Original Study

In-depth Analysis of Lorlatinib-related neurocognitive Adverse Events in Patients With Non–small-cell Lung Cancer

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Abstract

Lorlatinib represents a potent, and brain-penetrant, next-generation ALK/ROS1 TKI. Despite significant efficacy, a notable drawback is the emergence of neurocognitive adverse events (NCAEs). Our multicenter study involving comprehensive neurocognitive assessments failed to reveal a sustained deterioration within any of the assessed neurocognitive domains.

Introduction: Lorlatinib is a potent, brain penetrant, next-generation ALK/ROS1 TKI, with high response rates and durable responses, including the brain. However, a significant drawback is the manifestation of neurocognitive adverse events (NCAEs). Despite being generally low-grade in severity, these NCAEs can be physically and mentally disabling. Extensive neurocognitive testing in this group of patients is lacking; therefore we conducted this study. **Patients and methods:** This observational prospective study was conducted across 3 Dutch university hospitals. Patients with metastatic NSCLC with an *ALK*- or *ROS1*-rearrangement and having an indication to start lorlatinib in daily clinical practice were eligible. The primary endpoints were to identify changes in neurocognitive functioning, measured through neurocognitive assessment at intervals of 2 weeks and 2 months after starting lorlatinib, in comparison to baseline. As a secondary endpoint, the correlation between neurocognitive impairment and self-reported neurocognitive dysfunction was examined. **Results:** Between June 2019 and October 2022, 22 patients were included. Among the various neurocognitive tests administered, only the Hopkins Verbal Learning Test-Revised parts b and c demonstrated a significant and clinically relevant decrease in scoring 2 weeks post initiation of lorlatinib ($P = .036$ and $P = .003$, respectively). However, these returned to baseline at the 2-month evaluation. The questionnaires did not result in significantly different outcomes over time. **Conclusion:** Lorlatinib treatment did not result in a sustained and significant decline within any of the specified neurocognitive domains.

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Introduction

Targeted therapies, primarily tyrosine kinase inhibitors (TKIs), have led to significant advancements in both the survival and quality of life (QoL) of patients with metastatic non–small-cell lung cancer (NSCLC) and a targetable oncogenic driver.[1] Unfortunately, resistance inevitably occurs, including progression in the central nervous system (CNS).[2,3] Consequently, next-generation TKIs, with improved CNS penetration, have been developed to target the most common resistance mechanisms and to control CNS disease.[4-7]

Lorlatinib, a more recently developed TKI, is a selective and potent next-generation anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) inhibitor, notable for its capacity to cross the blood-brain barrier. This drug exhibits activity against most known ALK resistance mutations.[8] Treatment with lorlatinib yields high

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response rates and prolonged progression-free survival with durable disease control in the brain.[7,9,10] However, the use of lorlatinib is not without potential drawbacks, one of which is the occurrence of neurocognitive adverse events (NCAEs). These events manifest in diverse forms, encompassing cognitive, mood-related, and speech-related adverse events, affecting approximately 21% to 40%, 16% to 36%, and 9% to 23% of patients, respectively.[10-13] It is hypothesized that cognitive and mood alterations occur due to off-target inhibition of tropomyosin receptor kinase B within the CNS.[14] In a phase II trial involving patients with *ALK*-positive advanced NSCLC who were treated with lorlatinib (N = 276), the primary endpoints were overall and intracranial tumor response. Additionally, an assessment of neurocognitive functioning was performed. This assessment was conducted not only using the Common Terminology Criteria for Adverse Events (CTCAE) criteria, but also via the Cogstate assessment tool (Cogstate Inc, New Haven, CT), a computerized test,[12] designed to evaluate cognitive domains such as psychomotor function and working memory. The trial revealed grade 1 to 2 NCAEs in 17%, with 1% experiencing grade 3 effects. In addition, grade 1 to 2 mood effects were noted in 14% of patients, while grade 3 mood effects occurred in 1%. It was observed that NCAEs were frequently transient, with only a decline in attention within subpopulations of the expansion cohort. In the CROWN study, a phase III trial evaluating first-line lorlatinib versus crizotinib, the assessment of mood and suicidal tendencies was conducted using the MODD Beck depression inventory II scale and the Colombia Suicide Severity Rating Scale, respectively.[15] However, outcomes have not been reported so far.

