ORIGINAL ARTICLE

Factors Associated With Developing Neurocognitive Adverse Events in Patients Receiving Lorlatinib After Progression on Other Targeted Therapies

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ABSTRACT

Introduction: The safety profile of lorlatinib includes neurocognitive adverse events (NAEs). Baseline factors associated with developing NAEs remain poorly characterized.

Methods: Records from patients who received lorlatinib through prospective studies at Massachusetts General Hospital (MGH, n = 124) or the phase 1/2 B7461001 (NCT01970865; n = 248) study were reviewed to identify potential associations between comorbidities, baseline medications, and NAEs.

Results: Most patients experienced a NAE (MGH: 60%, B7461001: 49%). Cognitive effects occurred in 40% and 29% of patients in the MGH and B7461001 cohorts, respectively. Brain metastases ($p = 0.008$), brain radiation ($p = 0.033$), psychiatric illness ($p = 0.008$), psychiatric medications ($p < 0.001$), antiepileptics ($p < 0.001$), and stimulants ($p = 0.026$) were associated with developing cognitive effects in B7461001. Mood effects occurred in 36% and 23% of patients in the MGH and B7461001 cohorts, respectively. In the MGH cohort, psychiatric illness ($p = 0.02$) and stimulants ($p = 0.01$) were associated with developing mood effects whereas brain surgery ($p = 0.020$), psychiatric medications ($p < 0.001$), benzodiazepines ($p = 0.002$), and sedatives ($p = 0.034$) were associated with developing mood effects in B7461001. Psychotic effects were infrequent (MGH: 3%, B7461001: 9%) and were associated with brain surgery in the MGH cohort ($p =$

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0.001) and age in B7461001 ($p = 0.014$). Speech effects were observed in 23% and 11% of patients in the MGH and B7461001 cohorts, respectively. Brain radiation ($p = 0.012$) and antiepileptics ($p < 0.001$) were associated with speech effects in B7461001. Dose reductions were implemented for 52% and 18% of patients with NAEs in MGH and B7461001 cohorts, respectively, with mitigating effect.

Conclusions: Neurocognitive effects from lorlatinib are common. Lorlatinib-related NAEs may be influenced by multiple factors, including brain metastases, brain radiation, psychiatric illness, and use of neurotropic medications.

Keywords: Lung cancer; ALK; ROS1; Lorlatinib

Introduction

Lorlatinib is a next-generation ALK and ROS1 tyrosine kinase inhibitor (TKI) that is approved by the Food and Drug Administration for treatment of advanced *ALK*-rearranged (*ALK*-positive [ALK+]) NSCLC on the basis of robust intracranial and extracranial activity in newly diagnosed patients and patients progressing on other ALK TKIs.[1–4] Although lorlatinib has not been approved for the treatment of *ROS1*-rearranged (*ROS1*-positive [ROS1+]) NSCLC in the United States, it was found to have promising systemic activity in the post-crizotinib setting, including in patients with brain metastasis.[5] Compared with the first-generation ALK and ROS1 TKI crizotinib and second-generation ALK TKIs (i.e., ceritinib, alectinib, brigatinib, ensartinib), lorlatinib has a unique adverse event (AE) profile that includes cognitive, mood, psychotic, and speech effects.[6] These neurocognitive AEs (NAEs) have been partly attributed to pharmacokinetics, specifically the ability of lorlatinib to penetrate the blood-brain barrier and accumulate in the central nervous system (CNS).[7] Given the prevalence of this toxicity, it is important for clinicians to counsel patients and caregivers about the possibility of developing NAEs from lorlatinib and essential that providers familiarize themselves with guidelines for managing lorlatinib-related NAEs.[6]

As many patients treated with lorlatinib do not experience NAEs, it is likely that factors beyond drug concentration in the CNS affect susceptibility to NAEs from lorlatinib. Nevertheless, factors associated with developing NAEs from lorlatinib remain poorly characterized. Here, we analyzed the safety outcomes from two large cohorts encompassing more than 350 patients with ALK+ and ROS1+ NSCLC to describe potential association between baseline clinical characteristics (i.e., comorbidities, disease localization and treatment, and baseline medications) and risk of developing NAEs during treatment with lorlatinib.

