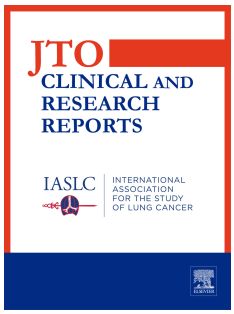


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**TITLE PAGE**

# LOREALAUS: LOrlatinib REAL world AUStralian experience in advanced anaplastic lymphoma kinase rearranged non-small cell lung cancer

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**CONFLICT OF INTEREST DECLARATIONS**

**Marliese Alexander:** Travel sponsorship: AZ**.** Advisory Boards: Pfizer/BMS

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**Sagun Parakh:** Advisory Boards: AZ, MSD. Speaking Honoraria: Roche, BMS. Research Funding: Bayer, Roche.

**Thomas John:** Advisory Boards: Roche, Merck, MSD, Puma, AstraZeneca, BMS, Novartis, Amgen, Gilead, PharmaMar, Specialised Therapeutics.

**Steven Kao:** Speaking honoraria: MSD, BMS, AstraZeneca, Pfizer, Roche and Boehringer. Travel sponsorship: Boehringer.

**Adnan Nagrial:** Advisory Boards: BMS, MSD, AZ, Pfizer, Roche, Takeda

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**Melissa Moore:** Advisory boards: Beigene, Takeda. Speaking honoraria: Astra Zeneca

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**LOREALAUS: LOrlatinib REAL world AUStralian experience in advanced anaplastic lymphoma kinase rearranged non-small cell lung cancer**

**ABSTRACT (250/250 words)**

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

***Methods:*** Multi-centre real-world study of individuals with pre-treated advanced *ALK*+ lung cancers managed on a lorlatinib access program between 2016-2020. 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/OSa), with ≥30 days (1-cycle) lorlatinib exposure (PFSb/OSb), and with good performance status (PFSc/OSc). Sub-groups of interest were analysed to assess signals of potential clinical applicability. Two OS index dates were analysed, from lorlatinib initiation and advanced *ALK*+ diagnosis.

***Results:*** The population (n=38, 10 sites) were heavily pre-treated (23 had ≥2 prior treatment lines) with high disease burden (26 had 2-4 sites and 11 had >4 sites of metastatic disease, 19 had brain metastases). ORR was 44% and DCR was 81%. Lorlatinib dose reduction (18%), interruption (16%) and discontinuation (3%) were consistent with the trial experience. From advanced *ALK*+ diagnosis median (m) OSa/b/c was 45.0mo/69.9mo/61.2mo. From lorlatinib initiation mPFSa/b/c was 7.3mo/13.2mo/27.7mo and mOSa/b/c 19.9mo/25.1mo/27.7mo. With versus without brain metastases mPFSa was 34.6mo vs 5.8mo (P=0.09). Intracranial mPFS was 14.2mo. Previous good response versus poor response to first *ALK* directed therapy mPFSa was 27.7mo vs 4.7mo, HR 0.3, P=0.01.

***Conclusion****:* Lorlatinib is a potent, highly active brain penetrant third-generation ALKi with benefit for most individuals in the later line setting in a real-world evaluation, consistent with clinical trial data.

## INTRODUCTION

Anaplastic lymphoma kinase (*ALK*) gene rearrangements are present in and molecularly define a distinct subset of non-small cell lung cancers (NSCLC), representing about 5% of NSCLCs. In Australia, with lung cancer being the fourth mostly commonly diagnosed cancer, 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 echinoderm-microtubule-associated protein-like 4 -*ALK* gene fusion (*EML4-ALK*).[3,4] Since the discovery of *EML4-ALK* in NSCLC,[5] and the subsequent development of *ALK*-tyrosine kinase inhibitors (ALKi), treatment and survival has been revolutionised 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 OS at 57 months.[7] Second-generation ALKi's, were next designed to be more potent to wild-type *ALK*, more brain penetrant, and active against *ALK* resistance mutations conferring crizotinib resistance – an eventuality for nearly all individuals either by on-target *ALK*-dependent, and/or off-target *ALK*-independent resistance mechanisms.[8,9] Clinical trial data supporting efficacy for ceritinib, alectinib, brigatinib and ensartinib followed in this order, with the later three demonstrating superior front line efficacy compared with crizotinib.[10-13]

Third-generation ALKi lorlatinib was then designed to overcome the common *ALK* kinase domain mutations (KDM's) conferring resistance to earlier generation ALKi's, notably *ALK* G1202R, and to be highly brain penetrant. The phase I/II single arm data reported PFS post one line of second-generation ALKi a modest 5.7months, and in those treated with multiple lines of ALKi, 6.9months. A strong signal was demonstrated in those with brain metastases with a CNS ORR was 53% to 87% across cohorts. Highly positive front-line interim data for lorlatinib versus crizotinib (CROWN) present landmark three-year PFS with more than 2/3 still on lorlatinib, and only one case of CNS recurrence.[14-17] As detailed relapse performance and resistance mechanisms are awaited from CROWN, exploration of real-world ALKi sequencing

provides novel data, not captured via 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 2016 to 2020. The objectives of LOREALAUS were to provide novel real-world data to complement and further the prior multi-national real world data report by Zhu and colleagues,[18] and to provide the first mature OS sequencing data with later line lorlatinib.