While these NCAEs generally manifest in a mild to moderate form (CTCAE 1-2), their impact on both physical and mental well-being can be substantial, affecting both patients and their family members. Moreover, these events frequently necessitate dose reduction or even discontinuation of lorlatinib treatment.[16] Furthermore, CTCAE criteria are limited to symptom description and do not encompass the underlying neurocognitive domains affected by lorlatinib. A comprehensive neurocognitive evaluation covering domains like psychomotor speed and fine motor control in lorlatinib-treated patients is lacking.

The current prospective study was performed to provide a deeper understanding of NCAEs associated with lorlatinib. By gaining insights into the potential causal factors underlying the observed neurocognitive decline, improved guidance could be offered to patients and their families, with the ultimate aim of improving their care and QoL.

Methods

Study Design and Patients

This observational prospective study was conducted across 3 university hospitals in the Netherlands.

Eligible patients, aged 18 years and above, had histologically or cytologically confirmed metastatic NSCLC with an *ALK* or *ROS1* rearrangement. They were candidates for lorlatinib treatment within routine clinical practice and were required to be capable to undergo all neuropsychological assessments. Written informed consent was obtained from all participants.

Excluded were patients with neurocognitive disorders (such as Alzheimer's disease) or psychiatric conditions, symptomatic brain metastases, neurological symptoms due to previous cranial irradiation, or an inability to understand the testing procedures. The study protocol was approved by the independent ethics committee of the Maastricht UMC+ and was in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki principles. The study was registered in the Dutch Trial Registry (NTR7565).

Assessments

NCAEs were evaluated by standardized neurocognitive tests targeting key neurocognitive domains. Additionally, subjective cognitive complaints and mood evaluation were conducted through questionnaires (the complete test battery is detailed in Table 1). All assessments occurred at 3 time points: baseline (within 1 week before commencing lorlatinib), 2 weeks (+/- 3 days) after initiation, and 2 months (+/- 1 week) post lorlatinib commencement. Trained nurses administered the tests and questionnaires. The test battery adopted was in line with the European Organization for Research and Treatment of Cancer (EORTC) recommendations[17] and included the following tests: Trail Making Test A and B; Controlled Oral Word Association (COWA); Hopkins Verbal Learning Test-Revised part A/B and C (HVLT-R); Digit Symbol Subtest of the WAIS-III; and the grooved pegboard test. Additional assessments included a depression and anxiety test (Hospital Anxiety and Depression Scale-HADS); a coping test (Utrecht Coping list – UCL) and a subjective cognitive failure

Table 1 Test Battery.

Neurocognitive Test	Domain Measured (outcome)
Trail Making Test A	Visual scanning speed (seconds)
Trial Making Test B	Divided attention (seconds)
Controlled Oral Word Association	Verbal fluency (number of words)
Hopkins Verbal Learning Test Revised	Verbal memory (number of words)
Digit Symbol Subtest of the WAIS III	Psychomotor speed (age-corrected subtest score (0-20))
Grooved pegboard test	Fine motor control (seconds)
Questionnaires	Domain Measured
The Hospital Anxiety and Depression scale (HADS)	Anxiety and depression
The Cognitive Failure Questionnaire (CFQ)	Subjective cognitive functioning
The Utrecht Coping List (UCL)	Passive and active coping

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Table 2 Baseline Characteristics.

	N = 22 (%)
Gender	
Male	10 (46)
Female	12 (54)
WHO PS	
0	11 (50)
1	11 (50)
Highest education	
Secondary education less than intermediate general secondary education	1 (5.3)
Intermediate general secondary education and secondary vocational education	3 (15.8)
Senior general secondary education and higher education	13 (68.4)
University	2 (10.5)
Unknown	3 (13.6)
Age at start lorlatinib	
Mean in years (range)	61.8 (32-83)
Baseline brain metastases	
Yes	14 (63.6)
No	8 (36.4)
If baseline brain metastases, previous cranial irradiation (N=14)	
Yes	6 (42.9)
No	8 (57.1)

Abbreviations: N = number; WHO PS = world health organization performance score.

test (Cognitive Failures Questionnaire-CFQ). AEs were categorized according to the CTCAE version 5.0.