Materials and Methods

Study Population

MGH Cohort. We identified a total of 124 patients with metastatic NSCLC harboring an *ALK* or *ROS1* rearrangement who received lorlatinib at Massachusetts General Hospital (MGH) between October 2014 and December 2020. All patients received lorlatinib through prospective studies after progression on other TKIs. Specifically, the 124 patients participated in the registrational phase 1/2 study (NCT01970865), an investigator-sponsored phase 2 study (NCT02927340), or the expanded access program (NCT03178071). Of note, most of the patients (54%) received lorlatinib by the expanded access program. Treatment-related AEs, dose interruptions, and dose modifications were recorded prospectively during the study visits. The NAEs were prospectively graded per the Common Terminology Criteria for Adverse Events version 4.03 and retrospectively grouped into cognitive, speech, psychotic, or mood effects cluster terms as described in Supplementary Table 1. Medical records were retrospectively reviewed to evaluate whether dose modification had a mitigating effect on NAEs. Medical records were also retrospectively reviewed to collect information on comorbidities (specifically, baseline cognitive, mood, and speech disorders) and disease characteristics (specifically, brain metastases, CNS radiation, and CNS surgery). Baseline medications (i.e., medications that patients were taking on the day lorlatinib was initiated) were captured during chart review and assigned to the following categories of interest, illustrated in Supplementary Table 2: psychiatric medications, benzodiazepines, opioids, sedatives, antiepileptics, neuropathic agents, stimulants, and steroids. The studies supporting this analysis were approved by the institutional review board. MGH co-authors were responsible for validation and analysis of the MGH cohort.

B7461001 Cohort. In addition to the institutional cohort, we identified a separate group of 248 patients with advanced ALK+ or ROS1+ NSCLC treated with lorlatinib in the second-line setting and beyond at a starting dose of 100 mg daily across multiple institutions as part of the global phase 1/2 B7461001 study (NCT1970865).[1,8] In this registrational study, AEs were also graded using the Common Terminology Criteria for Adverse Events version 4.03. Study data were extracted from study database, and there was no overlap between patients in the two cohorts (i.e., records of patients

treated at MGH while enrolled in the B7461001 study were removed from the B7461001 analysis presented in this article as they were already captured in the MGH data set discussed previously). Pfizer co-authors were responsible for validation and analysis of the B7461001 cohort.

Data from the MGH cohort were updated as of October 2021, whereas data from study B7461001 were based on a data snapshot with a cutoff date of May 14, 2019. A schema of the overall study population is presented in Figure 1.

Statistical Analysis

Fisher's exact test was used to evaluate the association between baseline characteristics and adverse effects and to compare the distribution of the study cohorts. Age was analyzed as continuous using Wilcoxon ranked sum test. Fisher's exact test was used to compare frequency of NAEs in the MGH cohort versus the B7461001 cohort. Landmark analysis was used to investigate the possible association between development of NAEs within 12 weeks of initiating lorlatinib and progression-free survival (PFS).[9] Analysis of MGH data was performed using Stata 12.1 (StataCorp). B7461001 data were analyzed using SAS 9.4. The *p* values are based on a two-sided hypothesis. As the retrospective study was not designed with specific hypotheses at a prespecified level of type 1 error, a *p* value less than 0.05 was used by convention to identify associations of potential significance without adjustment for multiple testing.

Results

Patient Characteristics

MGH Cohort. Between October 2014 and December 2020, a total of 124 patients were treated with lorlatinib at an initial dose of 100 mg daily after progression on other TKIs, including 91 patients (73%) with ALK+ NSCLC and 33 patients (27%) with ROS1+ NSCLC (Supplementary Table 3 and Supplementary Fig. 1). The median age of the overall cohort at initiation of lorlatinib was 56 (range: 21–83) years old with a predominant. The majority (97%) of tumors were adenocarcinomas. A total of 103 patients (83%) had baseline brain metastases. There were 63 patients (51%) who had previously received CNS radiation. Four patients (3%) had undergone brain surgery. Two-thirds (n = 83 of 124) of the patients had received greater than or equal to two TKIs before initiating lorlatinib, all of whom had ALK+ NSCLC. The median duration of follow-up after initiation of lorlatinib was 6.2 (range: 1.0–66.3) months.

B7461001 Cohort. The B7461001 cohort comprised 248 patients who received lorlatinib between January 2014 and October 2016 at a starting dose of 100 mg daily after progression on other TKIs. The cohort included 212 (85%) and 36 patients (15%) with ALK+

