Post Hoc Analysis of Lorlatinib Intracranial Efficacy and Safety in Patients With ALK-Positive Advanced Non–Small-Cell Lung Cancer From the Phase III CROWN Study

Dr. Mridul Malhotra

Medical Oncology

Asian Institute of Medical Sciences, Faridabad

Lorlatinib

- Potent, third-generation inhibitor of anaplastic lymphoma kinase (ALK) inhibitor
- Improved progression free survival (PFS) compared with crizotinib (hazard ratio [HR] for disease progression or death, 0.28; 95% CI, 0.19 to 0.41; P , .001) in CROWN phase III RCT
- At Baseline, app. 29%-40% ALK-positive NSCLC have brain metastases
- Later, more than half will develop brain metastases

- Better intracranial response rates seen.
  - RR was 66% with lorlatinib and 20% with crizotinib.

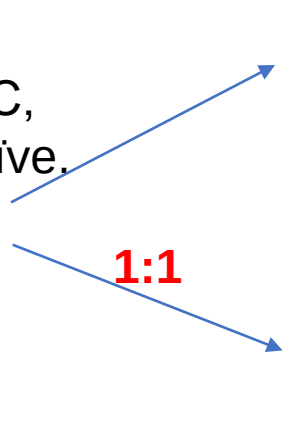
- Complete intracranial responses were seen in 61%

- Post hoc exploratory efficacy and safety outcomes from the CROWN study

- Subgroup analyses in patients with and without brain metastases at baseline, and data on the incidence and management of CNS-related AEs.

Study Design

Histologically or cytologically confirmed (≥18 y), locally advanced Metastatic NSCLC, *ALK IHC +ve (*Ventana ALK (D5F3). T/t naïve. Asymptomatic treated or untreated CNS Metastases were eligible.
At least one extracranial measurable target Lesion not been previously irradiated;
ECOG PS 0-2



Lorlatinib 100 mg OD q28 days

Crizotinib 250 mg BD q28 days

Tumor assessments every 8 weeks (CT TAP and MRI Brai

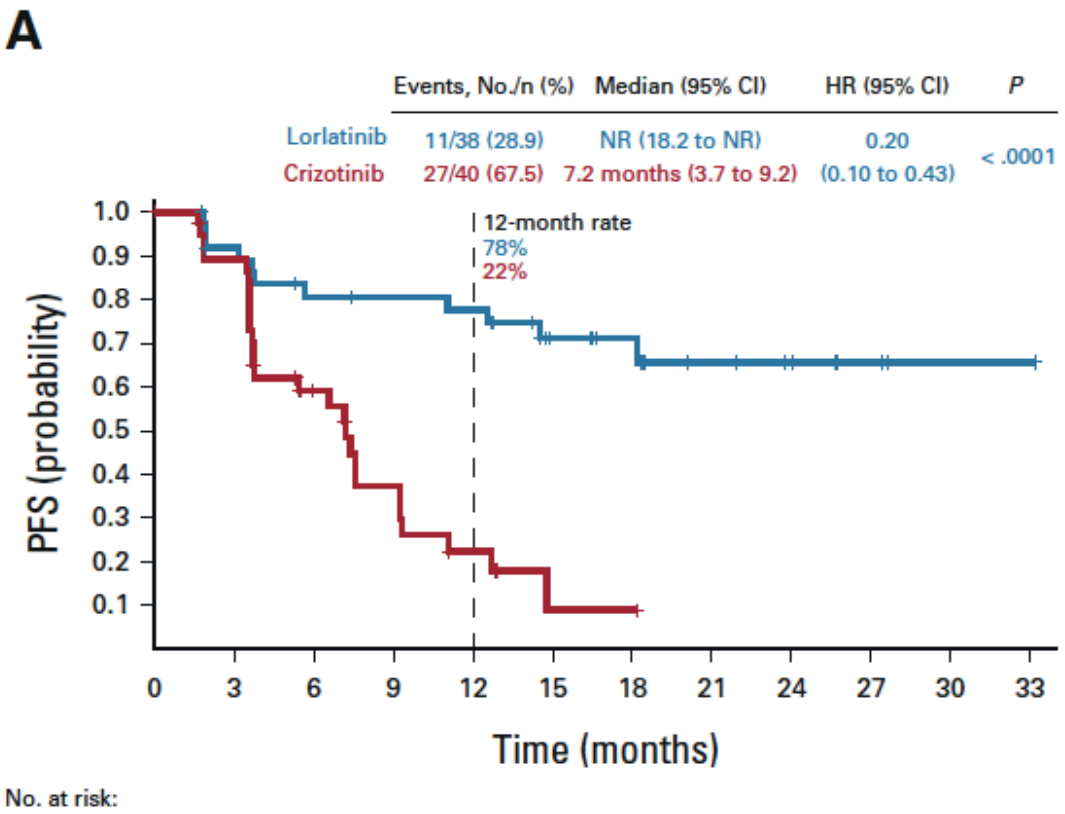
Stratified according to the presence of brain Metastases, ethnic group (Asian or non-Asian).
Per protocol, crossover between the treatment groups was not permitted

