Brigatinib in ALK+ crizotinib-refractory non-small cell lung cancer: Final results of the Phase 1/2 and Phase 2 (ALTA) trials

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- Treatment with anaplastic lymphoma kinase (ALK) inhibitors is standard for ALK-rearrangement—positive (ALK+) metastatic non–small cell lung cancer (NSCLC)¹
- Crizotinib, the first ALK tyrosine kinase inhibitor (TKI) approved for ALK+ NSCLC, demonstrated better efficacy than platinum-based doublet chemotherapy (median progression-free survival [PFS], 10.9 months vs 7.0 months) in patients with treatment-naive ALK+ NSCLC,² although most patients eventually develop progressive disease on crizotinib³
- Mechanisms of TKI resistance include acquisition of secondary mutations in ALK, amplification of the ALK fusion gene,
- and upregulation of bypass signaling pathways⁴
- Brigatinib is a next-generation ALK TKI that has potent and broad activity against ALK resistance mutations⁵
- The main results from the phase 1/2 study and a phase 2 randomized study (ALTA) of brigatinib were previously reported^{6,7}
- In patients with crizotinib-refractory ALK+ NSCLC, brigatinib 180 mg qd with 7-day lead-in at 90 mg demonstrated a systemic objective response rate (ORR) of 56% and an intracranial ORR of 67% in patients with measurable baseline brain metastases, with an acceptable safety profile⁷⁻⁹
- Results of these trials supported the initial approval of brigatinib in the US in 2017 for the treatment of patients with ALK+ NSCLC who have progressed on or are intolerant to crizotinib

Objective

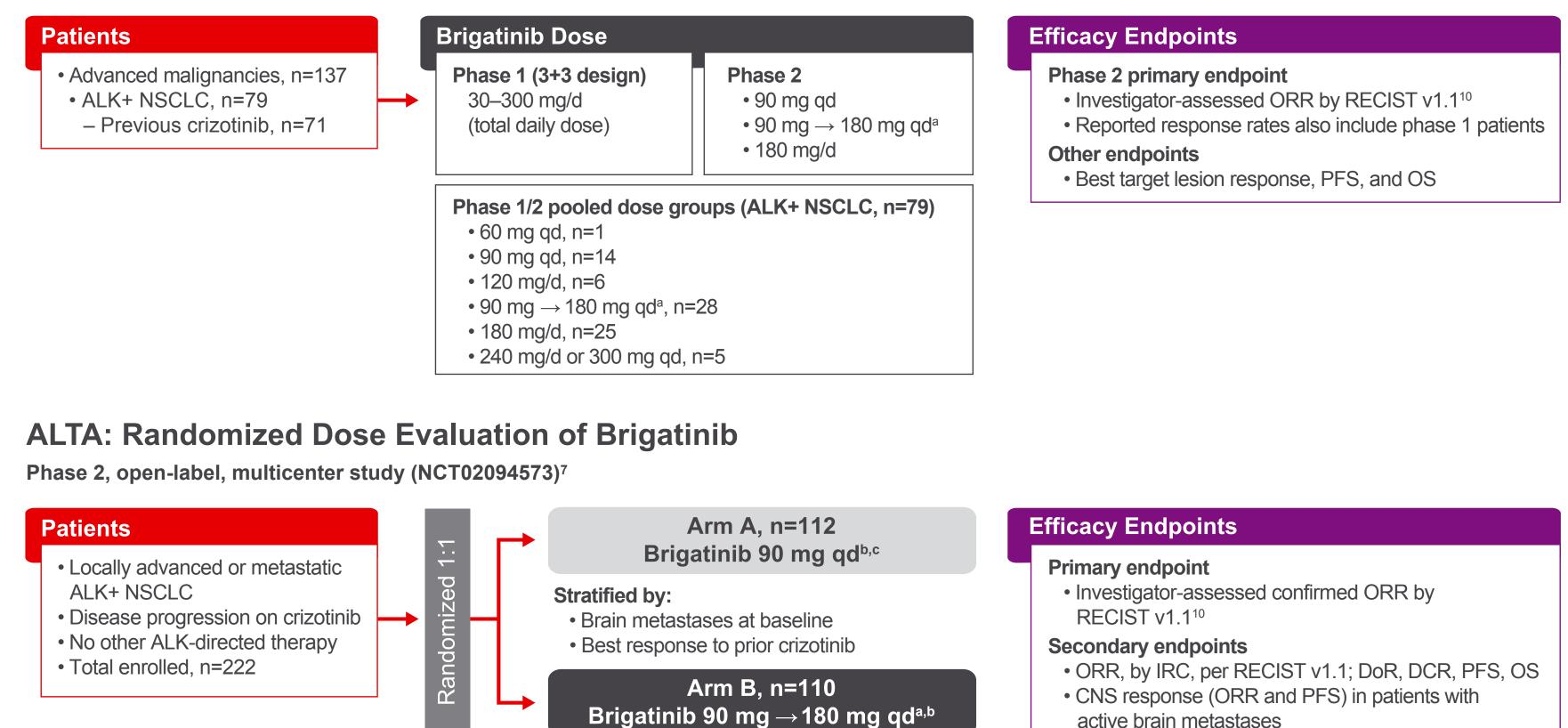
• To report long-term efficacy and safety results from the final analyses of the phase 1/2 and phase 2 (ALTA) trials of brigatinib, completed >5 years and >4 years, respectively, after the last patients enrolled