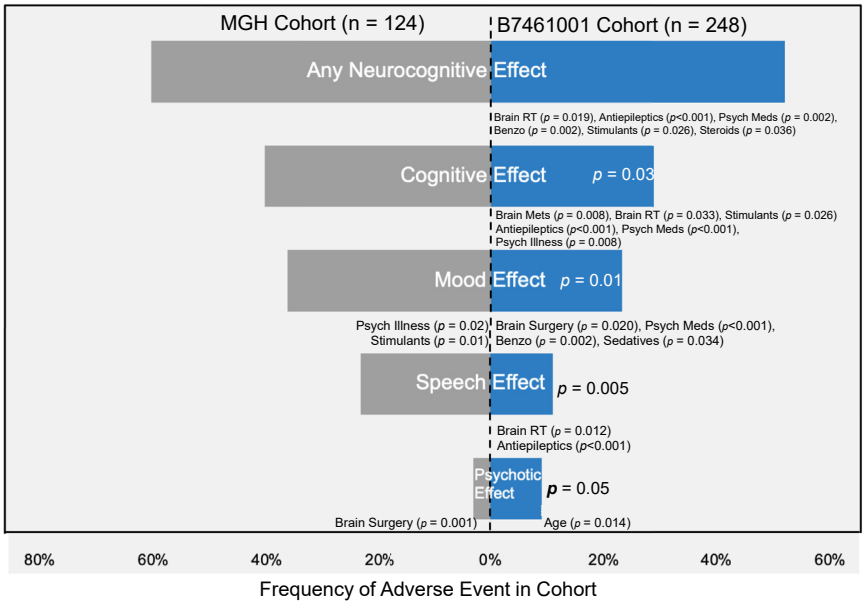

Figure 1. Frequency of and factors associated with neurocognitive effects from lorlatinib. The tornado plot reveals the frequency of any neurocognitive effect and frequency of specific categories of neurocognitive effects in the MGH cohort (gray) and B7461001 cohort (blue). Comparison of the prevalence of each category of neurocognitive adverse event in the two cohorts is summarized with *p* values. Factors statistically associated with development of each category of neurocognitive adverse event are listed with correspondng *p*-values. Benzo, benzodiazepine; med, medication; MGH, Massachusetts General Hospital; psych, psychiatric; RT, radiation therapy.

and ROS1+ NSCLC, respectively (Supplementary Table 3 and Supplementary Fig. 1). In total, 162 patients (65%) had baseline brain metastases, including 98 patients (40%) with irradiated brain metastases and eight patients (3%) with resected brain metastases. Nearly one-half of the patients (n = 120 of 248, 48%) had received multiple TKIs before commencing treatment with lorlatinib. The estimated median duration of follow-up after initiation of lorlatinib was 6.9 months (range: 9 d–51.6 mo). Compared with the MGH cohort (Supplementary Table 3), the B7461001 group contained fewer patients with *ROS1*-rearranged NSCLC (15% versus 27%, $p = 0.007$), fewer patients who had received greater than or equal to two previous TKIs (48% versus 67%, $p = 0.001$), and fewer patients with brain metastases (65% versus 83%, $p < 0.001$), including resected (8% versus 16%, $p = 0.018$) or irradiated brain metastases (40% versus 51%, $p = 0.046$).

Association Between Clinical Characteristics and Neurocognitive AEs

Cognitive Effects. In the MGH cohort, 50 patients (40%) developed cognitive effects from lorlatinib (Tables 1 and 2). There was no statistically significant association observed between age, sex, genotype, number of previous lines of therapy, brain metastasis status, brain radiation, brain surgery, baseline cognitive disorder, baseline mood disorder, or baseline speech disorder and occurrence of cognitive effects from lorlatinib. Similarly, none of the medication categories were associated with occurrence of cognitive effects. The overall rate of cognitive effects was significantly lower in the B7461001 cohort with 72 (29%; Fig. 1) patients experiencing this category of AE ($p = 0.03$). In contrast to findings from the institutional analysis (Tables 3 and 4 and Fig. 1), review of the B7461001 cohort identified several factors associated with developing cognitive effects from lorlatinib including brain metastases ($p = 0.008$), previous brain radiation ($p = 0.03$), baseline psychiatric illness ($p = 0.008$), psychiatric medications ($p < 0.001$), antiepileptics ($p < 0.001$), and stimulants ($p = 0.03$).

Among patients experiencing cognitive effects, dose interruption was implemented for 52% (n = 26 of 50) and 19% (n = 14 of 72) of patients in the MGH and B7461001 cohorts, respectively, to address the AE (Table 5). Dose reductions were necessary for 54% (n = 27 of 50) and 17% (n = 12 of 72) of patients experiencing this toxicity in the MGH and B7461001 cohorts, respectively. Dose reduction had a mitigating effect on cognitive effects for 26 of 27 patients (96%) and nine of 12 patients (75%) treated in the MGH and B7461001 cohorts, respectively (Table 5). The remaining patients had ongoing symptoms despite dose reduction.

Mood Effects. A total of 45 patients (36%) in the MGH group experienced mood effects during treatment with lorlatinib (Tables 1 and 2). In the MGH group, preexisting psychiatric illness ($p = 0.02$) and concomitant stimulant use ($p = 0.01$) were associated with a higher rate of developing mood effects (Tables 1 and 2 and Fig. 1). The remaining comorbidities, disease characteristics, and medications were not associated with statistically increased rate of mood toxicity. In the larger B7461001 study cohort, 58 patients (23%) developed mood effects on lorlatinib (Tables 3 and 4), corresponding to a significantly lower rate ($p = 0.01$; Fig. 1). In contrast to findings from the MGH analysis, neither stimulant use nor baseline psychiatric disorder was associated with this toxicity (Tables 3 and 4 and Fig. 1). Rather, the factors associated with increased frequency of mood effects included previous brain surgery ($p = 0.020$), baseline use of psychiatric medications ($p < 0.001$), benzodiazepines ($p = 0.002$), and sedatives ($p = 0.03$).