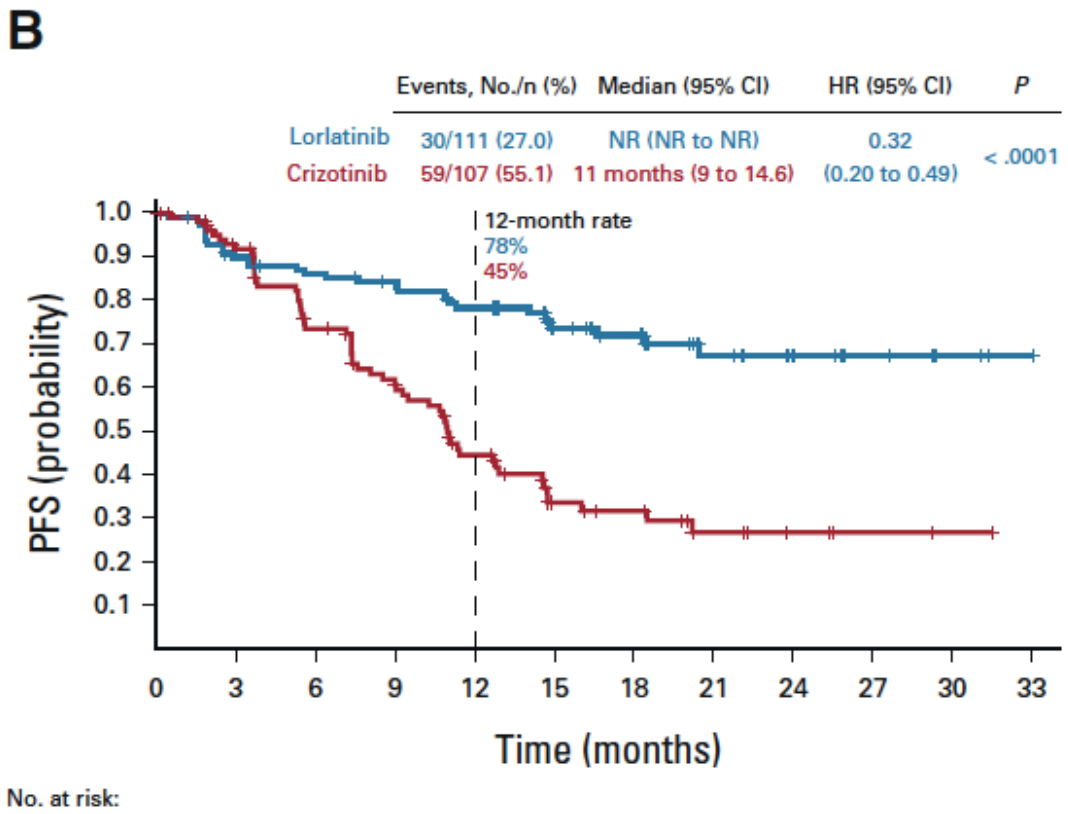
End Points

- PFS by BICR
- Cumulative incidence of CNS progression and non-CNS progression as first progression event
- Intracranial complete response rate, duration of response (DOR), and safety were assessed by patient subgroup (with or without brain metastases at baseline).
- PFS subgroups of patients with brain metastases with or without prior brain radiotherapy.
- PROs were assessed in patients with and without CNS AEs.

- Data cutoff for the primary analysis March 20, 2020

	Lorlatinib	Crizotinib
n	149	147
Brain Metastases Baseline	38(26%)	40(27%)
Prior Radiotherapy	8/38(21%)	10/40(25%)

