Phase II Study of Lorlatinib in Patients With Anaplastic Lymphoma Kinase–Positive Lung Cancer and CNS-Specific Relapse

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Key Objective

A subset of patients with ALK-rearranged lung cancer will experience CNS-only progression on second-generation anaplastic lymphoma kinase (ALK) inhibitors. The efficacy of the third-generation ALK inhibitor Lorlatinib in this context is not well- defined.

This is an open- label, investigator-initiated, single-arm phase II trial of lorlatinib in patients with ALK-rearranged NSCLC with CNS metastasis and no sites of active, measurable extracranial disease

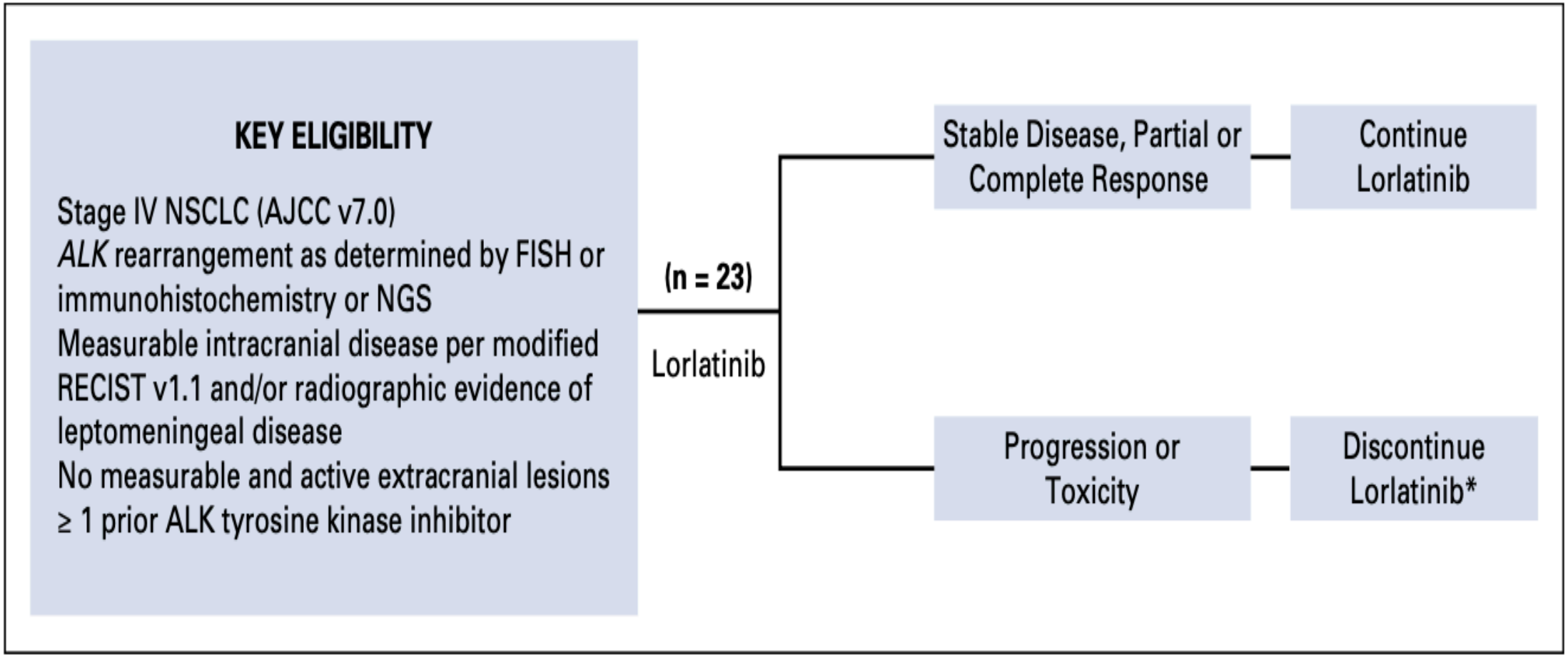