Among 45 patients who developed mood effects on lorlatinib in the MGH cohort, dose interruption and reduction were required for 21 (47%) and 24 (53%) patients, respectively (Table 5). Mood effects were ameliorated by dose reduction in all but one case. In comparison, 10 (17%) and nine (15%) patients required temporary interruption of lorlatinib dosing or lorlatinib dose reduction in the B7461001 group, respectively. Dose reduction improved mood effects in seven of nine cases (78%).

Psychotic Effects. The observed rate of psychotic effects was low overall, affecting four (3%) and 22 (9%) patients in the MGH and B7461001 cohorts, respectively (Fig. 1). The rate of this AE was significantly different between cohorts ($p = 0.05$). All patients experiencing this toxicity in the MGH cohort required dose interruption and eventual dose reduction (Table 5). In all four instances, the psychotic effects (specifically hallucinations) improved but did not resolve. In the B7461001 group, dose interruption was documented in six cases (27%), and four patients (18%) needed dose reduction. There was a statistically significant association between previous brain surgery and development of psychotic effects in the MGH cohort ($p = 0.001$; Table 1 and Fig. 1) which was not present in the B7461001 cohort ($p = 1.000$; Table 3). Age was associated with psychotic effects in the B7461001 cohort. Notably, baseline psychiatric disorder did not predict for psychotic effects in either group. Furthermore, none of the categories of medications evaluated seemed to predispose to this toxicity in either group.

Table 1. Association Between Baseline Characteristics and Neurocognitive Adverse Events in MGH Cohort

Characteristic		Cognitive Effects	*p* Value	Psychotic Effects	*p* Value	Mood Effects	*p* Value	Speech Effects	*p* Value	Neurocognitive Effects (Any)	*p* Value
MGH cohort, n (%)	N = 124	50 (40)		4 (3)		45 (36)		28 (23)		75 (60)	
Age at baseline, median (range)	56 (21-83)		0.779		0.081		0.801		0.825		0.198
Effects during lorlatinib		56 (21-83)		64 (54-83)		57 (21- 79)		57 (21-79)		57 (21-83)	
Effects absent		56 (27-71)		56 (21- 79)		55 (27-83)		55 (27-83)		54 (27-71)	
Sex, n (%)			0.099		1.000		1.000		1.000		0.853
Female	71 (57)	24 (34)		2 (3)		26 (37)		16 (23)		42 (59)	
Male	53 (43)	26 (49)		2 (4)		19 (36)		12 (23)		33 (62)	
Genotype, n (%)			0.681		0.573		0.678		0.231		0.684
ALK-rearranged	91 (73)	38 (42)		4 (4)		32 (35)		18 (20)		56 (62)	
ROS1-rearranged	33 (27)	12 (36)		0 (0)		13 (39)		10 (30)		19 (58)	
Previous TKI lines, n (%)			0.339		1.000		1.000		0.652		0.330
1	41 (33)	14 (34)		1 (2)		15 (37)		8 (20)		22 (54)	
≥2	83 (67)	36 (43)		3 (4)		30 (36)		20 (24)		53 (64)	
Brain metastases at baseline, n (%)			0.627		1.000		0.809		0.156		0.466
Present	103 (83)	43 (42)		4 (4)		38 (37)		26 (25)		64 (62)	
Absent	21 (17)	7 (33)		0 (0)		7 (33)		2 (10)		11 (52)	
Previous brain radiation, n (%)			0.587		0.119		0.712		0.522		0.199
Yes	63 (51)	27 (43)		4 (6)		24 (38)		16 (25)		42 (67)	
No	61 (49)	23 (38)		0 (0)		21 (34)		12 (20)		33 (54)	
Previous brain surgery, n (%)			0.081		0.001		1.000		0.774		0.804
Yes	20 (16)	12 (60)		4 (20)		7 (35)		5 (25)		13 (65)	
No	104 (84)	38 (37)		0 (0)		38 (37)		23 (22)		62 (60)	
Baseline cognitive impairment, n (%)			0.254		0.181		0.244		0.592		0.820
Yes	25 (20)	13 (52)		2 (8)		12 (48)		7 (28)		16 (64)	
No	99 (80)	37 (37)		2 (2)		33 (33)		21 (21)		59 (60)	
Baseline psychiatric illness, n (%)			0.537		0.057		0.019		0.811		0.102
Yes	33 (27)	15 (45)		3 (9)		18 (55)		8 (24)		24 (73)	
No	91 (73)	35 (38)		1 (1)		27 (30)		20 (22)		51 (56)	
Baseline speech disorder, n (%)			0.713		1.000		0.460		0.379		0.477
Yes	8 (6)	4 (50)		0 (0)		4 (50)		3 (38)		6 (75)	
No	116 (94)	46 (40)		4 (3)		41 (35)		25 (22)		69 (59)	

MGH, Massachusetts General Hospital; TKI, tyrosine kinase inhibitor.