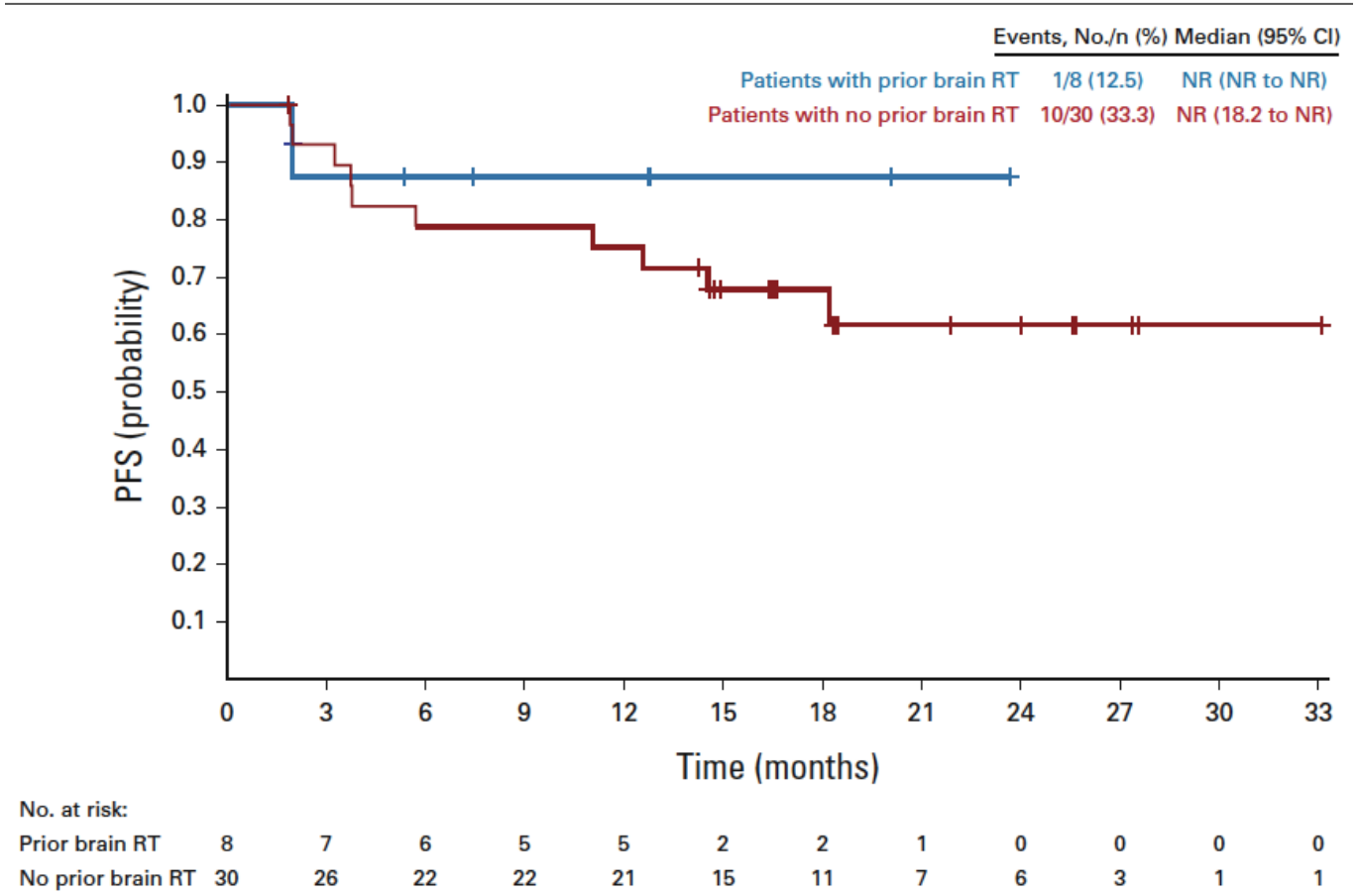




Brain Metastases

No Brain Metastases

PFS

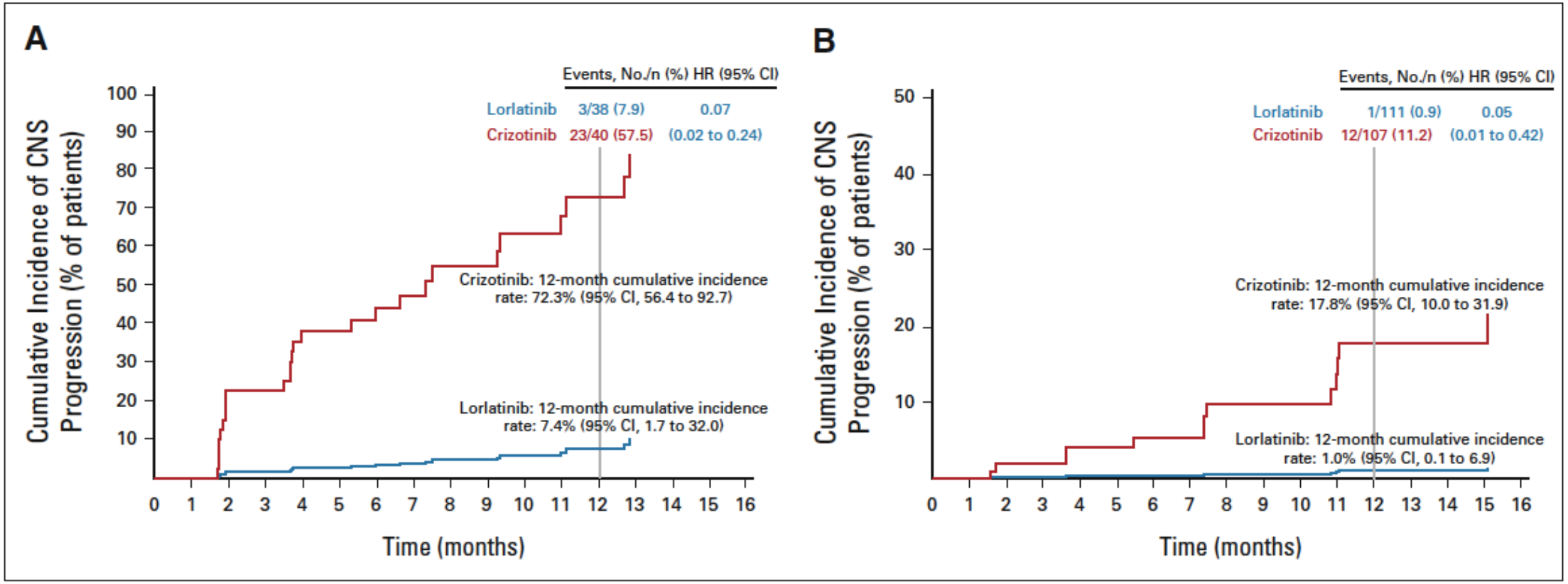


12 month PFS Rate
Brain Mets Lorlatinib Prior RT : 88%
(95% CI, 39 to 98).

