenced on more than one previous ALKi including crizotinib. This likely reflects "*ALK*-addiction," enabling latter-generation ALKi salvage.[27,28] In contrast, those with early relapse on second-generation ALKi likely have tumors intrinsically more molecularly diverse with *ALK*-independent resistance.

On the basis of the timeline of second-generation ALKi drug reimbursement and improved access outside of a clinical trial in the region, overlapping with the lorlatinib access program (crizotinib: July 2015, ceritinib: April 2017, alectinib: January 2018, brigatinib: March 2019, ensartinib: not Medicare reimbursed), it is notable the one-line second-generation ALKi treated individuals underperformed in this cohort with a frontline second-generation mPFS of a very modest 10 months. Using this median (n = 16), and the mPFS on the pan-ALKi frontline of 14 months (N = 38) as a delineator of "overperformers" and "underperformers," it becomes apparent that performance on previous ALKi determined durable benefit to lorlatinib in general. Personalized molecular profiling, especially with ctDNA, would help strengthen the confidence in response to lorlatinib particularly when the mechanism of drug escape to previous therapy is being driven by polygenomic, *ALK*-independent mechanisms in this group, away from *ALK*-addiction.[22] This is unavailable information in this real-world population—the authors note would be of great interest to understand. The potential for immortal time bias in this observation should also be noted.

With further molecular profiling, enabling rational onward drug selection, informing suitability to available further later-line clinical trials, and potentially exploring enhanced combination frontline therapies in "higher risk" new diagnoses, hope is offered to improve outcomes, particularly in the "underperformers.", The currently internationally recruiting fourth-generation ALKi trials ALKOVE-1/2 (A Study of NVL-655 in Patients With Advanced NSCLC and Other Solid Tumors Harboring ALK Rearrangement or Activating ALK Mutation, NCT05384626) and FORGE-1/2 (A Study of TPX-0131, a Novel Oral ALK Tyrosine Kinase Inhibitor, in Patients With ALK+ Advanced or Metastatic NSCLC, NCT04849273, currently paused to recruitment under review) are expected to deliver even greater *ALK* potency and be active in pretreated populations including those that have progressed on lorlatinib with compound mutations.[29,30] These studies were not available at the time of LOREALAUS recruitment, with an unmet need for treatments available after lorlatinib, as reflected in the poor PFS postlorlatinib: 4.9 months and 2.0 months first and second-line postlorlatinib, respectively.

Early resistance reports from the frontline lorlatinib CROWN data do not indicate sequencing in this approach will be as active in monotherapy with more *ALK*-independent resistance expected, perhaps by means of MET dysregulation, as compound *ALK* resistance kinase domain mutations have not yet experienced.[31]

In individuals with early ALKi progression, suspected waning *ALK*-addiction, and rapid drug failure inevitably leading to a deterioration in performance status, a timely switch to a chemotherapy-based approach plus or minus immunotherapy and an antiangiogenic agent combination approach such as ABCP (atezolizumab, bevacizumab, carboplatin, paclitaxel) may be more

appropriate; however, the noted international approval on the basis of small *ALK* numbers included in the trial has not been universal.[32] Some reassurances may come from the ORIENT-31 trial (Phase III study of sintilimab with or without IBI305 plus chemotherapy in patients with EGFR mutated nonsquamous NSCLC who progressed after EGFR-TKI therapy) describing improved outcomes with this approach in another (*EGFR*) oncogene population.[33] Such an improvement with the addition of immunotherapy to chemotherapy, over chemotherapy alone, is yet to be exhibited with the recently negative Checkmate 722 data (A phase 3 trial of nivolumab with chemotherapy or ipilimumab vs chemotherapy in epidermal growth factor receptor (EGFR)-mutation, T790M-negative stage IV or recurrent non-small cell lung cancer (NSCLC) after EGFR tyrosine kinase inhibitor (TKI) therapy) in again an *EGFR* population.[34] It must be noted almost 2/3 managed in the IMpower150 trial (Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC), recruiting an inherently fit population, encountered at least grade 3 toxicity. In contrast, our real-world lorlatinib experience had just one individual hospitalized with potential lorlatinib-related toxicity with an appealing tolerability profile comparable with clinical trial experience.[35] The availability of further well-tolerated, convenient oral agents to salvage (and prevent) drug resistance, is certainly preferable in the pursuit to optimally sequence therapies for *ALK* lung cancers chronically.

The CNS protective potential of lorlatinib makes it a preferential early-line treatment; with an appeal, this protection may persist beyond extracranial progression, and consideration of adding further therapies to lorlatinib is plausible in this circumstance (an evidence-evolving area). In LOREALAUS, progression with new CNS disease was rare (n = 1) and intracranial PFS was encouraging (14 months). Superior OS among individuals with brain metastases at study entry versus none (35 months versus 12 months, $p = 0.10$) is interpreted with the caveat of small numbers and potential confounding of further disease biological factors between the groups. Real-world data exist for the potential for PFS2 benefit in adding chemotherapy and continuing a later-line ALKi which may offer further confidence in CNS control than removing ALKi therapy and moving to a chemotherapy-based approach.[36]

To our knowledge, LOREALAUS offers the first mature OS data in individuals managed with later-line lorlatinib. The median PFS from lorlatinib initiation was 20 months in the whole population, 25 months with at least 30 days lorlatinib exposure, and 27 months with baseline ECOG 0 to 1. This translated to an OS from advanced *ALK* diagnosis of 45 months, 70 months, and 61 months in the three groups, respectively. Outcomes compare favorably to PROFILE 1014 (First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer) in which OS in frontline treated crizotinib was 50 months[37] representing the only current mature OS data from phase 3 clinical trial investigation, albeit with first-line crizotinib, which has now been superseded.