Endpoints

The primary endpoints were changes in neurocognition, as determined by neurocognitive tests and questionnaires, at 2 weeks, and 2 months postlorlatinib relative to baseline (Table 1).

The secondary endpoint was the correlation between neurocognitive impairment detected through neurocognitive tests, and self-reported neurocognitive impairment.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM statistics, version 20). Demographic and clinical variables were reported by frequencies and descriptive statistics each visit. Cognitive tests and questionnaires were examined using the Friedman test to explore score variations across the 3-time points. Patients without any questionnaire data at 2 weeks as well as 2 months were excluded. However, participants attending all 3 visits but not completing all questionnaires during each visit, were included. Analysis was restricted to participants with complete data for a specific test across all 3 visits. Clinically relevant differences were defined as deviations of one standard deviation from the baseline test across the 3 time points.

Results

Between June 2019 and October 2022, a total of 31 patients provided informed consent for participation. Out of these, 22 were eligible for inclusion in the analysis. Nine patients were excluded due to restrictions related to COVID-19 waves, completely preventing research-related visits at the participating hospitals. Consequently, these individuals were unable to complete any follow-up assessments. Data regarding NCAE is therefore missing in the latter group.

All included patients had a good performance status (WHO PS 0-1), with a median age of 61.8 years, and approximately half of the participants were female (54%). Further details regarding baseline characteristics are presented in Table 2.

Neurocognitive Testing

All 22 patients completed the neurocognitive tests at each visit. For the majority of neurocognitive tests, no significant differences were observed between baseline, 2 weeks after initiating lorlatinib and 2 months after commencement. However, the HVLT-R (assessing verbal memory) parts b and c showed a significant decrease in scores at 2 weeks after the beginning of lorlatinib ($P = .036$ and $P = .003$, respectively), with subsequent recovery at 2 months (Table 3, Supplemental Table 1 and Figure 1). A clinically relevant difference was primarily detected in the HVLT-R parts b and c at 2 weeks following lorlatinib initiation. In part b, this relevant decrease was reversed in 2 out of 3 patients at 2 months. In part c, the relevant decrease reversed in 90% of patients at 2 months (Supplemental Table 2). Complete testing scores and relevant differences are available in Supplemental Table 1.

Questionnaires

Among the 22 included patients, 4 (18%) did not complete the HADS at all 3 visits due to study staff accidentally not providing the

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Table 3 Median (interquartile range) and *P*-Value of the Different Tests at 3 Time Points.

	Visit 1 (Baseline) Median (IQR)	Visit 2 (2 wk) Median (IQR)	Visit 3 (2 mo) Median (IQR)	*P*-value
HADS (a)	3 (2-6)	3 (1-5)	3 (1-4)	.144
HADS (d)	2 (1-9)	2 (1-7)	1 (1-4)	.012
CFQ	31 (21.3-32)	33 (20.3-37)	30 (26.3-35.8)	.123
HVLT-R part a	25 (21.8-29.5)	23.5 (19-26.3)	24 (19.8-29)	.629
HVLT-R part b	9 (7-11)	7 (5-10.3)	8.5 (6.8-10.3)	.036
HVLT-R part c	11 (10-12)	8.5 (6.8-10.3)	11.5 (9.8-12)	.003
Trail Making a	32.5 (26.8-41.5)	29.5 (26.3-47)	32.5 (23.8-40.3)	.223
Trail Making b	65 (50.8-88.5)	71.5 (49.8-87.3)	62.5 (45.8-88)	.446
COWA	43 (35.3-48.3)	38 (30-47.5)	42.5 (35-52)	.413
WAIS III	60.5 (52.5-69)	64.5 (56-70.3)	59 (49-74.5)	.102
Grooved pegboard (DH)	82.5 (73-90.3)	75.5 (67.8-89)	77.5 (72.8-96.5)	.186
Grooved pegboard (NDH)	80.5 (70.8-105.8)	83 (71.5-102.3)	78 (69.8-111.8)	.163