Brain Mets Lorlatinib No prior Raidotherapy: 75%
(95% CI, 55 to 87

Effect of prior Radiotherapy to Brain Metastases

Cumulative Incidence CNS Progression



Baseline Brain Metastases

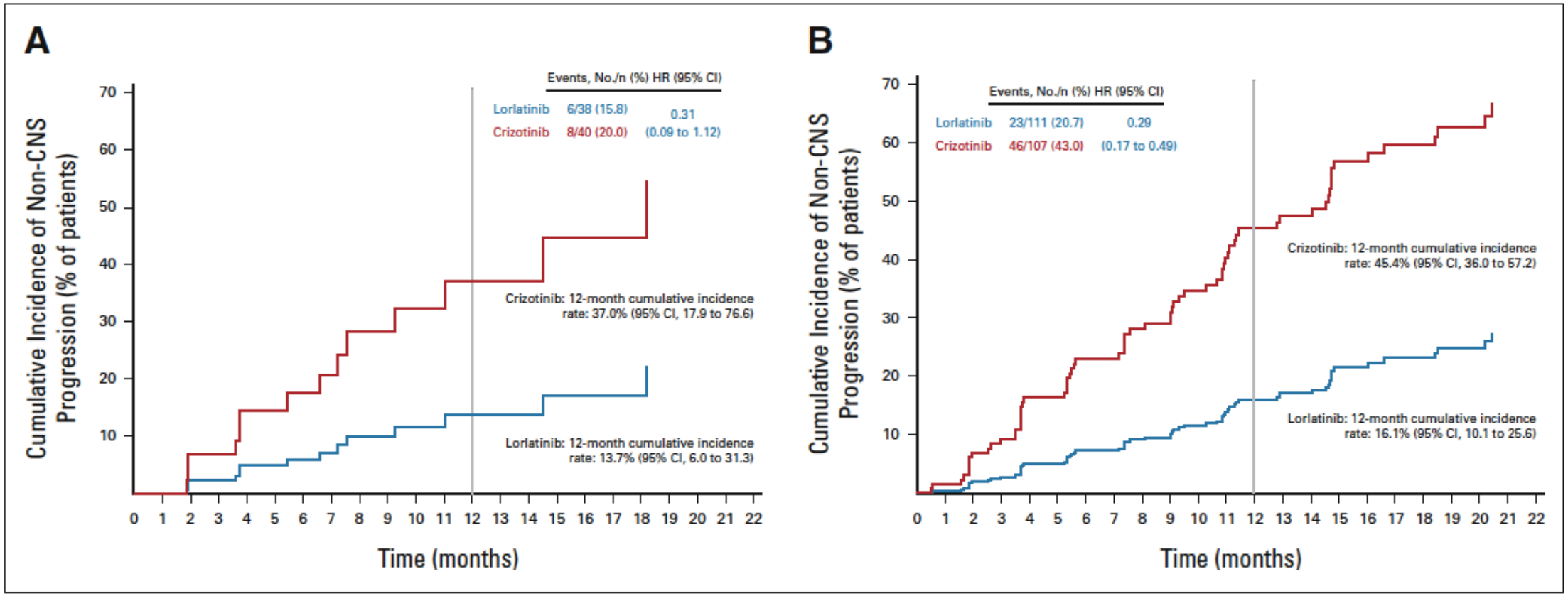
No Baseline Brain Metastases

12 month Cumulative Incidence CNS Progression

	CROWN	ALEX
Baseline Brain Mets	7%	16%
No Baseline Brain Mets	1%	5%

Lorlatinib was highly effective at preventing CNS progression in the majority of patients.

Cumulative Incidence Non CNS Progression



Brain Metastases

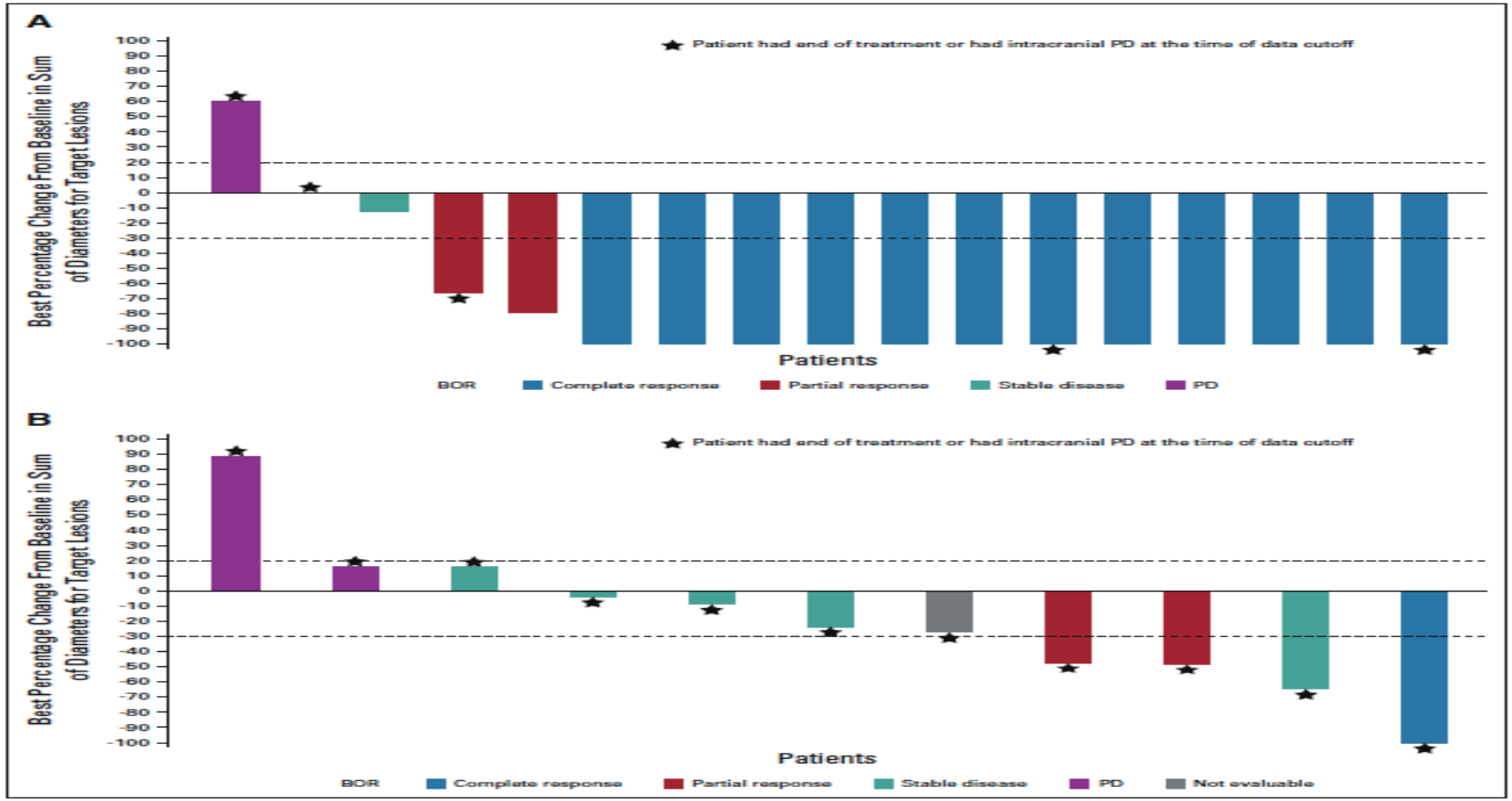
No Brain Metastases

Intracranial Complete Responses

	Lorlatinib	Crizotinib
CR	61% (23/38)	15% (6/40)
CR with atleast 1 target lesion	12/17(71%)	1/13(8%)
Median DOR	NR (7.4 to 31.4 m)	

10/12 patients (83%) had a DOR ≥12 months and 5/12 patients (42%) had a DOR ≥18 months.