**METHODS**:

**Cohort Selection**

Eligibility criteria included: advanced *ALK*+ NSCLC (IHC screened, FISH diagnosed), prior 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 multicentre investigator-initiated study (IIS) was conducted through the AUstralian Registry and biObank of thoRacic cAncers (AURORA) – ethics approval no. HREC/17/PMCC/42. The AURORA platform facilitates a coordinated approach to the collection of diagnostic, treatment, and clinical outcomes data for Australian's 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. Ten AURORA sites having enrolled people onto the lorlatinib access program contributed patients into LOREALAUS. De-identified multisite data were extracted from the AURORA database with analyses performed according to a pre-specified study-specific statistical analysis plan. Pfizer® provided de-identified 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 results, or content of this IIS.

**Interventions**

As part of the access program all individuals commenced lorlatinib at the registered dose of 100mg daily. All clinical management was at discretion of the treating clinician including dose reductions and delays, imaging modality and frequency, use of local therapies for olio-progressive disease. CT staging imaging on an 8-12 weekly basis was common practice, with the addition of FDG-PET increasingly utilised during the recruitment period, intermingled with CT, and/or to validate findings on CT imaging. CNS imaging was performed via at least CT, with MRI-B increasingly intermingled and replacing CT during the recruitment period depending on local access. Re-biopsy 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®) real-time.

**Objectives and endpoints**

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

Real-world PFS[19] was calculated as the time from lorlatinib treatment initiation to 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 analysed: 1) whole population (PFSa/OSa); 2) ≥30 days (one-cycle) lorlatinib exposure (PFSb/OSB); and 3) baseline ECOG performance status 0-1 (PFSc/OSc). Intracranial PFS was calculated as the time from lorlatinib initiation to 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 standard of care imaging as complete response (CR), partial response (PR),

stable disease (SD), and progressive disease (PD). Real-world overall response rate (ORR) and disease control rate (DCR) were defined respectively as the proportion of individuals with CR/PR and CR/PR/SD among individuals with available response assessments guided by RECIST 1.1 definitions.[20] Intracranial ORR and DCR were similarly reported, with the denominator being individuals with intracranial disease at lorlatinib initiation and available intracranial response assessment (CT-brain and/or MRI-brain accepted based on local practice).

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

**Statistical analysis**

Institutions who 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 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 compared using the log rank test. Association between patient and treatment factors and OS/PFS were analysed using univariate Cox proportional hazards regression. Exploratory comparative analyses were performed according to sex, ethnicity (Caucasian vs Asian), prior lines of therapy, and presence/absence of brain metastasis. Two-sided p-values were set at a 0.05 significance level. Hazard ratio (HR) and 95% confidence intervals (CI) were reported. Systemic treatment lines are visualised using a using swimmer plot. Analyses and swimmer plot generation were performed using STATA v15.0 software.[21]

**RESULTS**:

**Individuals and patterns of disease**

LOREALAUS included 38 individuals from 10 Australian sites who commenced lorlatinib between October 2016 and August 2020. Last follow-up was completed June 2022 with 24 individuals (63%) deceased and median follow-up from lorlatinib initiation 32.5 months (mo) (95%CI 28.3 to 57.6mo). Follow-up from *ALK* diagnosis was 87.6mo (95%CI 58.3 to 112.6), and longer among those who received first-line crizotinib compared to those who received a second-generation ALKi first-line (median 99.7mo vs 54.2mo). Demographics, disease characteristics, and treatment pathways are presented in **Table 1**.

**Treatment sequencing**

Prior to lorlatinib treatment, eight (21%) individuals experienced recurrent advanced disease after initially undergoing curative intent treatments for early/locally advanced stage diagnoses. Lines of systemic treatment in the advanced/metastatic setting are summarized in aggregate (**Table 1**) and for individuals (**Figure 1)**. Most received first generation (n=12, 32%) or second-generation (n=20, 53%) ALKi as first line therapy. Lorlatinib was given in second line (n=15, 40%), third (n=13, 34%), fourth (n=5, 13%), and later lines (n=5, 13%) of therapy – median two prior lines (third line), maximum eight prior lines (ninth line). Local treatment for oligo-progressive 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.

Thirteen (34%) individuals 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 prior exposure on clinical trial. Rechallenge post suspected lorlatinib related bilateral hearing loss (Patient 1 on Swimmer Plot) was successful with the patient remaining on treatment after 18.3mo (additional to initial treatment period of

14.5mo). Rechallenge post progression (Patient 3 on Swimmer Plot) occurred in the fifth line setting with limited lorlatinib exposure (11 days) prior to death.

**Lorlatinib duration of therapy**

At data cut, 12 (32%) remained on lorlatinib with overall median duration 14.8mo (range 5 days to 5.3 years). Six individuals received <30 days lorlatinib including two <14 days; 5/6 (83%) were ECOG 2 at lorlatinib initiation and 4/6 (67%) received lorlatinib as third line treatment.