(X) Methods

Figure 1. Study Design

Phase 1/2 Trial

Single-arm, open-label, multicenter study (NCT01449461)⁶



^a 180 mg qd with 7-day lead-in at 90 mg; ^b Patients could continue brigatinib until disease progression requiring an alternate therapy or intolerable toxicity; patients could continue treatment after progression if there was evidence of clinical benefit, at the investigator's discretion; ° Patients in arm A could transition to brigatinib 180 mg qd after progression at 90 mg qd

Safety and tolerability

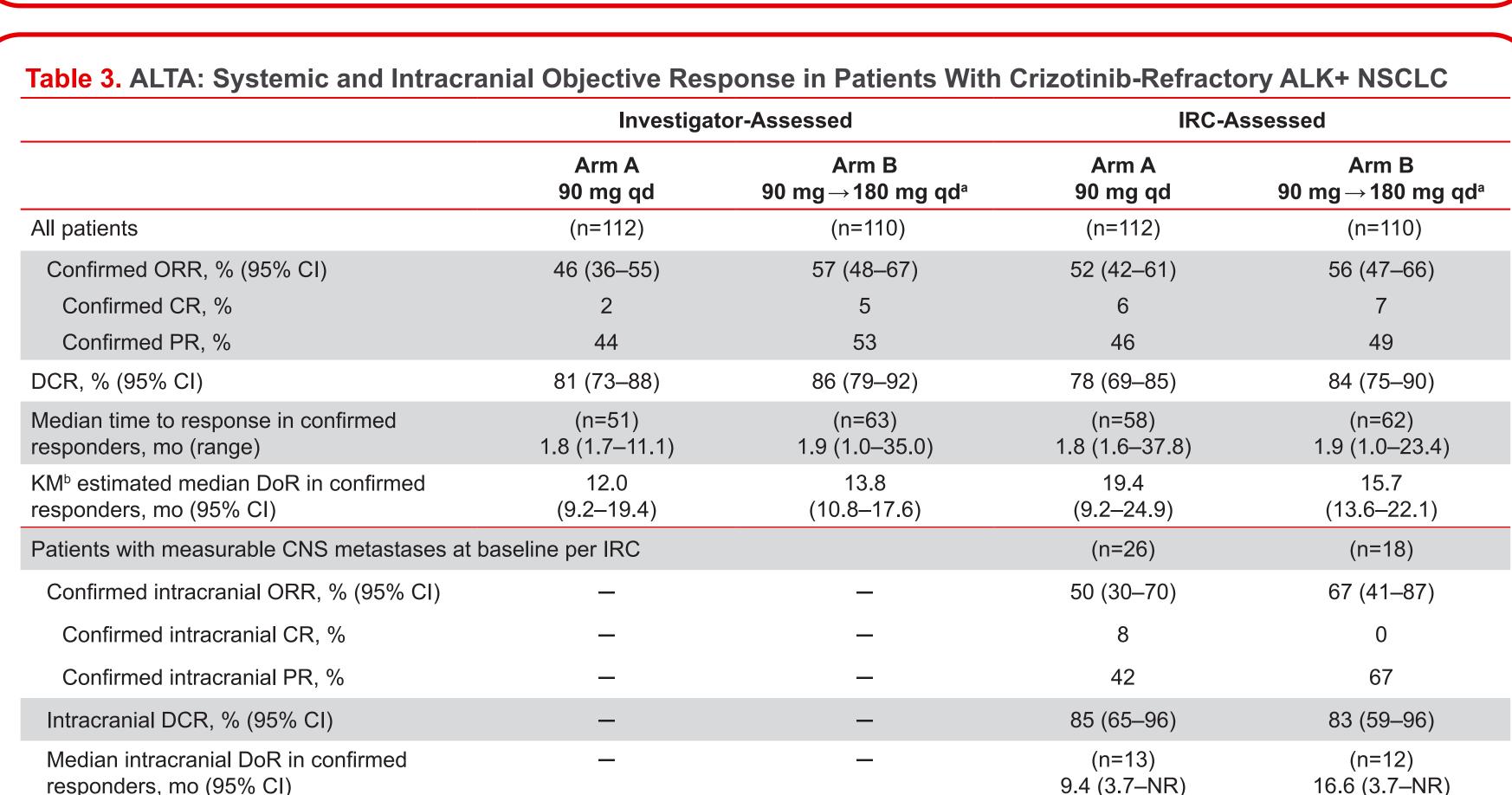
		Phase 1/2 Study	ALTA		
		Patients With ALK+ NSCLC n=79	Arm A 90 mg qd n=112	Arm B 90 mg → 180 mg qdª n=110	
Median age (range), y		54 (29, 83)	51 (18, 82)	57 (20, 81)	
Sex, %	Female	49	55	58	
Race, %	White, Asian, Other	82, 13, 5	64, 35, 1	69, 27, 4	
ECOG performance status, %	0, 1, 2	34, 65, 1	28, 64, 5	41, 51, 8	
Histologic type of NSCLC, %	Adenocarcinoma, Squamous, Other	94, 3, 4	96, 2, 3	98, 1, 1	
Brain metastases at baseline, %		63	71	67	
Prior chemotherapy, %		72	74	74	
Prior crizotinib, %		90	100	100	