Table 2. Association Between Baseline Medications and Neurocognitive Adverse Events in MGH Cohort

Characteristic		Cognitive Effects	*p* Value	Psychotic Effects	*p* Value	Mood Effects	*p* Value	Speech Effects	*p* Value	Neurocognitive Effects (Any)	*p* Value
MGH cohort, n (%)	N = 124	50 (40)		4 (3)		45 (36)		28 (23)		75 (60)	
Baseline psychiatric med, n (%)			0.661		0.206		0.368		0.435		0.511
Yes	27 (22)	12 (44)		2 (7)		12 (44)		4 (15)		18 (67)	
No	97 (78)	38 (39)		2 (2)		33 (34)		24 (25)		57 (59)	
Benzodiazepine at baseline, n (%)			0.085		0.120		0.116		0.368		0.082
Yes	43 (35)	22 (51)		3 (7)		20 (47)		12 (28)		31 (72)	
No	81 (65)	28 (35)		1 (1)		25 (31)		16 (20)		44 (54)	
Opioid at baseline, n (%)			0.043		0.576		0.063		0.476		0.042
Yes	35 (28)	9 (26)		0 (0)		8 (23)		6 (17)		16 (46)	
No	89 (72)	41 (46)		4 (4)		37 (42)		22 (25)		59 (66)	
Sedative at baseline, n (%)			0.121		1.000		0.756		1.000		1.000
Yes	12 (10)	2 (17)		0 (0)		5 (42)		2 (17)		7 (58)	
No	112 (90)	48 (43)		4 (4)		40 (36)		26 (23)		68 (61)	
Antiepileptic at baseline, n (%)			0.522		0.289		0.167		0.231		1.000
Yes	10 (8)	5 (50)		1 (10)		6 (60)		4 (40)		6 (60)	
No	114 (92)	45 (39)		3 (3)		39 (34)		24 (21)		69 (61)	
Neuropathic at baseline, n (%)			0.311		1.000		0.722		0.421		0.739
Yes	9 (7)	2 (22)		0 (0)		4 (44)		3 (33)		5 (56)	
No	115 (93)	48 (42)		4 (3)		41 (36)		25 (22)		70 (61)	
Stimulant at baseline, n (%)			0.739		1.000		0.011		0.421		0.481
Yes	(7)	(33)		(0)		(78)		3 (33)		7 (78)	
No	115 (93)	47 (41)		4 (3)		38 (33)		25 (22)		68 (59)	
Steroid at baseline, n (%)			0.285		1.000		0.185		1.000		1.000
Yes	29 (23)	9 (31)		1 (3)		14 (48)		6 (21)		18 (62)	
No	95 (77)	41 (43)		3 (3)		31 (33)		22 (23)		57 (60)	

Med, medicine; MGH, Massachusetts General Hospital.

Table 3. Association Between Baseline Characteristics and Neurocognitive Adverse Events in B7461001 Cohort

Characteristic		Cognitive Effects	*p* Value	Psychotic Effects	*p* Value	Mood Effects	*p* Value	Speech Effects	*p* Value	Neurocognitive Effects (Any)	*p* Value
B7461001 cohort, n (%)	N = 248	72 (29)		22 (9)		58 (23)		27 (11)		121 (49)	
Age at baseline: median (range)			0.626		0.014		0.453		0.941		0.561
Effects during lorlatinib		52 (26-77)		59 (38-85)		51 (26-85)		52 (31-78)		52 (26-85)	
Effects absent		52 (30-85)		52 (26-83)		52 (30-83)		52 (26-85)		52 (30-83)	
Sex, n (%)			0.672		0.022		0.880		0.410		0.898
Female	142 (57)	43 (30)		18 (13)		34 (24)		13 (9)		70 (49)	
Male	106 (43)	29 (27)		4 (4)		24 (23)		14 (13)		51 (48)	
Genotype, n (%)			1.000		0.216		0.832		0.389		0.594
ALK-rearranged	212 (85)	62 (29)		21 (10)		49 (23)		25 (12)		105 (50)	
ROS1-rearranged	36 (15)	10 (28)		1 (3)		9 (25)		2 (6)		16 (44)	
Previous TKI lines, n (%)			1.000		0.826		0.766		0.541		1.000
1	128 (52)	37 (29)		12 (9)		31 (24)		12 (9)		62 (48)	
≥2	120 (48)	35 (29)		10 (8)		27 (23)		15 (13)		59 (49)	
Brain metastases at baseline, n (%)			0.008		0.348		0.755		0.085		0.142
Present	162 (65)	56 (35)		12 (7)		39 (24)		22 (14)		85 (52)	
Absent	86 (35)	16 (19)		10 (12)		19 (22)		5 (6)		36 (42)	
Previous brain radiation, n (%)			0.033		0.649		0.542		0.012		0.019
Yes	98 (40)	36 (37)		10 (10)		25 (26)		17 (17)		57 (58)	
No	150 (60)	36 (24)		12 (8)		33 (22)		10 (7)		64 (43)	
Previous brain surgery, n (%)			0.197		1.000		0.020		0.137		0.095
Yes	19 (8)	8 (42)		1 (5)		9 (47)		4 (21)		13 (68)	
No	229 (92)	64 (28)		21 (9)		49 (21)		23 (10)		108 (47)	
Baseline cognitive impairment, n (%)			0.084		1.000		0.466		0.341		0.129
Yes	11 (4)	6 (55)		1 (9)		1 (9)		2 (18)		8 (73)	
No	237 (96)	66 (28)		21 (9)		57 (24)		25 (11)		113 (48)	
Baseline psychiatric illness, n (%)			0.008		0.265		0.191		1.000		0.113
Yes	49 (20)	22 (45)		2 (22)		15 (31)		5 (10)		29 (59)	
No	199 (80)	50 (25)		20 (10)		43 (22)		22 (11)		92 (46)	
Baseline speech disorder, n (%)			1.000		0.312		1.000		0.371		0.360
Yes	4 (2)	1 (25)		1 (25)		1 (25)		1 (25)		3 (75)	
No	244 (98)	71 (29)		21 (9)		57 (23)		26 (11)		118 (48)	