TABLE 1. Baseline Characteristics of the Study Population

Characteristic	All Patients (N = 23), No. (%)
Age, years	
Median	58
Range	22-84
Sex	
Male	13 (57)
Female	10 (43)
Race	
White	15 (65)
Asian	5 (22)
Hispanic	3 (13)
Smoking history	
Never	18 (78)
Former	5 (22)
ECOG PS	
0	8 (35)
1	12 (52)
2	3 (13)
Symptomatic brain metastases	
Yes	5 (22)
No	18 (78)
Prior brain radiation	
Yes	15 (65)
No	8 (35)
No. of prior lines of therapy	
1	4 (17)
2	7 (30)
3+	12 (52)
Prior chemotherapy	
Yes	8 (35)
No	15 (65)
No. of prior ALK inhibitors	
1	5 (22)
2	11 (48)
3+	7 (30)

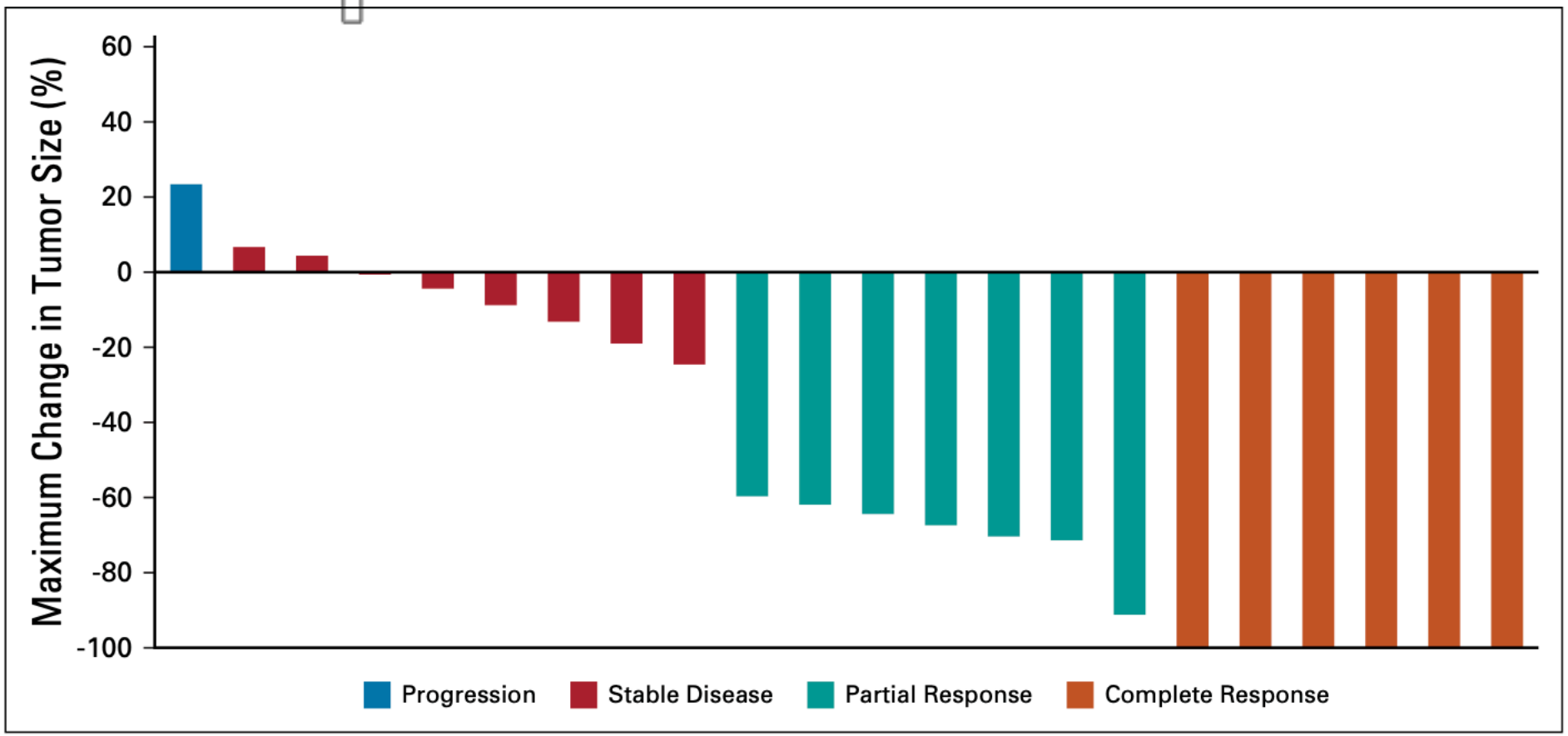
Abbreviations: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status.