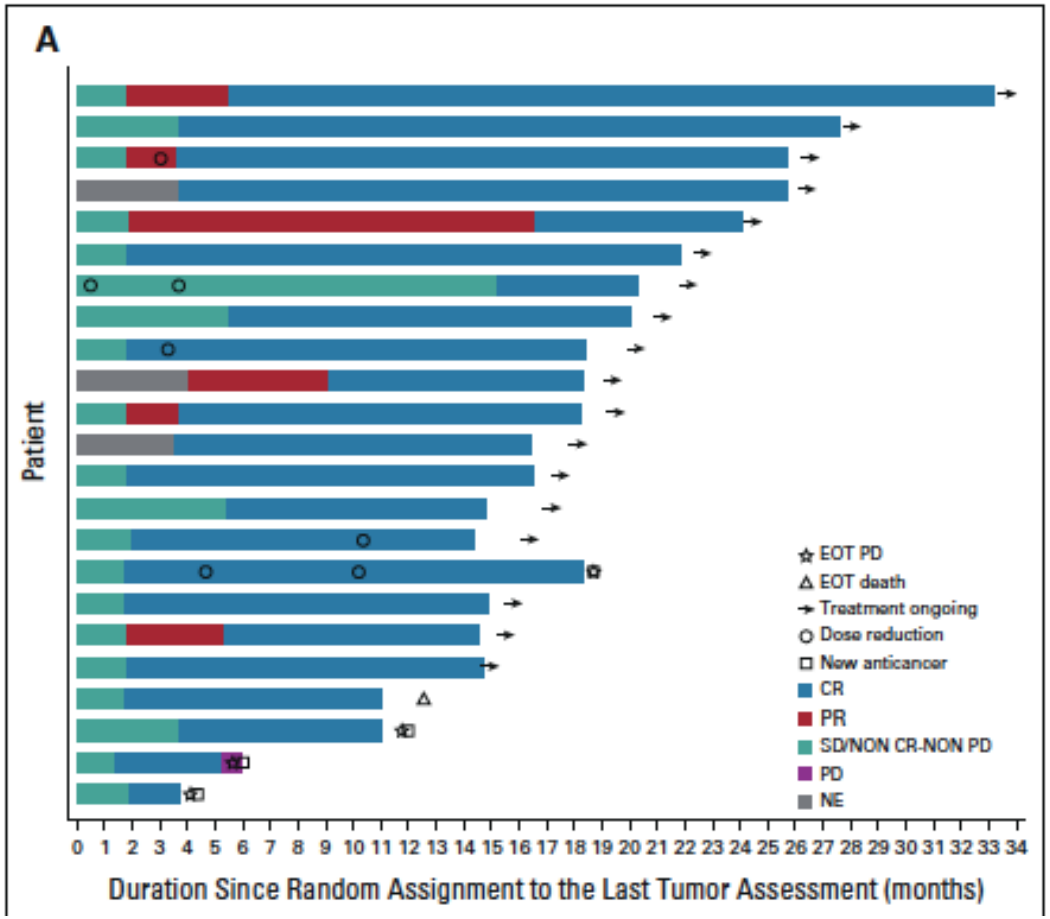
Intracranial Responses



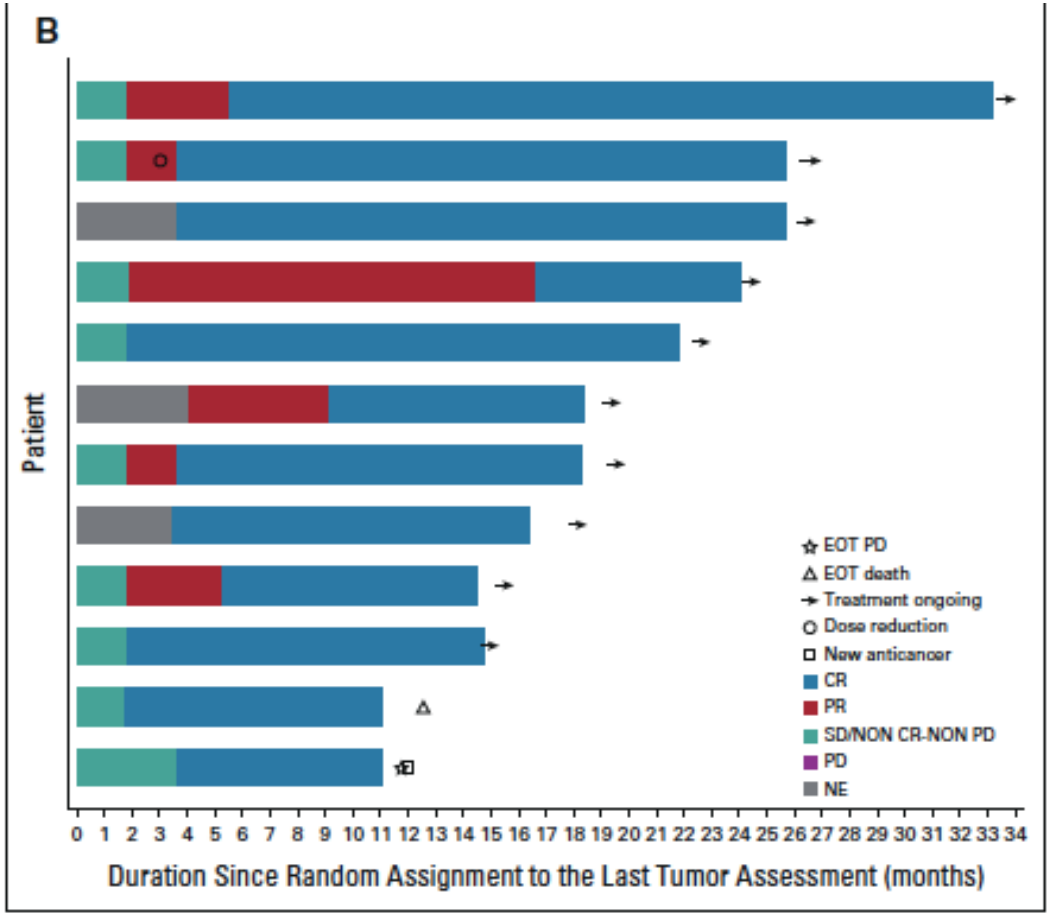
Lorlatinib

Crizotinib

Intracranial complete responses with lorlatinib treatment at data cutoff in patients with measurable or nonmeasurable brain metastases (n 23)



Intracranial complete responses lorlatinib treatment at data cutoff in patients with at least one measurable brain metastasis (n 12).