**Lorlatinib disease response rates**

Response evaluations were available for 95% of individuals (n=36/38). ORR was 44% (n=16/36) and DCR was 81% (n=29/36) including: CR (n=3), PR (n=13), SD (n=13), PD (n=7), and NA (n=2, died, assumed PD). Therefore, PD as a best response was encountered in 24% (9/38).

**Progression free survival**

Median PFSa was 7.3mo (95%CI 4.7 to 27.7) – **Figure 2.** mPFSb was 13.2mo (95%CI 6.0 to NR) including only individuals with ≥30-days lorlatinib exposure treatment and mPFSc was 27.7mo (95%CI 4.7 to 39.5) including only individuals with baseline ECOG 0-1. mPFS for first subsequent therapy after lorlatinib was 4.9mo (95%CI 1.3 to 6.8) among 13 individuals and for second subsequent therapy was 2.0mo (95%CI 0.4 to NR) among 6 individuals.

Progression free survival according to prior ALKi exposure (**Figure 3**) and response (**Figure 4**) and among individuals with/without brain metastasis (**Figure 5**) are shown. In subgroups, mPFSa was 34.6mo (95%CI 4.7 to NR) with >1 prior ALKi which included crizotinib (Group 1); 10.5mo (95%CI 3.1 to 39.5) with 1 prior second-generation ALKi (Group 2; HR 1.7, P=0.16 vs Group 1), and 1.1mo (95%CI 0.6 to NR) in the small group (n=6) treated with multiple prior second-generation ALKi (Group 3; HR 4.3, P<0.01 vs Group 1) – **Figure 3A.** mPFS was

27.7mo (95%CI 6.0 to NR) compared to 4.7mo (95%CI 0.9 to 10.5) among individuals with previous good/poor response (defined as PFS above versus below the median of 14.3mo ) to first *ALK* directed therapy (first- or second-generation ALKi); HR 0.3, P=0.01 – **Figure 4A**. A similar trend was observed in the subgroup of individuals who only received one line of *ALK* directed therapy being a second-generation ALKi prior to lorlatinib (PFS above versus below the median of 10.4mo) – **Figure 4B**. Acknowledging small numbers, no obvious differences in PFS were observed according to ethnicity (Caucasian vs Asian), sex, or prior chemotherapy exposure and lorlatinib efficacy.

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

**Overall survival, advanced *ALK* diagnosis**

Median OS from advanced *ALK* diagnosis was 45.0mo (95%CI 31.8 to 84.0) **– Figure 6A.** mOSb was 70.0mo (95%CI 39.4 to NR) including only individuals with ≥30-days lorlatinib exposure and mOSc was 61.3mo (95%CI 28.4 to NR) including only individuals with baseline ECOG 0-1.

In subgroups, mOS was 116.3mo (95%CI 45.0 to NR) for individuals with >1 prior ALKi including crizotinib (Group 1), 39.4mo (95%CI 27.0 to 50.8) in those receiving only 1 prior ALKi line being a second-generation drug (Group 2; HR 3.3, P=0.02 vs Group 1), and 32.0mo (95%CI 9.3 to NR) in the small group (n=6) treated with multiple prior second-generation ALKi (Group 3; HR 5.7, P<0.01 vs Group 1) – **Figure 5C.** In the population treated with only second generation ALKi prior to lorlatinib (Group 2 and Group 3 combined), mOS was 35.8mo.

**Overall survival, lorlatinib initiation**

mOS from lorlatinib initiation was 19.9mo (95%CI 8.8 to 34.6) – **Figure 2.** mOSb was 25.1mo (95%CI 11.9 to NR) including only individuals with ≥30-days lorlatinib exposure and mOSc was 27.7mo (95%CI 8.8 to 39.5) including only individuals with baseline ECOG 0-1.

In subgroups, mOS was 34.6mo (95%CI 8.8 to NR) with >1 prior ALKi including crizotinib (Group 1), 19.9mo (95%CI 7.2 to 39.5) with one prior second-generation ALKi (Group 2; HR 1.8, P=0.23 vs Group 1), and 2.1mo (Group 3; 95%CI 0.6 to NR) in the n=6 treated with multiple prior second-generation ALKi (Group 3; HR 8.7, P<0.01 vs Group 1) – **Figure 3B.** In the population treated with only second generation ALKi prior to lorlatinib (Group 2 and Group 3 combined), mOS was 11.7mo. Acknowledging small numbers, no obvious difference was observed in OS according to ethnicity (Caucasian vs Asian), sex, or prior chemotherapy exposure.