TKI, tyrosine kinase inhibitor.

Table 4. Association Between Baseline Medications and Neurocognitive Adverse Events in B7461001 Cohort

Characteristic		Cognitive Effects	*p* Value	Psychotic Effects	*p* Value	Mood Effects	*p* Value	Speech Effects	*p* Value	Neurocognitive Effects (Any)	*p* Value
B7461001 cohort, n (%)	N = 248	72 (29)		22 (9)		58 (23)		27 (11)		121 (49)	
Baseline psychiatric med, n (%)			<0.001		0.394		<0.001		0.796		0.002
Yes	48 (19)	24 (50)		6 (13)		21 (44)		6 (13)		33 (69)	
No	200 (81)	48 (24)		16 (8)		37 (19)		21 (11)		88 (44)	
Benzodiazepine at baseline, n (%)			0.057		0.819		0.002		0.833		0.002
Yes	87 (35)	32 (37)		7 (8)		31 (36)		10 (11)		54 (62)	
No	161 (65)	40 (25)		15 (9)		27 (17)		17 (11)		67 (42)	
Opioid at baseline, n (%)			1.000		0.498		0.444		1.000		0.605
Yes	99 (40)	29 (29)		7 (7)		26 (26)		11 (11)		46 (46)	
No	149 (60)	43 (29)		15 (10)		32 (21)		16 (11)		75 (50)	
Sedative at baseline, n (%)			0.073		0.149		0.034		0.434		0.199
Yes	47 (19)	19 (40)		7 (15)		17 (36)		3 (6)		27 (57)	
No	201 (81)	53 (26)		15 (7)		41 (20)		24 (12)		94 (47)	
Antiepileptic at baseline, n (%)			<0.001		0.748		0.076		<0.001		<0.001
Yes	33 (13)	22 (67)		2 (6)		12 (36)		11 (33)		26 (79)	
No	215 (87)	50 (23)		20 (9)		46 (21)		16 (7)		95 (44)	
Neuropathic at baseline, n (%)			0.055		0.744		0.496		1.000		0.338
Yes	31 (12)	14 (45)		3 (10)		9 (29)		3 (10)		18 (58)	
No	217 (88)	58 (27)		19 (9)		49 (23)		24 (11)		103 (47)	
Stimulant at baseline, n (%)			0.026		1.000		1.000		0.441		0.026
Yes	5 (2)	4 (8)		5 (100)		1 (20)		1 (20)		5 (100)	
No	243 (98)	68 (28)		22 (9)		57 (23)		26 (11)		116 (48)	
Steroid at baseline, n (%)			0.148		0.364		0.120		0.056		0.036
Yes	92 (37)	32 (35)		6 (7)		27 (29)		15 (16)		53 (58)	
No	156 (63)	40 (26)		16 (10)		31 (20)		12 (7)		68 (44)	

med, medicine.

Table 5. Frequency of Dose Modifications Prompted by Neurocognitive Adverse Events

	Cognitive Effects	Psychotic Effects	Mood Effects	Speech Effects	Neurocognitive Effects (Any)
MGH cohort (N = 124), n (%)	50 (40)	4 (3)	45 (36)	28 (23)	75 (60)
Dose hold for AE	26 (52)	4 (100)	21 (47)	13 (46)	35 (47)
Dose reduction for AE	27 (54)	4 (100)	24 (53)	14 (50)	39 (52)
Dose hold/reduction (any)	28 (56)	4 (100)	25 (56)	14 (50)	39 (52)
Improvement in AE with dose reduction	26 (96)	4 (100)	23 (96)	14 (100)	–
B7461001 cohort (N = 248), n (%)	72 (29)	22 (9)	58 (23)	27 (11)	121 (49)
Dose hold for AE	14 (19)	6 (27)	10 (17)	0 (0)	22 (18)
Dose reduction for AE	12 (17)	4 (18)	9 (15)	1 (4)	22 (18)
Dose hold/reduction (any)	20 (28)	7 (32)	13 (22)	1 (4)	30 (25)
Improvement in AE with dose reduction	9 (75)	3 (75)	7 (78)	1 (100)	–

AE, adverse event; MGH, Massachusetts General Hospital.