TABLE 2. Treatment-Related AEs Occurring in ≥ 10% of Patients

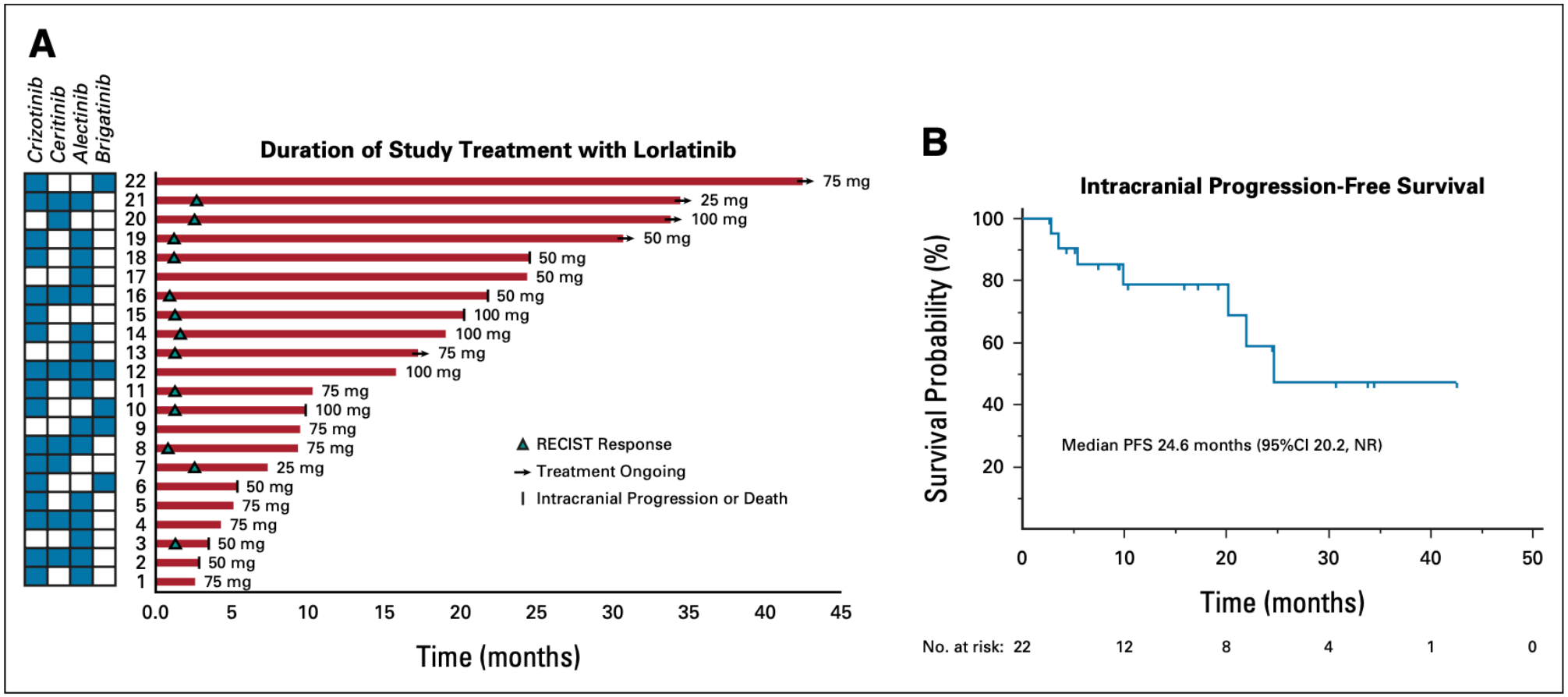
	Patients With Treatment-Related AEs by Grade, No. (%)					
AE	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**All Grades**
Cholesterol elevation	10 (43)	10 (43)	1 (4)	1 (4)	0 (0)	22 (96)
Triglyceride elevation	11 (48)	6 (26)	2 (9)	1 (4)	0 (0)	20 (87)
Peripheral edema	12 (52)	3 (13)	0 (0)	0 (0)	0 (0)	15 (65)
Cognitive effects	6 (26)	5 (22)	1 (4)	0 (0)	0 (0)	12 (52)
Mood effects	6 (26)	4 (17)	0 (0)	0 (0)	0 (0)	10 (43)
Weight gain	6 (26)	2 (9)	1 (4)	0 (0)	0 (0)	9 (39)
ALT elevation	6 (26)	1 (4)	0 (0)	0 (0)	0 (0)	7 (30)
Neuropathy	6 (26)	1 (4)	0 (0)	0 (0)	0 (0)	7 (30)
AST elevation	6 (26)	0 (0)	0 (0)	0 (0)	0 (0)	6 (26)
Lipase elevation	2 (9)	1 (4)	2 (9)	0 (0)	0 (0)	5 (22)
Speech effects	4 (17)	0 (0)	0 (0)	0 (0)	0 (0)	4 (17)
Diarrhea	3 (13)	0 (0)	0 (0)	0 (0)	0 (0)	3 (13)
Amylase elevation	1 (4)	2 (9)	0 (0)	0 (0)	0 (0)	3 (13)