**Central nervous system outcomes**

Response evaluations were available for 89% (n=17/19) of individuals with intracranial disease at lorlatinib initiation. Intracranial ORR was 35% (n=6/17) and DCR was 77% (n=13/17) including: CR (n=2), PR (n=4), SD (n=7), PD (n=4). Over one third with brain metastases at study entry had received CNS radiotherapy prior to commencing lorlatinib (n=7, 37%). One individual received radiotherapy to CNS disease during and one after discontinuation of lorlatinib. Intracranial mPFS was 14.2mo (95%CI 6.6 to 34.6) – **Figure 4A**. One individual (3%) developed a new brain metastasis whilst receiving lorlatinib with normal baseline CNS imaging. Among individuals with brain metastases at initiation of lorlatinib, mPFS was 34.6mo (95%CI 5.2 to NR) and 5.8mo in those without brain metastases (95%CI 5.9 to 25.1) – **Figure 4C**. mOS was 34.6mo (95%CI 8.8 to NR) with and 11.9mo (95%CI 5.9-25.1) without brain metastases – **Figure 4C**.

**Lorlatinib safety and tolerability**

Six individuals were hospitalised whilst receiving lorlatinib with five events disease related 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 drug due to treatment related toxicity on the lorlatinib access program (pneumonitis not requiring hospitalisation; no rechallenge). Another individual had previously discontinued lorlatinib on clinical trial due to 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 Caucasian; one Asian). There was no difference in rates of dose modifications or hospitalisations according to ethnicity (Caucasian vs Asian).

## DISCUSSION

This multi-centre multi-cultural 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 upon the only prior published real-world report of this nature by Zhu and colleagues,[18] providing mature overall survival data in an ethnically diverse cohort and a further depth of understanding of this important population when sequencing multi-generation ALKi's.

In a small, yet meaningful cohort size respective to tumour 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 re-biopsy. Whilst 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 ctDNA profiling clinical trial 'DYNAMALK' will open in Australia in 2023, to inform ALKi and broader therapeutic selection which may assist optimal sequencing including treatment naïve and pre-treated lorlatinib arms. Similarly, a European study (ALKALINE, NCT04127110) is undertaking longitudinal ctDNA profiling to define previously treated *ALK* populations that may benefit most from subsequent line lorlatinib treatment based on detected resistance mutations.[25]

In 2022, International guidelines recommend front line second-generation ALKi with lorlatinib second line.[26] Sixteen individuals (40%) in LOREALAUS managed with this approach with demonstrated less favourable PFS/OS of 11mo/20mo versus 35mo for both PFS and OS in those sequenced on more than one prior 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 tumours intrinsically more molecularly diverse with *ALK*-independent resistance.

Based on 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 front line second-generation mPFS of a very modest 10mo. Utilising this median (n=16), as well as the mPFS on pan-ALKi front line of 14mo (n=38) as a delineator of 'over-performers' and 'under-performers', it become apparent performance on prior ALKi determined durable benefit to lorlatinib in general. Personalised molecular profiling, especially with ctDNA would help strengthen the confidence in response to lorlatinib particularly if the mechanism of drug escape to prior therapy is being driven by poly-genomic, *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 front line 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 NVL 655 (NCT05384626) and FORGE-1/2 TPX-0131 (NCT04849273, currently paused to recruitment under review) are expected to deliver even greater *ALK* potency, and be active in pre-treated populations including those that have progressed on lorlatinib with compound mutations.[29,30] These studies were not available at the time of LORELAUS recruitment, with an unmet need for treatments available post lorlatinib reflected in the poor PFS's post lorlatinib: 4.9mo and 2.0mo first and second-line post lorlatinib respectively.

Early resistance reports from the front line lorlatinib CROWN data do not indicate sequencing in this approach will be as active in monotherapy with more *ALK*-independent resistance expected, perhaps via MET dysregulation, as compound *ALK* resistance KDMs 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 +/- immunotherapy and an anti-angiogenic agent combination approach such as atezolizumab/bevacizumab/carboplatin/paclitaxel (ABCP) may be more appropriate; however, noted International approval based on small *ALK* numbers included in the trial has not been universal.[32] Some reassurances may come from the ORIENT-31 trial 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 demonstrated with with the recently

negative Checkmate 722 data in again an *EGFR* population.[34] It must be noted almost 2/3 managed in the IMpower150 trial, an inherently fit population, encountered Grade ≥3 toxicity. Contrastingly, our real-world lorlatinib experience had just one individual hospitalised 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, are 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 appeal this protection may persist beyond extracranial progression, and considering adding further therapies to lorlatinib plausible in this circumstance (an evidence evolving area). In LOREALAUS, progression with new CNS disease was rare (n=1) and intracranial PFS encouraging (14mo). Superior OS among individuals with brain metastases at study entry versus none (35mo vs 12mo, 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]

LOREALAUS offers the first mature OS data in individuals managed with later line lorlatinib. Median PFS from lorlatinib initiation was 20mo in the whole population, 25mo with ≥30days lorlatinib exposure, and 27mo with baseline ECOG 0-1. This translated to an OS from advanced *ALK* diagnosis of 45mo, 70mo, and 61mo in the three groups respectively. Outcomes compare favourably to PROFILE 1014 in which OS in front line treated crizotinib was 50mo[37] representing the only current mature OS data from PIII clinical trial investigation, albeit with first line crizotinib which has now been superseded.