Abbreviations: CFQ = cognitive failure questionnaire; COWA = controlled oral word association; DH = dominant hand; HADS = hospital anxiety and depression scale; HVLT-R = Hopkins verbal learning test revised; IQR = interquartile range; NDH = nondominant hand; SCF = subjective cognitive functioning; WAIS = digit symbol subtest of the Wechsler adult intelligence scale.

Table 4 Utrecht Coping List.

UCL	Decrease Visit 2 vs. 1	N (%) Visit 3 vs. 2	Visit 3 vs. 1	Visit 2 vs. 1	Increase Visit 3 vs. 2	N (%) Visit 3 vs. 1
Act	1 (4.5)	2 (9.1)	1 (4.5)	8 (36.4)	1 (4.5)	6 (27.3)
Pal	4 (18.2)	9 (40.9)	5 (22.7)	8 (36.4)	3 (13.6)	7 (31.8)
Ver	6 (27.3)	3 (13.6)	4 (18.2)	4 (18.2)	3 (13.6)	6 (27.3)
Soc	4 (18.2)	5 (22.7)	6 (27.3)	3 (13.6)	2 (9.1)	2 (9.1)
Pas	6 (27.3)	3 (13.6)	4 (18.2)	5 (22.7)	6 (27.3)	8 (36.4)
Exp	6 (27.3)	11 (50)	8 (36.4)	6 (27.3)	3 (13.6)	4 (18.2)
Ger	3 (13.6)	6 (27.3)	3 (13.6)	4 (18.2)	9 (40.9)	7 (31.8)

Abbreviations: Act = active coping; Exp = expression of emotions; Ger = comforting thoughts; N = number; Pal = palliative reaction; Pas = passive reaction pattern; Soc = seeking social support; UCL = Utrecht coping list; Ver = avoiding; vs. = versus.

questionnaire to the patients. Except for the HADS test for depression, which showed a decrease in scores over time ($P = .012$, indicating reduced feelings of depression), other questionnaires showed no significant differences compared to baseline (see Table 3, Supplemental Table 1 and Figure 1). Clinically relevant differences (HADS score for depression of anxiety ≥ 8 or ≤ 8) were observed in the HADS anxiety scores for 3 patients. Two patients experienced a relevant decrease, while one displayed an increase in the HADS anxiety score on the third visit. Similarly, clinically relevant differences in HADS depression scores were identified in 3 patients. Two displayed a relevant decrease, whereas one showed an increase at the third visit (this patient also had a relevant increase in HADS anxiety score at the same visit).

The Utrecht Coping List (UCL) scores are shown in Table 4. Of the 22 patients, 4 (18%) did not complete all UCL scores at all 3 visits. Two patients forgot the UCL at visit 1, one patient forgot the UCL at visit 2 to 3, and 1 patient forgot the UCL at visit 3. The scores exhibit variations in both active and passive coping styles, although no distinct trend is readily apparent.

CTCAE (NCAE)

At baseline, 1 patient reported a NCAE in the form of a headache (grade 1), unrelated to lorlatinib. After 2 weeks, NCAEs were reported in 3 patients (13.6%) which included mood change (n = 1, grade 2), paresthesia (n = 1, grade 1), and sensory impairment (n = 1, grade 2). After 2 months, NCAEs were reported in 4 patients (18.2%) involving speech change (n = 1, grade 1), mood change (n = 1, grade 1), and blurred vision (n = 2, grade 1).