Incidence of CNS Adverse Effects Following Treatment

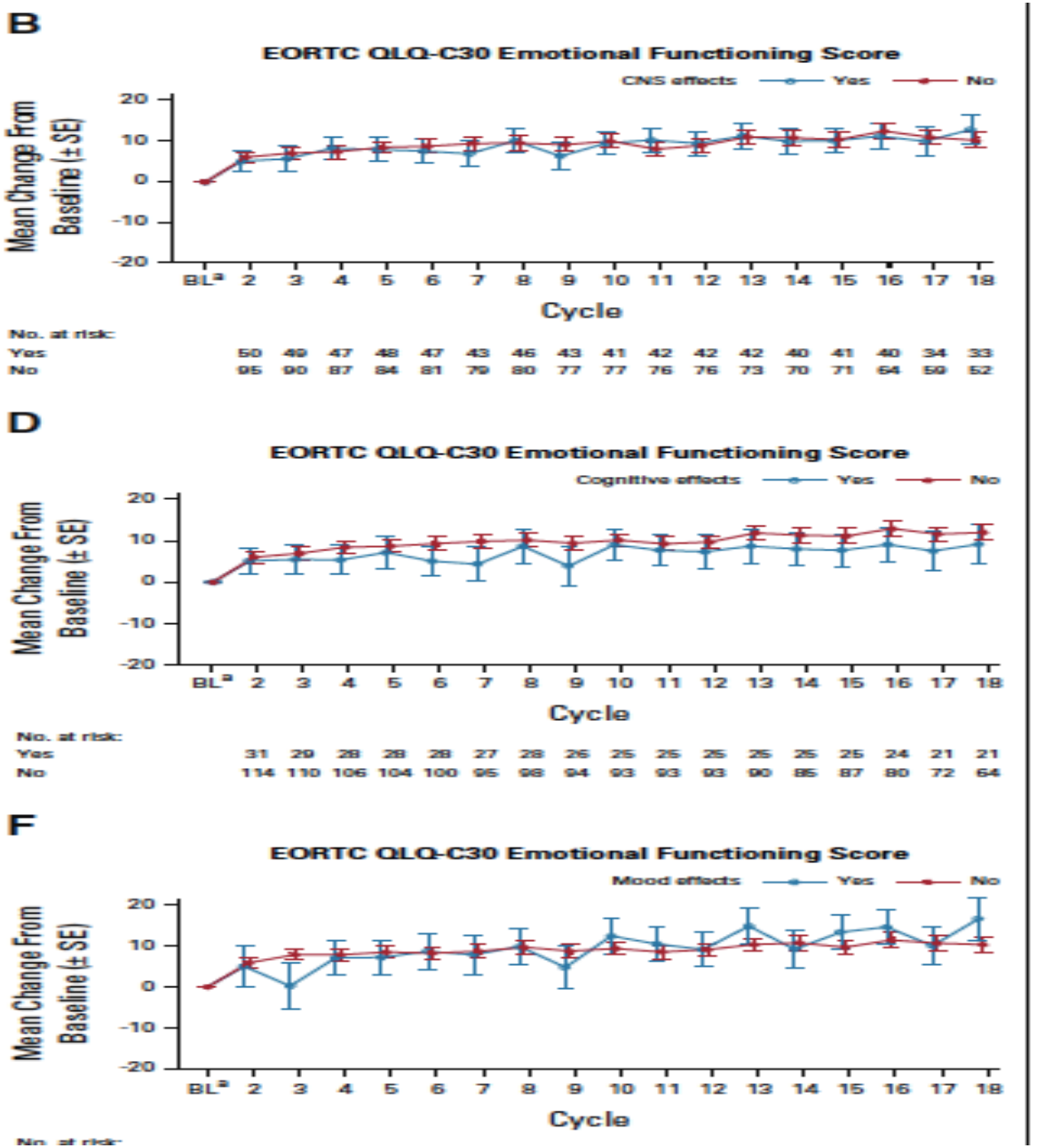
	Lorlatinib	Crizotinib
Overall CNS AEs	52/149(35%)	15/142(11%)
Grade 1	32/52(62%)	11/15(73%)
Grade 2	15/52(29%)	4/15(27%)
Grade 3	5/52(10%)	None
Grade4/5	None	None

- CNS AEs more in Brain Metastases vs Non Brain Metastases at baseline
  - 16/38(42%) versus 36/111 patients (32%)

- CNS AEs higher among patients who had prior brain radiotherapy (5/9; 56%) than patients without prior brain radiotherapy (47/140; 34%)