LOREALAUS also compares favourably to several real-world reports. The landmark 2017 ALKi sequenced OS report by Duruisseaux and French colleagues, in a select historical

population managed with crizotinib and then a second-generation ALKi (n=84)reported mOS 87mo.[38] Subsequent 2019 report by Pacheco and colleagues (n=110, USA) among the 105 individuals treated with crizotinib and a next-generation ALKi (not necessarily at second line),a consistent mOS 86mo was encountered.[39] Recent 2023 report by Schmid and colleagues (n=148, Canada) included a population with majority receiving front-line crizotinib (54%) or alectinib (44%) in which median OS was 54mo.[40] In the LOREALAUS population treated with first line crizotinib and a next generation ALKi, mOS was 116mo.

Contrastingly, LOREALAUS also highlights 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 prior to lorlatinib (one or two lines), mOS from diagnosis of advanced disease was 36mo and 12mo from lorlatinib initiation, disappointingly low for the survival potential now carried for *ALK*. In the small population treated with two second-generation then lorlatinib, mOS was 32mo from diagnosis of advanced disease and 2.2mo from lorlatinib initiation. The LOREALAUS authors reiterate their preferred approach would be timely liquid biopsy analysing ctDNA via NGS in this circumstance if available, as is now a recommended International preferred approach.[41]

In 2022, first-line lorlatinib was shown to be substantially superior to crizotinib, with the PFS HR 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 0.32-0.58) from ALEX,[42,43] and brigatinib versus crizotinib PFS HR 0.48 (95%CI 0.35 to 0.66) from ALTA-1L.[44] Given lorlatinib is forging to the front-line,[45] learnings from LOREALAUS with regards to treatment sequencing may become less relevant, with new real-world studies required proactively exploring 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, not only front-line as illustrated in Figure 2 in the review article by Itchins/Pavlakis.[46]

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 the majority. 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 due to a number of factors limiting the design and conduct of such a trial, whilst Industry sponsored clinical trials focus heavily on securing the indication in the front-line space, particularly in rare-tumours, 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 were heterogeneous in demographics, disease trajectory, and prior therapies limiting ability to draw definitive conclusions. Sub-groups of interest contain small numbers, amplified by poor capture of performance status, which may skew results by outlier good/poor performers. Detailed toxicity profiling data (events and grading) are lacking due to retrospective design with reporting restricted to sentinel events, to avoid recall bias and underreporting. Evaluation of the impact of treatment sequencing is limited by 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/reporting consistency), whilst meeting acceptable international definitions of ‘real-world’ PFS, should be a recognised limitation and potential impact to over- or under-call estimated PFS.

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

## CONCLUSION

This real-world multi-centre 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 sub-groups encountering superior outcomes, including those with CNS metastases and in prior durable response to multi-generation prior lines of ALKi. Overall survival from lorlatinib initiation was 20mo overall, 25mo in those with at least 30days lorlatinib exposure, and 27mo 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'. Whilst lorlatinib is forging to the front line setting globally, treatment stratification by further establishing individual- and tumour informed biomarkers could inform personalised treatment(s) to maximise the opportunity for all individuals to achieve greatest possible outcomes.



## AUTHOR CONTRIBUTIONS

The study was conceived and designed by MI, MA, BS, and NP. All authors contributed to data collection. Material preparation and analysis were performed by MA and MI. The first draft of the manuscript was written by MA and MI, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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## Tables and Figures

**Table 1.** Patient, diagnostic and treatment information.

**Figure 1**. Swimmer plot displaying treatment sequences from diagnosis of advanced or metastatic non-small cell lung cancer, best response to lorlatinib, duration of benefit on lorlatinib and current mortality status, with time zero reflecting initiation of lorlatinib on the drug access program.

**Figure 2.** Real-world progression free survival (A) and overall survival (B) from initiation of lorlatinib.

**Figure 3.** Real-world progression free survival (A) and overall survival (B) from initiation of lorlatinib according to prior exposure to ALKi.

**Figure 4.** Real-world progression free survival from initiation of lorlatinib according to prior response to first ALKi among all comers (A), and among the subgroup who received only one second-generation ALKi prior to lorlatinib (B).

**Figure 5.** Central nervous system 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 presence of brain metastasis at initiation of lorlatinib.