Speech Effects. A total of 28 patients (23%) in the MGH group developed speech effects on lorlatinib (Tables 1 and 2 and Fig. 1). In comparison, speech effects were observed at a significantly lower rate ($p = 0.005$; Fig. 1) in the B7461001 cohort where they were documented in 27 patients (11%) (Table 3 and Fig. 1). Brain radiation ($p = 0.019$) and concomitant use of antiepileptics ($p < 0.001$) were associated with a higher frequency of speech effects in the B7461001 cohort (Tables 3 and 4 and Fig. 1). In contrast, none of the clinical factors or medications assessed in the MGH group were predictive of developing speech effects. Dose interruptions occurred in 13 of 28 patients (46%) in the MGH group who experienced speech effects and 14 patients (50%) required dose reduction (Table 5). For all patients in the MGH group who required dose reduction, speech effects improved or resolved at the lower dose. In the B7461001 cohort, no dose interruptions were reported, but one patient (4%) required dose reduction (Table 5). Dose reduction had an ameliorative effect on speech toxicity for the patient.

Overall and Multiple Neurocognitive Effects. Finally, we analyzed both cohorts to determine the overall prevalence of neurocognitive AEs (Fig. 1) and assess for overlap of categories of neurocognitive toxicities. Overall, 60% of patients (n = 75 of 124) in the MGH group experienced a neurocognitive AE. There were 36 patients (29%) who developed greater than or equal to two categories of neurocognitive AEs on treatment. Thus, 48% of patients experiencing a neurocognitive AE in the institutional cohort had overlapping (i.e., co-occurring) neurocognitive toxicities. In the B7461001 cohort, 121 patients (49%) experienced a neurocognitive effect on lorlatinib. In total, 38% (n = 46 of 121) of patients who developed a neurocognitive toxicity in the B7461001 cohort had overlapping neurocognitive AEs. Development of a NAE within 12 weeks of initiating lorlatinib was associated with poorer PFS in the overall B7461001 cohort (Supplementary Fig. 2A) in a landmark analysis limited to patients who had a PFS on lorlatinib of at least 12 weeks. Finally, we evaluated the impact of developing a NAE within 12 weeks of initiating lorlatinib on PFS in two predefined cohorts of patients with ALK+ NSCLC grouped by treatment history: EXP2-3A (previous crizotinib with or without chemotherapy, Supplementary Fig. 2B) and EXP3B-5 (at least one previous non-crizotinib ALK TKI with or without chemotherapy, Supplementary Fig. 2C). The impact of development of a NAE within 12 weeks of initiating lorlatinib on PFS was only evident in EXP2-3A.

Discussion

Lorlatinib is a potent next-generation ALK and ROS TKI with proven antitumor activity across multiple indications and settings. In the registrational B7461001 phase 1/2 study,[1] lorlatinib induced responses in approximately 40% of patients previously treated with a second-generation ALK TKI triggering its initial authorization as a salvage therapeutic option in many countries. Among the subset of patients with ROS1+ NSCLC participating in the B7461001 study, objective responses were observed in 35% of patients with crizotinib-resistant NSCLC.[5] More recently, lorlatinib has gained regulatory approval in many countries for untreated metastatic ALK+ NSCLC on the basis of marked improvement in PFS relative to crizotinib in the global CROWN study.[4] The emergence of lorlatinib in the clinic has called attention to a unique group of CNS-related AEs—cognitive, mood, psychotic, and speech effects—that distinguish lorlatinib from earlier generation ALK and ROS1 TKIs. The pathogenesis of these neurocognitive effects has not been fully elucidated. To improve understanding of clinical factors potentially

associated with this unique group of toxicities, we rigorously evaluated the safety outcomes from greater than 350 patients from two distinct cohorts. Our findings suggest that most of the patients (49%–60%) treated with lorlatinib 100 mg after progression on another ALK/ROS1 TKI will develop a NAE and support the notion that factors associated with these effects may differ for distinct categories of NAEs.

Treatment with lorlatinib yields favorable intracranial outcomes, including durable suppression of brain metastases in the first-line setting and reinduction of CNS responses in patients with intracranial progression on other TKIs.[1,4,10,11] On the basis of this observation, the characteristic NAEs associated with lorlatinib have been speculated to originate from its ability to penetrate the blood-brain barrier and reach therapeutic levels. In our study, most of the patients (65%–83%) had baseline brain metastases. Although findings from our analysis of the B7461001 cohort suggested that patients with brain metastases developed cognitive effects more frequently, neither cohort identified a statistically significant association between brain metastasis and other categories of neurocognitive toxicity. As it is possible that further disruption of the blood-brain barrier resulting from CNS-specific therapies such as surgery and radiation may modulate the risk of developing NAEs, we also evaluated safety outcomes of patients receiving local CNS therapies. We observed a statistically significant higher rate of cognitive and speech effects among patients participating in the B7461001 study who had received CNS radiation compared with those who had not. This increased frequency of NAEs among patients who had received previous CNS radiation was also noted in a post hoc analysis of the CROWN study.[11] Neither cohort (MGH or B7461001) identified an association between previous resection of brain metastases and development of NAEs. Overall, our analysis suggests that CNS involvement of the NSCLC may contribute to but is not the primary factor driving development of the diverse lorlatinib-related neurocognitive effects.