LOREALAUS also compares favorably to several real-world reports. The landmark 2017 ALKi sequenced OS report by Duruisseaux et al.[38] in a select historical population managed with crizotinib and then a second-generation ALKi (n = 84) reported an mOS of 87 months. The subsequent 2019 report by Pacheco et al.[39] (n = 110, United States) among the 105 individuals treated with crizotinib and a next-generation ALKi (not necessarily at the second line), a consistent median OS of 86 months was encountered. A recent 2023 report by Schmid et al.[40] (n = 148, Canada) included a population with most receiving frontline crizotinib (54%) or alectinib (44%), in which the median OS was 54 months. In the LOREALAUS population treated with first-line crizotinib and a next-generation ALKi, the median OS was 116 months.

In contrast, LOREALAUS also highlights that there is a population of ALKi-managed individuals who certainly underperform the clinical trial–expected survival in sequencing ALKi's, particularly those who relapse early on second-generation ALKi's or those receiving two second-generation empirically and then third-generation ALKi's. In the LOREALAUS population treated with only second-generation ALKi before lorlatinib (one or two lines), the median OS from diagnosis of advanced disease was 36 months and 12 months from lorlatinib initiation—disappointingly low for the survival potential now carried for *ALK*. In the small population treated with two second generations then lorlatinib, the median OS was 32 months from diagnosis of advanced disease and 2.2 months from lorlatinib initiation. The LOREALAUS authors reiterate that their preferred approach would be a timely liquid biopsy analyzing ctDNA by means of next-generation sequencing (NGS) in this circumstance, when available, as it is now recommended internationally as the preferred approach.[41]

In 2022, first-line lorlatinib was found to be substantially superior to crizotinib, with a PFS HR of 0.28 (95% CI: 0.19–0.41) from the CROWN trial,[14–17] as compared across trials with alectinib versus crizotinib PFS (HR = 0.43, 95% CI: 0.3–20.58) from the ALEX study (Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer),[6,42] and brigatinib versus crizotinib PFS (HR = 0.48, 95% CI: 0.35–0.66) from the ALTA-1L (Brigatinib versus Crizotinib in *ALK*-Positive Non–Small-Cell Lung Cancer) study.[43] Given lorlatinib is forging to the front line,[44] learnings from LOREALAUS with regard to treatment sequencing may become less

relevant, with new real-world studies required to proactively explore the evolving optimal sequencing landscape. Moreover, a concerted focus is required in investigating rational drug combination therapies informed by molecular profiling to prevent and overcome drug resistance, at each line of therapy and not only in the frontline (as illustrated in Fig. 2 in the review article by Itchins et al.[45]).

LOREALAUS did not capture the rate of attrition of *ALK*+ individuals at progression on each line of therapy. In oncology, the usual treatment paradigm advocates for the use of the most potent drug available at each line of therapy to ensure maximal benefit to most. However, in the *ALK*+ space, with the availability of multiple active lines of therapy, studies informing the best first and later-line approach are lacking, and may not be available because of a number of factors limiting the design and conduct of such a trial. In addition, industry-sponsored clinical trials tend to focus heavily on securing the indication in the frontline space, particularly in rare tumors, as this will take their drug to market again for the majority.

In interpreting the survival data of this cohort, some key limitations are acknowledged. The population entered was heterogeneous in demographics, disease trajectory, and previous therapies limiting the ability to draw definitive conclusions. Subgroups of interest contain small numbers, amplified by poor capture of performance status, which may skew results by outlier good and poor performers. Detailed toxicity profiling data (events and grading) are lacking because of the retrospective design with reporting restricted to sentinel events, to avoid recall bias and underreporting. The evaluation of the impact of treatment sequencing is limited by a lack of attrition data and immortal time bias. The attenuated precision and accuracy of PFS reporting in a retrospective cohort with variation in response assessment (timing, modality and reporting consistency), while meeting acceptable international definitions of "real-world" PFS, should be a recognized limitation and potential impact to over- or under-call estimated PFS.

Despite the above caveats, the described PFS and OS are favorable with lorlatinib, including the PFS in the overall population, which was at least comparable to the phase 2 experience reported by Solomon et al.,[28] or even superior. The LOREALAUS mPFS of 7 months in the whole population, 20 months with at least 30 days lorlatinib exposure, and 27 months with good baseline performance status is encouraging and informative for the clinician and consumer awareness.

In conclusion, this real-world multicenter experience of the third-generation ALKi lorlatinib in *ALK*+ lung cancer provides valuable information to clinicians treating this rare yet biologically and clinically unique condition. The overall performance with lorlatinib is comparable to the clinical trial experience with certain subgroups encountering superior outcomes, including those with CNS metastases and in previous durable responses to multigeneration before lines of ALKi. The OS from lorlatinib initiation was 20 months overall, 25 months in those with at least 30 days lorlatinib exposure, and 27 months in those with good baseline performance status.

In LOREALAUS, reflecting global practice at this time, there were no treatments initiated for biomarker-guided variables beyond *ALK*-positivity. Whereas lorlatinib is forging to the frontline setting globally, treatment stratification by further establishing individual- and tumor-informed biomarkers could inform personalized treatment(s) to maximize the opportunity for all individuals and achieve the greatest possible outcomes.

CRediT Authorship Contribution Statement

Study conceptualization and methodology was performed by MI, MA, BS, and NP. Data collection was performed by all aurthors, curation was performed by MA and MI and formal data analysis by MA, cross checked by MI and BS. Funding was acquired by MI and NP. The original draft of the manuscript was written by MA and MI, and all authors reviewed and edited previous versions of the manuscript. All authors read and approved the final manuscript.

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