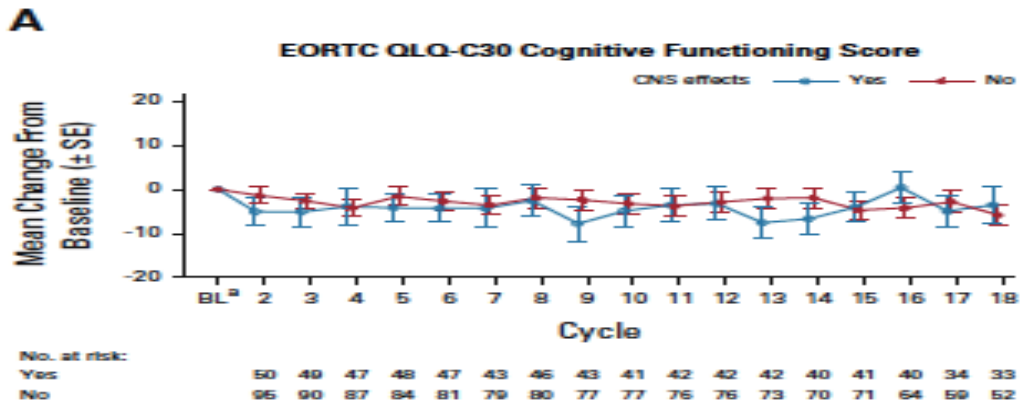
Patient Reported Outcomes

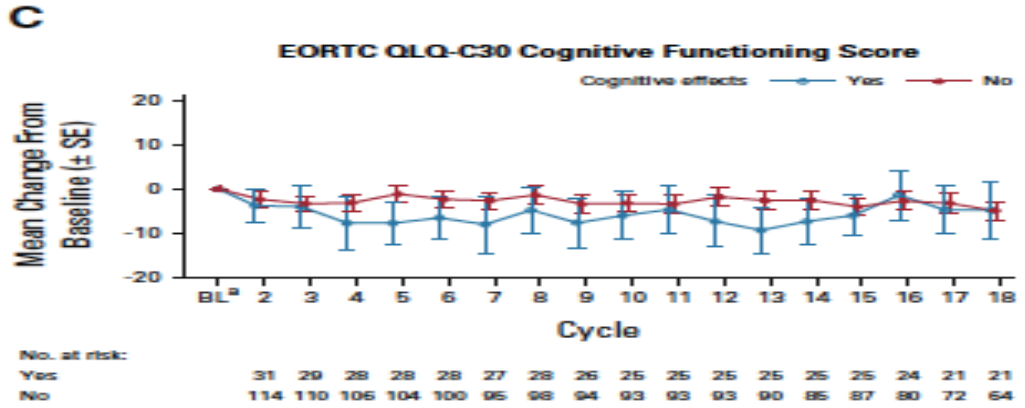
PRO – Emotional Fn Score



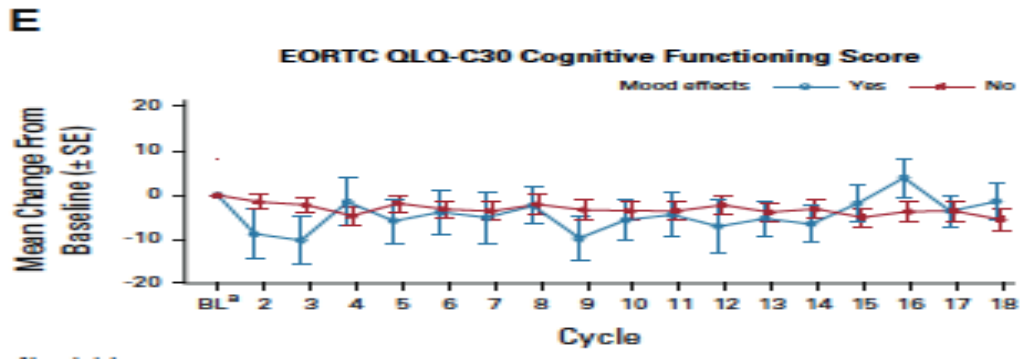
PRO – Cognitive Fn Score

-4.85





-6.34



Management of ADRs on Lorlatinib

Intervention	Total CNS AEs, No. (%)[a]	Resolved, No. (%)	Improved, No. (%)	Not Resolved, No. (%)
Total	86 (100)	48 (56)	3 (3)	33 (38)
No intervention	53 (62)	28 (33)	1 (1)	24 (28)
Intervention	31 (36)	20 (23)	2 (2)	9 (10)
CM only	11 (13)	5 (6)	0	6 (7)
Lorlatinib dose modification ± CM	20 (23)	15 (17)	2 (2)	3 (3)

Lorlatinib dose modification alone was used for the management of 15 (23%)CNS AEs, of which 13 (87%) resolved

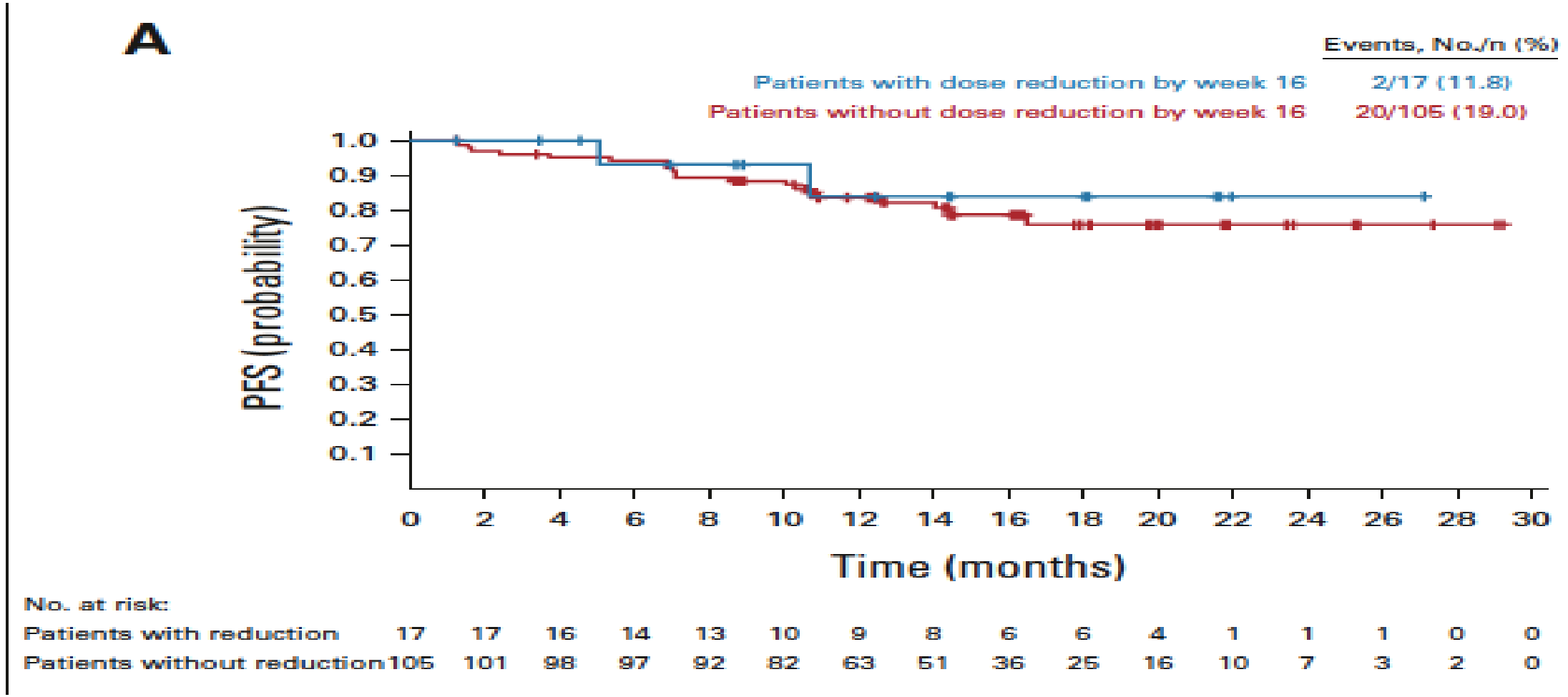
CNS AEs led to permanent treatment discontinuation in 2 cases (2%)