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

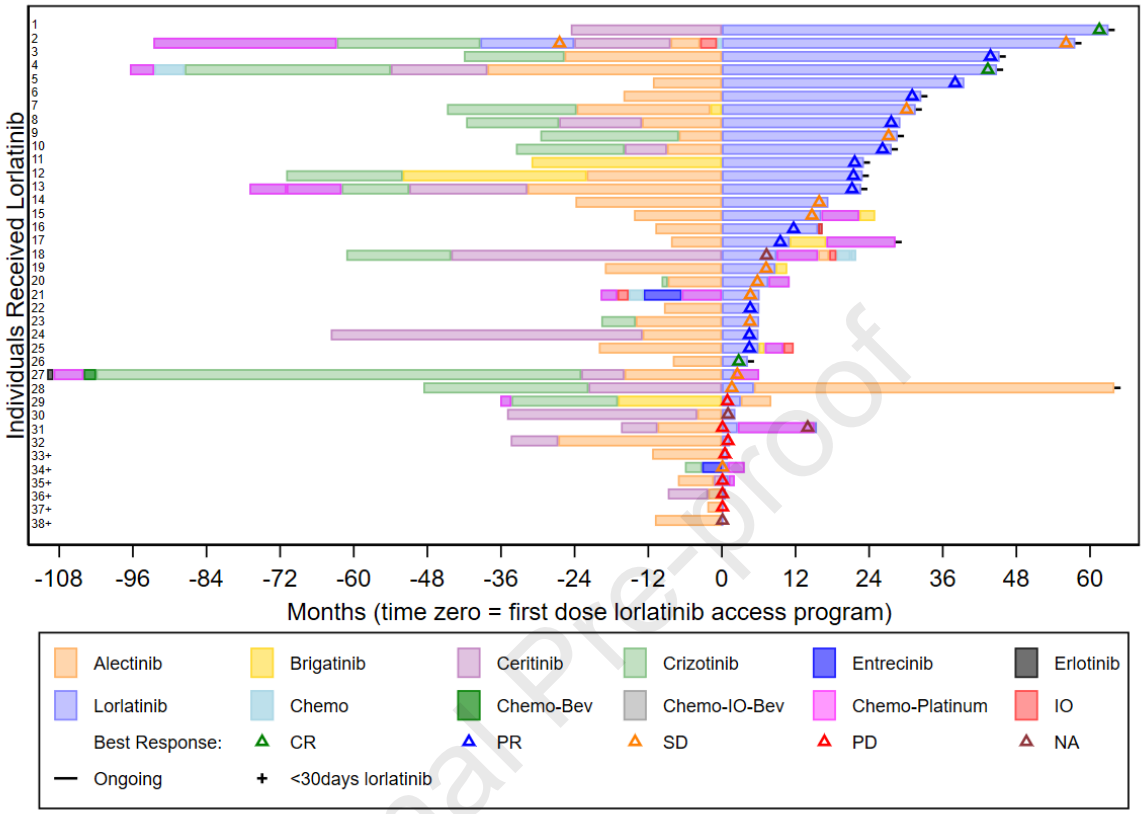
**Table 1. Patient, diagnostic and treatment information**

| Characteristic | N=38 | %[a] |
|---|---|---|
| Age at diagnosis of NSCLC, median (range) | 50 (35-82) | |
| Age at lorlatinib initiation, median (range) | 53 (35-89) | |
| Sex, % female | 25 | 65.8% |
| Ethnicity | | |
| White/Caucasian | 25 | 67.5% |
| Asian | 12 | 32.4% |
| Other/Unknown[1] | 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 prior to 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 prior to lorlatinib | | |
| 1 line | 15 | 39.5% |
| 2 lines | 13 | 34.2% |
| >=3 lines | 10 | 26.3% |
| Exposure to ALKi prior to 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[b] | 1 | 2.6% |
| Radiotherapy during lorlatinib | 2 | 5.3% |
| Lines of therapy post lorlatinib | | |
| 0 | 25 | 65.8% |
| 1 | 8 | 21.1% |
| >=2 | 5 | 13.2% |

Footnotes: (a) Proportions expressed amongst 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 first line of empiric treatment overseas prior to ALK testing/diagnosis on arrival in Australia

Abbreviations: ALKi: *ALK* tyrosine kinase inhibitor; CNS: central nervous system; CT: computerised tomography); ECOG: Eastern Cooperative Oncology Group; MRI: magnetic resonance imaging

**Figure 1**. Swimmer plot displaying treatment sequences from diagnosis of advanced or metastatic non-small cell lung cancer, best response to lorlatinib, duration of benefit on lorlatinib and current mortality status, with time zero reflecting initiation of lorlatinib on the drug access program.




**Footnotes**: Patient 2 received lorlatinib initially on clinical trial prior to re-exposure on the access program and their lorlatinib PFS has been included as their PFS2 on lorlatinib under the study protocol analysing patients' performance on lorlatinib under the compassionate access program.
**Abbreviations:** Chemo: non-platinum 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