Abbreviation: AEs, adverse events; No., number.

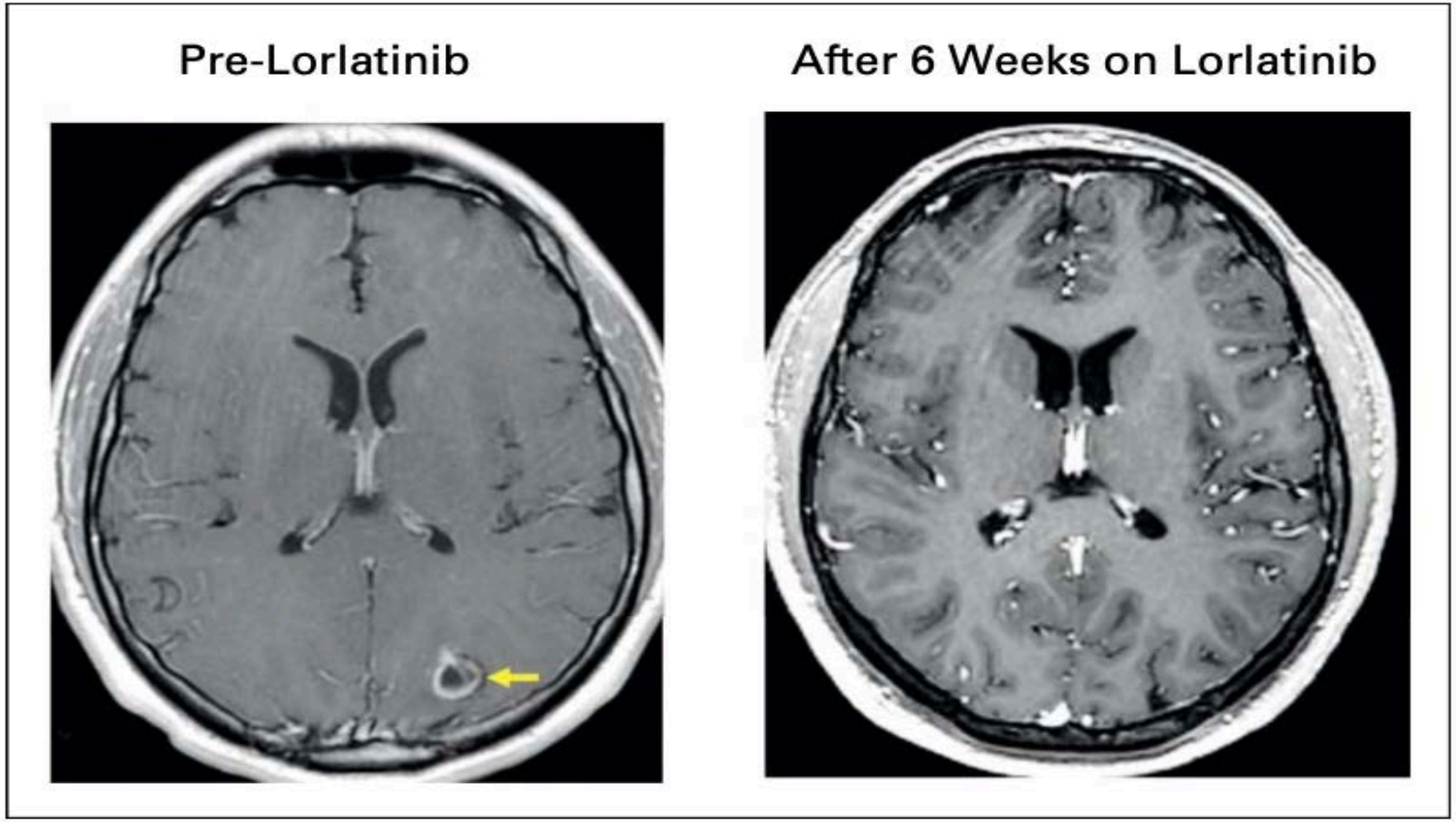
Bestintracranialresponsetolorlatinib.Thewaterfallplotdepictsbestintracranialtumorresponseasassessed by modified RECIST version 1.1.