- Grade 2 confusion and Grade 3 Confusion Each of the cases

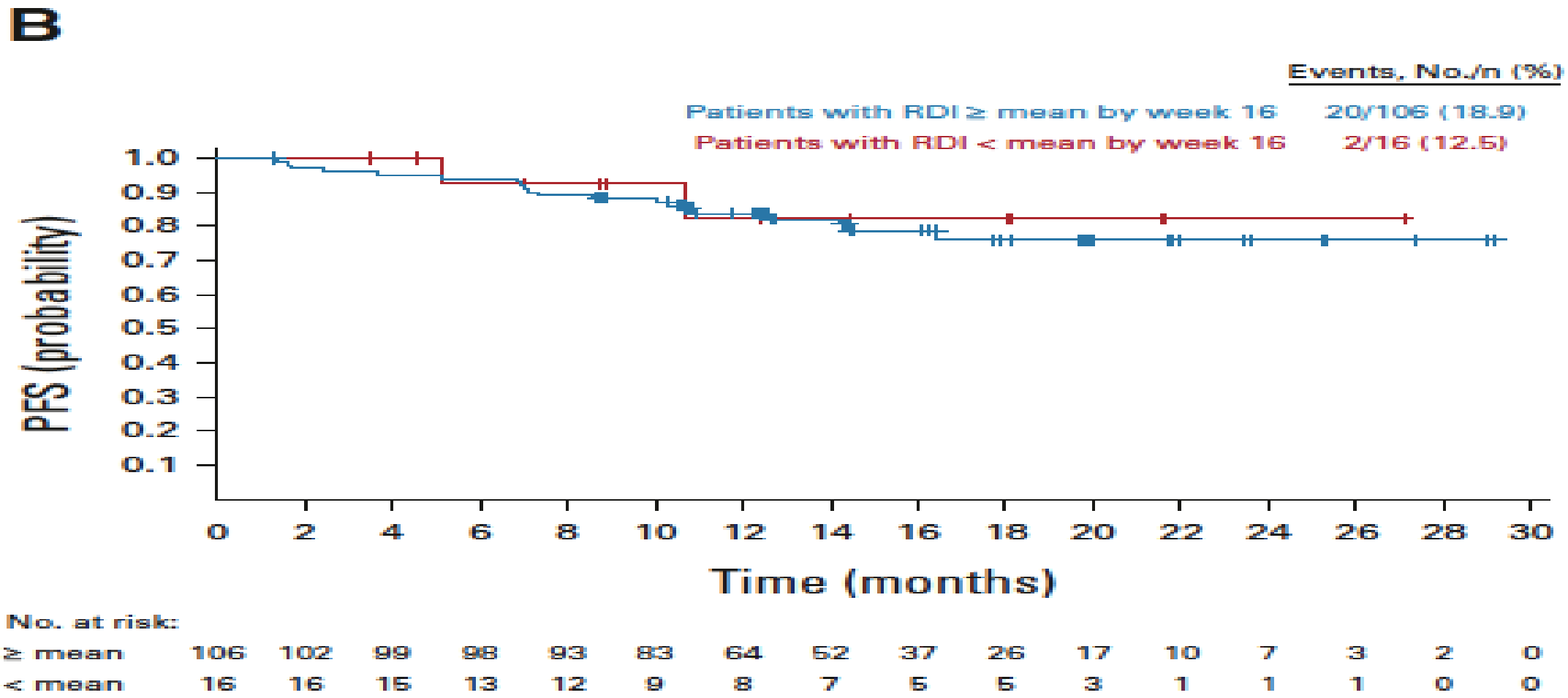
Impact of Lorlatinib Dose Modification on PFS

- In total, 41/149 (28%) patients in CROWN had at least one lorlatinib dose reduction because of AEs.

Landmark analysis of PFS with or without lorlatinib dose reduction within 16 weeks



Landmark Analysis of PFS with categorized by the mean RDI of 98.6% by week 16.



	CROWN	ALEX	ALTA-1
PFS in Baseline Brain Metastases	HR, 0.20	HR, 0.37	HR, 0.25
PFS without Baseline Brain Mettastases	HR, 0.32	HR: 0.46	HR: 0.65
Intracranial Response Rates	71%	38%	28%

Conclusion

- Lorlatinib improved PFS outcomes and reduced CNS progression 1st line dvanced ALK-positive NSCLC with or without brain metastases at baseline.
- Intracranial responses were durable
- Many CNS AEs resolved without intervention, or with lorlatinib dose modification and/or concomitant medication.
- These data support the use of lorlatinib as firstline treatment in patients with advanced ALK-positive NSCLC.

Thank You