**Figure 2.** Real-world progression free survival (A) and overall survival (B) from initiation of lorlatinib.

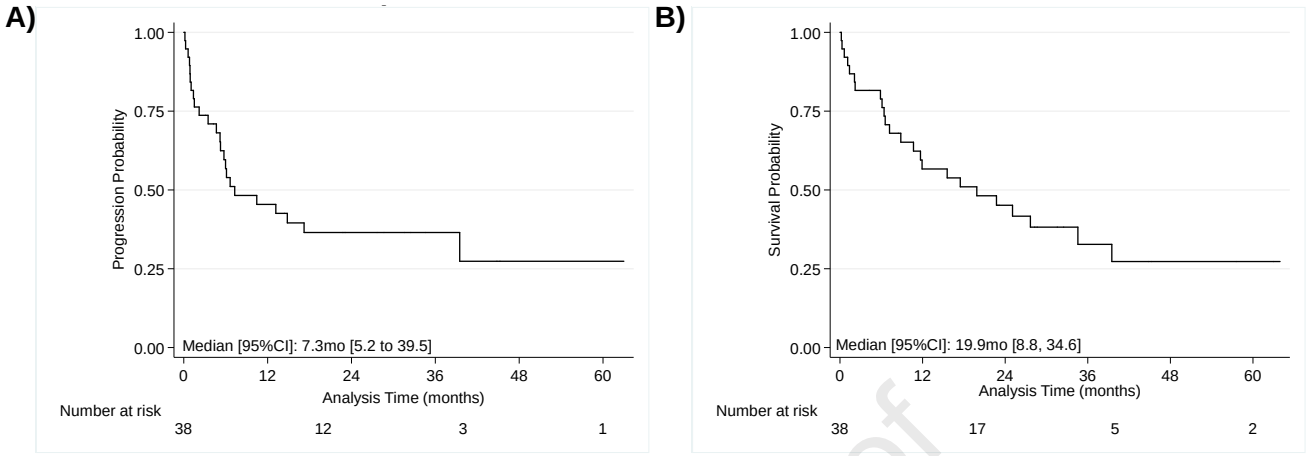
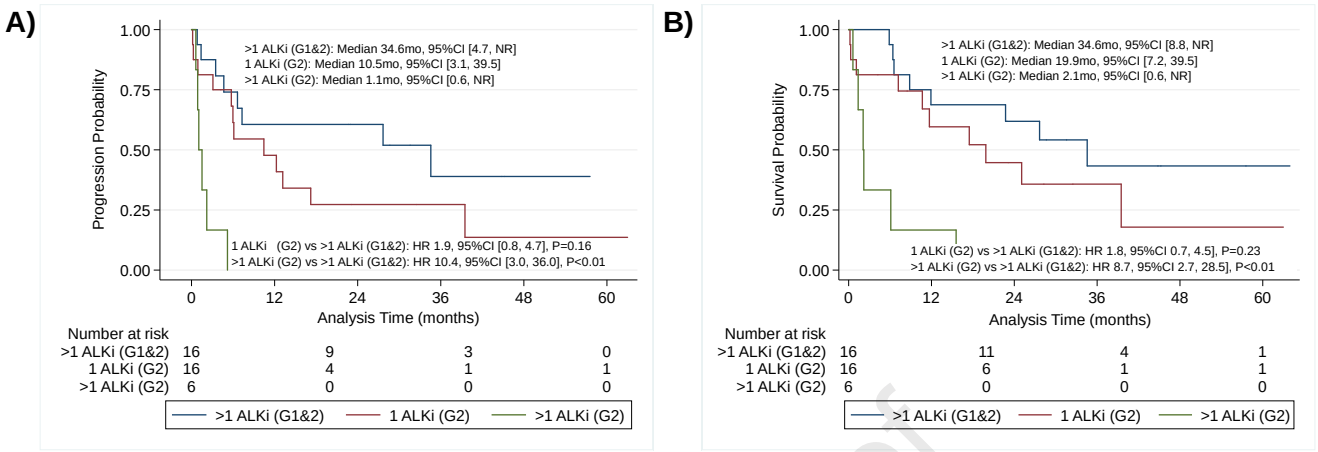


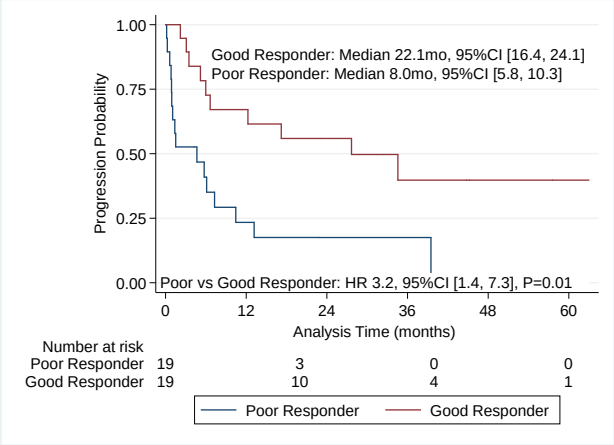
**Figure 3.** Real-world progression free survival (A) and overall survival (B) from initiation of lorlatinib according to prior exposure to ALKi.



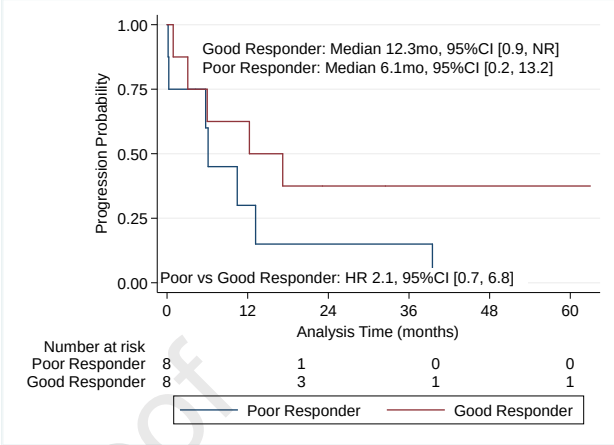

**Footnote**: Treatment group classification according to ALKi only; patents may have received chemotherapy and/or immunotherapy.
**Abbreviations**: *ALK*-tyrosine kinase inhibitor (ALKi); G1: first-generation ALKi; G2: second-generation ALKi.