We hypothesized that certain neurotropic medications and comorbid medical conditions such as cognitive impairment, psychiatric illness, and speech disorders would increase risk of developing specific NAEs. In our analysis, baseline cognitive impairment and speech disorders did not affect development of NAEs. In contrast, having a preexisting psychiatric illness was associated with a statistically significant increase of developing lorlatinib-related mood disorder in the MGH cohort. Although this trend was not apparent in the B7461001 group, use of psychiatric medications was associated with a higher rate of mood effects in the B7461001 study. In addition to psychiatric medications, stimulants, benzodiazepines, and sedatives were associated with developing mood effects in at least one of the cohorts. Overall, of all the categories of neurotropic medications assessed as part of our analysis, psychiatric medications, antiepileptic agents, and stimulants seemed to have the greatest impact on developing NAEs, with each associated with increased risk of developing multiple categories of NAEs. All three types of medications predisposed to cognitive effects. Notably, steroids were not implicated in increasing risk of any category of neurocognitive effect in either cohort.

In our analysis, we intentionally chose to study the two cohorts in parallel rather than pooling the data for several reasons. We hoped that using two independent cohorts spanning multiple clinical trials would generate a diverse and representative patient population. We anticipated that the institutional cohort, which predominantly included patients treated in the lorlatinib expanded access program, would more closely approximate a real-world setting than a first-in-human study. Perhaps owing to heterogeneity of the two cohorts, there was lack of consensus regarding factors associated with NAEs. Furthermore, the impact of NAEs on patient well-being, as deduced from the rate of dose interruption/reduction, differed across cohorts. Pertinent to real-world clinical practice, our analysis suggested that dose reduction ameliorated NAEs in nearly all cases, allowing patients to remain on treatment for an extended period. The responsiveness of NAEs to dose reduction and interruption noted in our study is consistent with recently published observations from the first-line CROWN study.[11] Interestingly, we observed shorter PFS for patients who developed a lorlatinib-related NAE within 12 weeks of initiating treatment in the B7461001 study, suggesting this class of toxicity may have detrimental effects on durability of benefit from treatment. The detrimental effects of NAE on PFS were most pronounced for patients who had only received crizotinib plus or minus chemotherapy before lorlatinib. Of note, an analysis evaluating PFS of patients requiring dose reduction versus those maintaining full dose in the CROWN study did not observe significant differences in treatment failure rates at 12 months. As a subset of those dose reductions were likely driven by NAEs, it is possible that findings from the pretreated cohort in our analysis may not be applicable to outcomes of treatment-naive patients receiving lorlatinib. Thus, additional studies are needed to further characterize neurocognitive toxicity among patients receiving lorlatinib in multiple contexts (first line versus later line).

Our study has several limitations. First, although we used prospective populations for our analysis, associations between potential factors and the development of NAEs were interpreted retrospectively. To this end, when the particular NAE prompting dose reduction was

not specified in the MGH cohort, all NAEs documented at the visit during which the lorlatinib dose was reduced were considered to have contributed to dose modification. This may have resulted in incorrect attribution of NAEs leading to dose change. Second, owing to unfortunate stigma surrounding mental illness and the prevalence of undiagnosed mood disorder, it is possible that we have underestimated the prevalence of baseline mental health conditions in our study population which may have obscured our ability to detect an association between baseline mood disorder and development of NAEs. Third, despite our large overall sample size, the number of patients experiencing specific NAEs was low, particularly psychotic and speech effects. Consequently, we could not thoroughly evaluate the confounding effects of multiple factors, as multivariable analysis was constrained by the total NAE numbers. Thus, it is important to validate our findings in additional larger cohorts. Finally, although we included patients in the expanded access program in the institutional cohort, it must be acknowledged that most patients captured in this analysis were eligible for clinical trials and, thus, findings may not be fully generalizable to the real-world setting.

In conclusion, our analysis of safety outcomes of greater than 350 patients treated with lorlatinib through prospective studies exploring its efficacy after progression on other TKIs suggests that NAEs from lorlatinib are prevalent, represent four distinct categories of CNS effects rather than a single entity, respond to dose reduction, may be associated with shorter PFS, and are potentially associated with factors other than baseline brain metastases, including CNS radiation, preexisting psychiatric illness, and baseline use of certain neurotropic medications.

CRediT Authorship Contribution Statement

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Pfizer Data Sharing Statement

On request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.09.219.

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