Appendix A.

Brain penetration of lorlatinib: cumulative incidences of CNS and non–CNS progression with lorlatinib in patients with previously treated ALK–positive non-small cell lung cancer

Running head: CIRs of CNS and non-CNS progression with lorlatinib in ALK-positive NSCLC

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TABLE A.1. Cumulative incidence probabilities for CNS progression, non-CNS progression, and death at 6 and 12 months for patients who had received a second-generation ALK TKI* as their last prior ALK TKI (n = 121)

	Cumulative incidence probability (95% CI)	
Months	**Baseline CNS metastases (n = 80)**	**No baseline CNS metastases (n = 41)**
CNS progression		
6 months	0.15 (0.08–0.24)	0.11 (0.03–0.23)
12 months	0.23 (0.14–0.33)	0.11 (0.03–0.23)
Non-CNS progression		
6 months	0.27 (0.18–0.38)	0.38 (0.23–0.54)
12 months	0.37 (0.26–0.48)	0.53 (0.35–0.67)
Death		
6 months	0.06 (0.02–0.13)	0.06 (0.01–0.17)
12 months	0.06 (0.02–0.13)	0.08 (0.02–0.20)

ALK, anaplastic lymphoma kinase; CI, confidence interval; CNS, central nervous system; TKI, tyrosine kinase inhibitor.

*Second-generation ALK TKIs included: alectinib (n=62), ceritinib (n=47), brigatinib (n=8); other TKI (ensartinib or entrectinib) (n=4).

Table A.2. Intracranial response* by derived independent central review in patients with previously irradiated brain lesions in progression at baseline

	Prior crizotinib† (EXP2–3A; n = 8)	At least 1 prior second-generation ALK TKI† (EXP3B–5; n = 30)
Best overall intracranial response, n (%)		
Complete response	1 (12.5)	5 (16.7)
Partial response	3 (37.5)	7 (23.3)
Stable disease	3 (37.5)	10 (33.3)
Objective progression	0	7 (23.3)
Indeterminate	1 (12.5)	1 (3.3)
Objective response rate, n (%)	4 (50.0)	12 (40.0)
95% CI	15.7–84.3	22.7–59.4
Duration of intracranial response, months		
Median	NR	12.4
95% CI	2.8–NR	11.1–NR

ALK, anaplastic lymphoma kinase; CI, confidence interval; EXP, expansion cohort; NR, not reported; TKI, tyrosine kinase inhibitor

*Intracranial response based on irradiated brain lesions with progression at baseline and new brain lesions only

†With or without chemotherapy.

TABLE A.3. Treatment-related AEs associated with the CNS in patients with ≥1 ALK TKI (EXP2–5; n = 198)

	Baseline CNS metastases (n = 131)			No baseline CNS metastases (n = 67)		
TRAE	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**
Any TRAE	71 (54.2)	3 (2.3)	0	33 (49.3)	4 (6.0)	1 (1.5)
Nervous system disorders*						
Cognitive effects†	34 (26.0)	1 (0.8)	0	13 (19.4)	1 (1.5)	0
Speech effects†	11 (8.4)	0	0	7 (10.4)	1 (1.5)	0
Headache	11 (8.4)	0	0	6 (9.0)	0	0
Dizziness	10 (7.6)	0	0	6 (9.0)	0	0
Dysgeusia	5 (3.8)	0	0	4 (6.0)	0	0
Psychiatric disorders*						
Mood effects†	22 (16.8)	2 (1.5)	0	11 (16.4)	1 (1.5)	0
Insomnia	8 (6.1)	0	0	2 (3.0)	0	0
Hallucinations†	5 (3.8)	0	0	9 (13.4)	1 (1.5)	1 (1.5)

NOTE. Data are given as No. (%)

ALK, anaplastic lymphoma kinase; AE, adverse event; CNS, central nervous system; EXP, expansion cohort; TKI, tyrosine kinase inhibitor; TRAE, treatment-related AE

*TRAEs are listed if they were reported in ≥5% of patients in either subgroup

†This item comprised a cluster of AEs that may represent similar clinical symptoms or syndromes