Correlation Between NCAE and Neurocognitive Results/Questionnaires

Among the 7 patients who experienced NCAEs, 4 (57%) also had a clinically relevant difference in the HVLT-R tests at the second visit, with recovery by the third visit. One patient had a clinically relevant difference in the Trial Making Test Part A at 2 weeks, which subsequently recovered at 2 months. Another patient showed a relevant difference in the COWA score at 2 weeks, with recovery at 2 months. Furthermore, 1 patient had a difference in the WAIS score on the second visit, which further declined by the third

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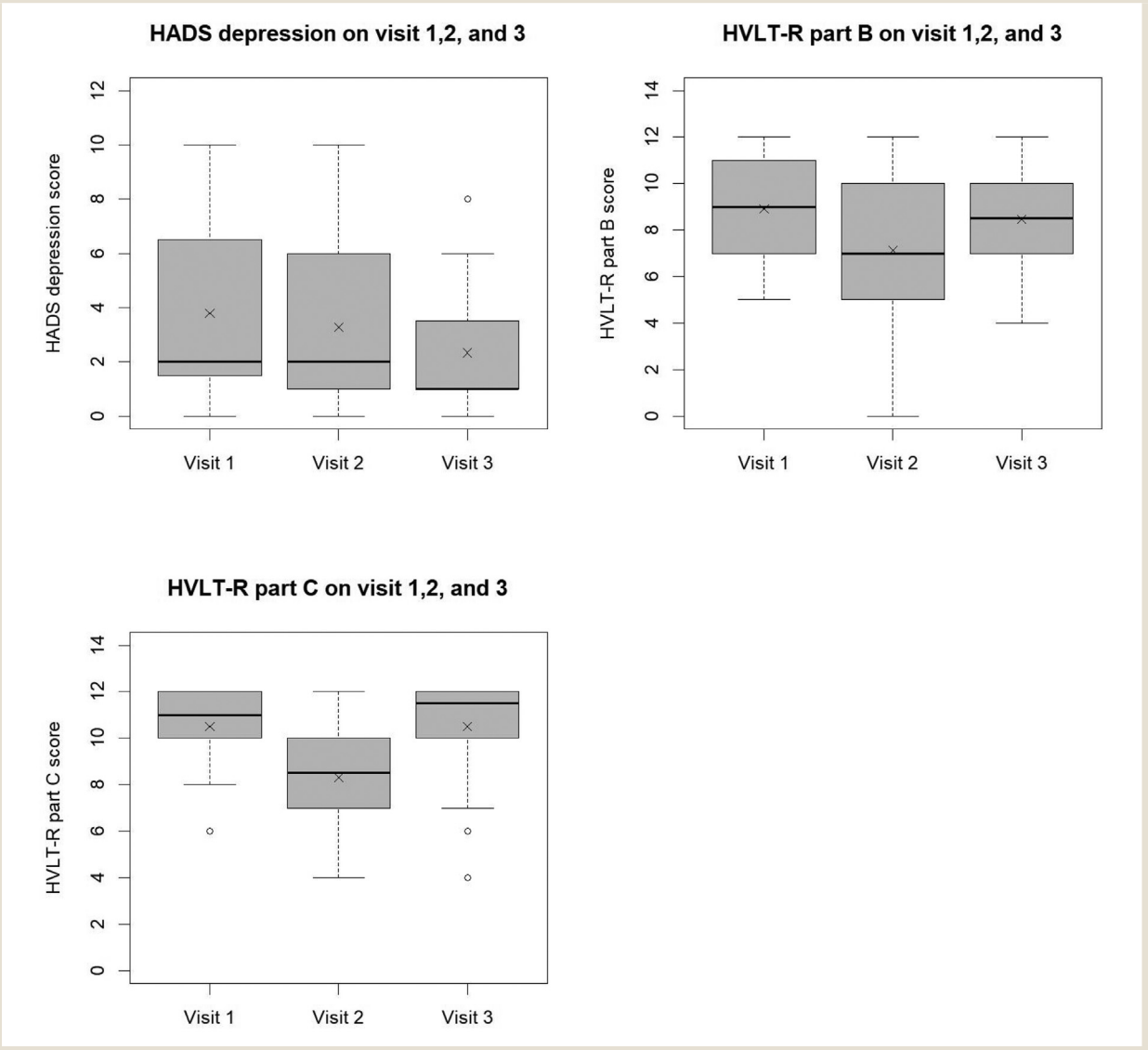
Figure 1 Neurocognitive tests and questionnaires with significant difference.



visit (Supplemental Table 2). No clinically relevant differences in questionnaires were found among these patients. Of these 7 patients reporting an NCAE, 3 (43%) had baseline brain metastases, and one of these (14%) had undergone previous cranial irradiation.