Durability of intracranial responses to lorlatinib.

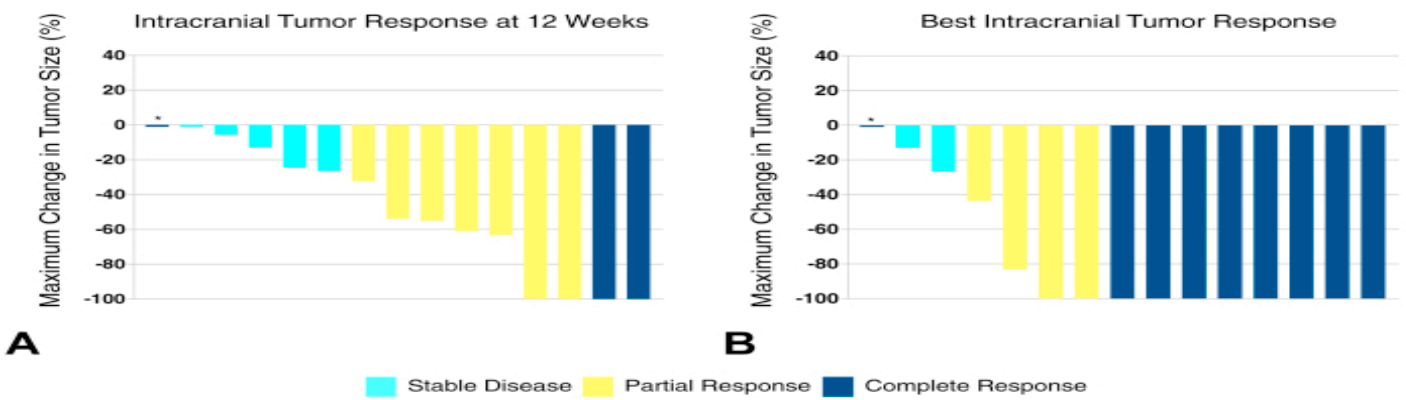


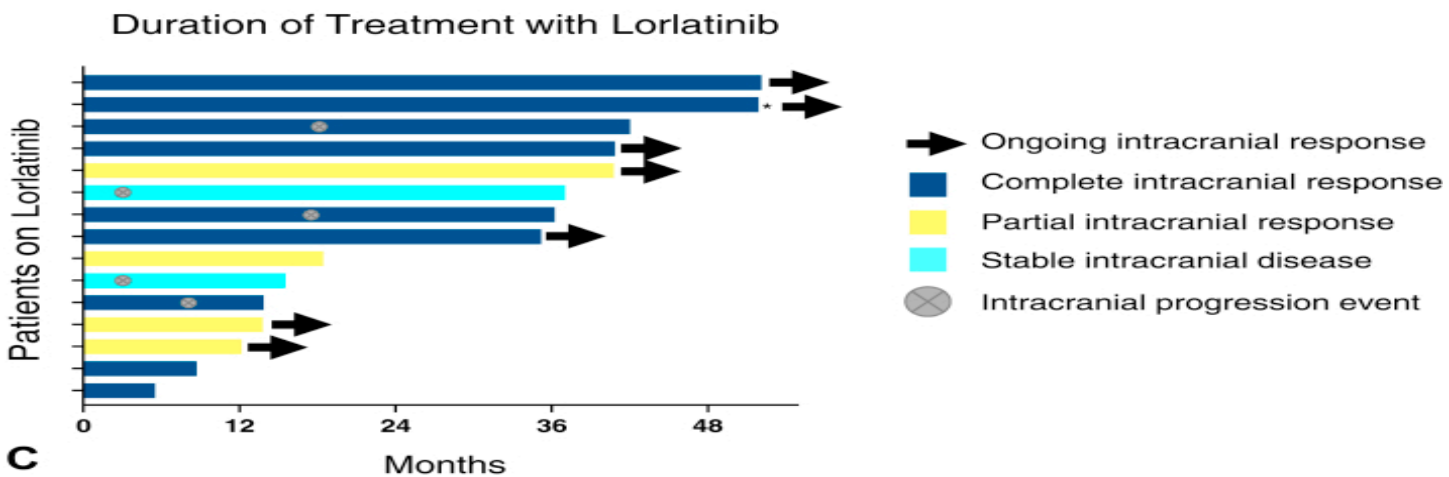
Resolution of brain metastasis on Lorlatinib



Summary…!

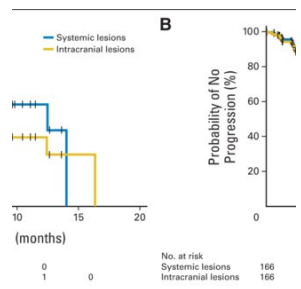
In this phase II study, It is observed that there is robust intracranial activity of lorlatinib in patients with isolated CNS progression on second-generation ALK TKIs. The intracranial DCR of 95% with lorlatinib in this context suggests that brain metastases from patients with CNS- only progression remain ALK-dependent.


Intracranial Tumor Response at 12 Weeks
Maximum Change in Tumor Size (%)
40
20
0
-20
-40
-60
-80
-100
A
Best Intracranial Tumor Response
Maximum Change in Tumor Size (%)
40
20
0
-20
-40
-60
-80
-100
B
Stable Disease
Partial Response
Complete Response


Duration of Treatment with Lorlatinib
Patients on Lorlatinib
0
12
24
36
48
Months
C
Ongoing intracranial response
Complete intracranial response
Partial intracranial response
Stable intracranial disease
Intracranial progression event

Relevance

This prospective clinical trial suggests that lorlatinib has robust intracranial activity in patients with CNS-only progression on second-generation ALK inhibitors. Given the challenges of characterizing molecular mechanisms underlying CNS-specific progression events, this study supports empiric use of lorlatinib for patients experiencing this unique pattern of progression.


B
Systemic lesions
Intracranial lesions
Probability of No Progression (%)
100
80
60
40
20
0
10
15
20
(months)
No. at risk
Systemic lesions 166
Intracranial lesions 166
0
1
0