**Figure 4.** Real-world progression free survival from initiation of lorlatinib according to prior response to first ALKi among all comers (A), and among the subgroup who received only one second-generation ALKi prior to lorlatinib (B).

**A)**



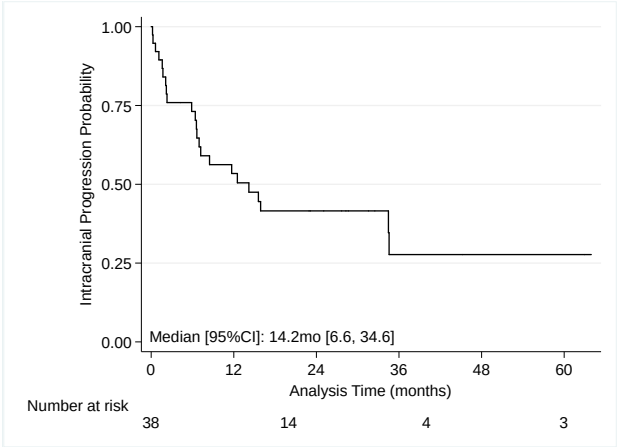

**B)**



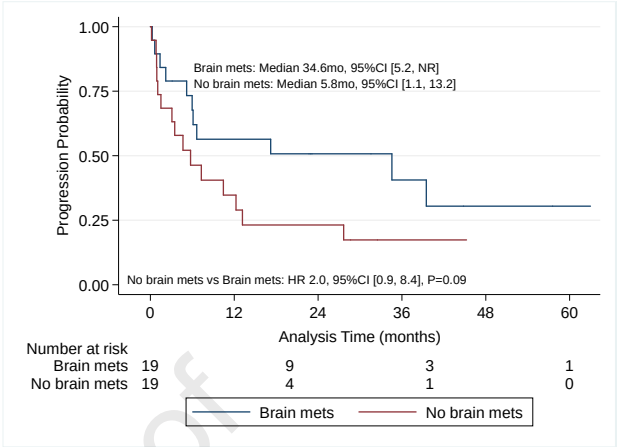

**Footnote**: Groups classified according to PFS to first ALK-directed therapy with individuals having PFS less than the median grouped as 'poor responders' and greater than the median grouped as 'good responders'. Figure A includes all patients regardless of first systemic treatment line (some individuals had chemotherapy and/or immunotherapy prior to first ALKi) and regardless of first ALKi generation (first or second-generation ALKi). Figure B includes the subgroup who received only first line second-generation ALKi followed by second line lorlatinib.

**Figure 5.** Central nervous system 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 presence of brain metastasis at initiation of lorlatinib.

**A)**




**B)**




**C).**

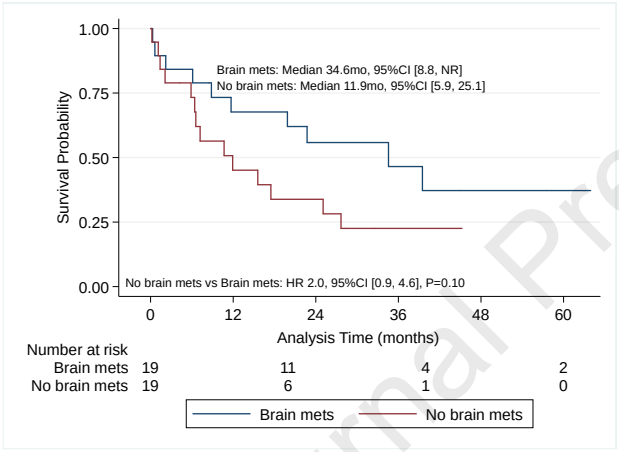
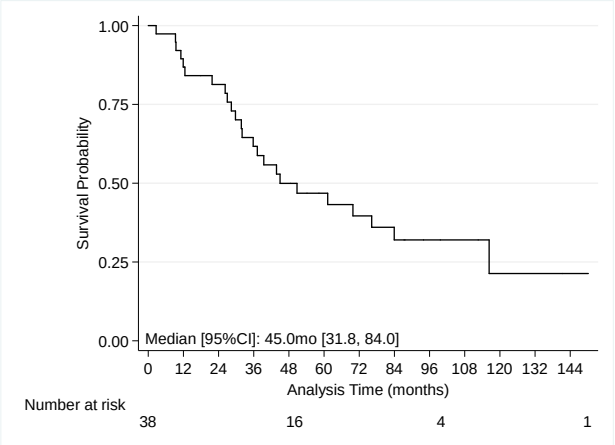


**Figure 6.** Overall survival from advanced *ALK* diagnosis



## AUTHOR CONTRIBUTIONS

The study was conceived and designed by MI, MA, BS, and NP. All authors contributed to data collection. Material preparation and analysis were performed by MA and MI. The first draft of the manuscript was written by MA and MI, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.