Dose Modification

Only 1 patient in this study needed a lorlatinib dose reduction, due to a non-NCAE. As the other patients did not have dose reductions of lorlatinib, the clinically relevant differences in the neurocognitive assessments that improved at the third visit, improved without any modifications of the dose of lorlatinib.

Discussion

This study represents the most comprehensive investigation to date of NCAE in patients with NSCLC undergoing lorlatinib treatment. Uniquely, this study incorporates subjective functioning scales and establishes correlations between these scales and formal neurocognitive outcomes – an approach that has not been explored before. We were unable to demonstrate a sustained and statistically significant decline across neurocognitive domains, consistent with earlier research.[12]

With the recent approval of lorlatinib as a first-line therapeutic option, following the results of the phase III CROWN study, its use is expected to significantly increase.[10,15] Notably the median treatment duration in this trial was 33.3 months,[10] implying that patients could experience low-grade NCAEs over an extended period. Therefore, understanding and managing NCAEs, including the ability to predict which patients might be susceptible, becomes important. Given the availability of other first-line next-generation ALK-TKIs,[4,18] identifying individuals prone to (prolonged) NCAEs gains significance, as these patients might potentially benefit more from an alternative ALK-TKI in the first-line treatment. Based on a

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large retrospective study involving 372 patients with *ALK* and *ROS1* positive NSCLC who underwent treatment with lorlatinib, several baseline characteristics were found to be associated with NCAEs. These include the presence of brain metastases, prior cranial radiation, psychiatric comorbidities, and the use of neurotropic medications.[19] In our study a relatively high percentage, 42%, of patients who reported an NCAE had baseline brain metastases, which is in line with the previously reported data. In our series, cranial irradiation did not seem to be a large contributing factor as only 1 patient reporting NCAE had previously underwent cranial irradiation, while the 5 other patients with previous cranial irradiation did not report NCAE. In contrast to the reported retrospective series, in our study patients with psychiatric comorbidities were already excluded, as were patients with neurocognitive disorders (such as Alzheimer's disease), symptomatic brain metastases, and neurological symptoms due to previous cranial irradiation. The use of neurotropic drugs was not available for our study.

Although we could not demonstrate a significant decline in neurocognitive domains within the initial 2 months of lorlatinib treatment, 18% of patients reported a NCAE 2 months after lorlatinib initiation and therefore it remains important to address NCAEs in these patients. Changes in speech and mood were observed in 4.5% each, while alterations in cognitive functioning were reported in 9%. Evaluating how patients perceive and experience their NCAEs remains an ongoing consideration, as objective tests may reveal impairments that patients do not notice. While CTCAE grading takes into account the impact on daily functioning, it remains a crude measure to assess the overall impact on the patient's life.

A limitation of our study is its descriptive nature, with a limited patient cohort. Nevertheless, this study represents the first prospective evaluation of lorlatinib-treated patients outside of a clinical trial, with an extensive assessment across all neurocognitive domains. Consistent with prior phase I/II and III trials,[12,15] the incidence of NCAEs was low and predominantly low-grade. Notably, the majority of the NCAEs improved without intervention within 2 months of lorlatinib start. A second limitation is the relatively short follow-up.

For future reference, it is important to consider and discuss NCAE with the use of lorlatinib. Potential risk factors such as brain metastases or previous cranial irradiation should be taken into account. However, as these risk factors were only identified in a retrospective study,[19] prospective research is necessary to validate these risk factors for use in counseling and shared decision-making concerning treatment options.

In conclusion, we found no evidence that lorlatinib results in a clinically relevant and persistent neurocognitive decline in more than one domain at each time point. However, even grade 1 NCAEs could be of clinical significance to specific patients, necessitating their incorporation into patient counseling regarding available TKI treatment options.

Clinical Practice Points

- Lorlatinib represents a potent and brain-penetrating next generation tyrosine kinase inhibitor. Treatment with lorlatinib results in high response rates and durable responses. Nevertheless, a significant drawback is the risk of neurocognitive adverse events (NCAE). Although these NCAEs are often low-grade, they can result in substantial physical and psychological impairment.
- Based on extensive neurocognitive assessments and questionnaires, this study showed that the occurrence of NCAEs cannot be attributed to a persistent decline in any of the specific neurocognitive domains. Furthermore, no correlation was found between self-reported NCAEs and potential deterioration in the neurocognitive assessments.
- In the near future it is important to conduct further research aimed at identifying significant risk factors that may predispose patients to NCAEs, such as brain metastases or a history of previous brain radiation. The underlying etiological factors should also be evaluated. This deeper understanding is essential to offer counseling regarding available TKI treatment options.

Disclosure

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CRediT authorship contribution statement

Janna Schoenmaekers: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft. **Jeanet Dijkstra:** Methodology, Supervision, Writing – review & editing. **Anthonie van der Wekken:** Investigation, Resources, Writing – review & editing. **Marthe Paats:** Investigation, Resources, Writing – review & editing. **Martijn Broen:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Lloyd Brandts:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Anne-Marie Dingemans:** Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing.

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In-depth Analysis of Lorlatinib-related neurocognitive Adverse Events

Appendix

Table S1 and Table S2.

Table S1 Mean of the tests.

	Visit 1 (baseline; max 1 week before start lorlatinib)		Visit 2 (2 weeks; +/- 3 days)		Visit 3 (2 months; +/- 1 week)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
HADS (a)	18 *	4.2 (4.3)	20	3.6 (3.5)	18 +	3.7 (3.4)
HADS (d)	18 *	3.4 (3.4)	20	3.1 (3.2)	18 *	2.9 (2.9)
CFQ	21	27.2 (9.2)	21	28.2 (11.1)	21	29.3 (9.0)
HVLT-R part a	22	24.8 (6.5)	22	23.5 (4.9)	22	24.3 (4.9
HVLT-R part b	22	8.9 (2.2)	22	7.1 (3.5)	22	8.5 (2.5)
HVLT-R part c	22	10.5 (1.6)	22	8.3 (2.3)	22	10.5 (2.2
Trail Making a	22	35.9 (11.8)	22	35.0 (12.3)	22	35.1 (13.4)
Trail Making b	22	71.7 (26.3)	22	73.1 (26.3)	22	69.3 (25.2)
COWA	22	40.5 (10.5)	22	38.6 (11.7)	22	42.7 (12.3)
WAIS III	22	60.3 (13.0)	22	64.5 (15.5)	22	60 (16.6)
Grooved pegboard (DH)	22	88.1 (31.7)	22	77.5 (16.2)	22	86.1 (24.1)
Grooved pegboard (NDH)	22	115.7 (133.3)	22	91 (33.2)	22	90.5 (29.1)

SD: standard deviation, N: number, SCF: subjective cognitive functioning, HADS: hospital anxiety and depression scale, CFQ: cognitive failure questionnaire, HVLT-R: hopkins verbal learning test revised, COWA: controlled oral word association, WAIS: digit symbol subtest of the Wechsler adult intelligence scale, DH: dominant hand, NDH: non dominant hand.
* Because not every patient has filled in all questionnaires at each time, the number of patients is variable.

Table S2 Clinically relevant difference of neurocognitive tests.

	Clinical relevant difference (% of pts)
HVLT-R part a	18
HVLT-R part b	27
HVLT-R part c	55
Trail Making a	18
Trail Making b	4.5
COWA	9
WAIS III	9
Grooved pegboard (DH)	0
Grooved pegboard (NDH)	0

HVLT-R: hopkins verbal learning test revised, COWA: controlled oral word association, WAIS: digit symbol subtest of the Wechsler adult intelligence scale, DH: dominant hand, NDH: non dominant hand.

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