• The phase 1/2 study was completed on February 18, 2020, with median (range) follow-up of 27.7 (0.2–88.3) months among the 79 ALK+ NSCLC patients; 10 patients were still receiving brigatinib up to study end, which was 5.6 years after the last patient enrolled

• ALTA was completed on February 27, 2020, with median follow-up of 19.6 (0.1–62.8) months in arm A and 28.3 (0.1–66.8) months in arm B; 10 patients in arm A and 17 patients in arm B were still on brigatinib up to study end, which was 4.4 years after the last patient enrolled

	Patients With ALK+ NSCLC			Patients With ALK+ NSCLC and Prior Crizotinib		
	All Dosesª n=79	90 mg→180 mg qd ^ь n=28	180 mg/d⁰ n=25	All Doses n=71	90 mg→180 mg qd ^ь n=25	180 mg/d⁰ n=23
Confirmed ORR, % (95% C)	67 (56–77)	79 (59–92)	68 (47–85)	63 (51–75)	76 (55–91)	65 (43–84)
Confirmed CR, %	10	14	8	7	12	9
Confirmed PR, %	57	64	60	56	64	57
DCR, % (95% CI)	89 (80–95)	89 (72–98)	80 (59–93)	87 (77–94)	88 (69–98)	78 (56–93)
Median time to response in confirmed responders, mo (range)	(n=53) 1.9 (1.2–29.4)	(n=22) 1.9 (1.2–6.0)	(n=17) 1.9 (1.6–29.4)	(n=45) 1.8 (1.2–29.4)	(n=19) 1.8 (1.2–6.0)	(n=15) 1.9 (1.6–29.4
KM ^d estimated median DoR in confirmed responders, mo (95% CI)	14.9 (9.9–29.5)	14.8 (7.9–33.3)	20.4 (7.6–44.5)	14.5 (9.0–22.1)	14.8 (7.9–25.1)	20.4 (7.5–51.6)

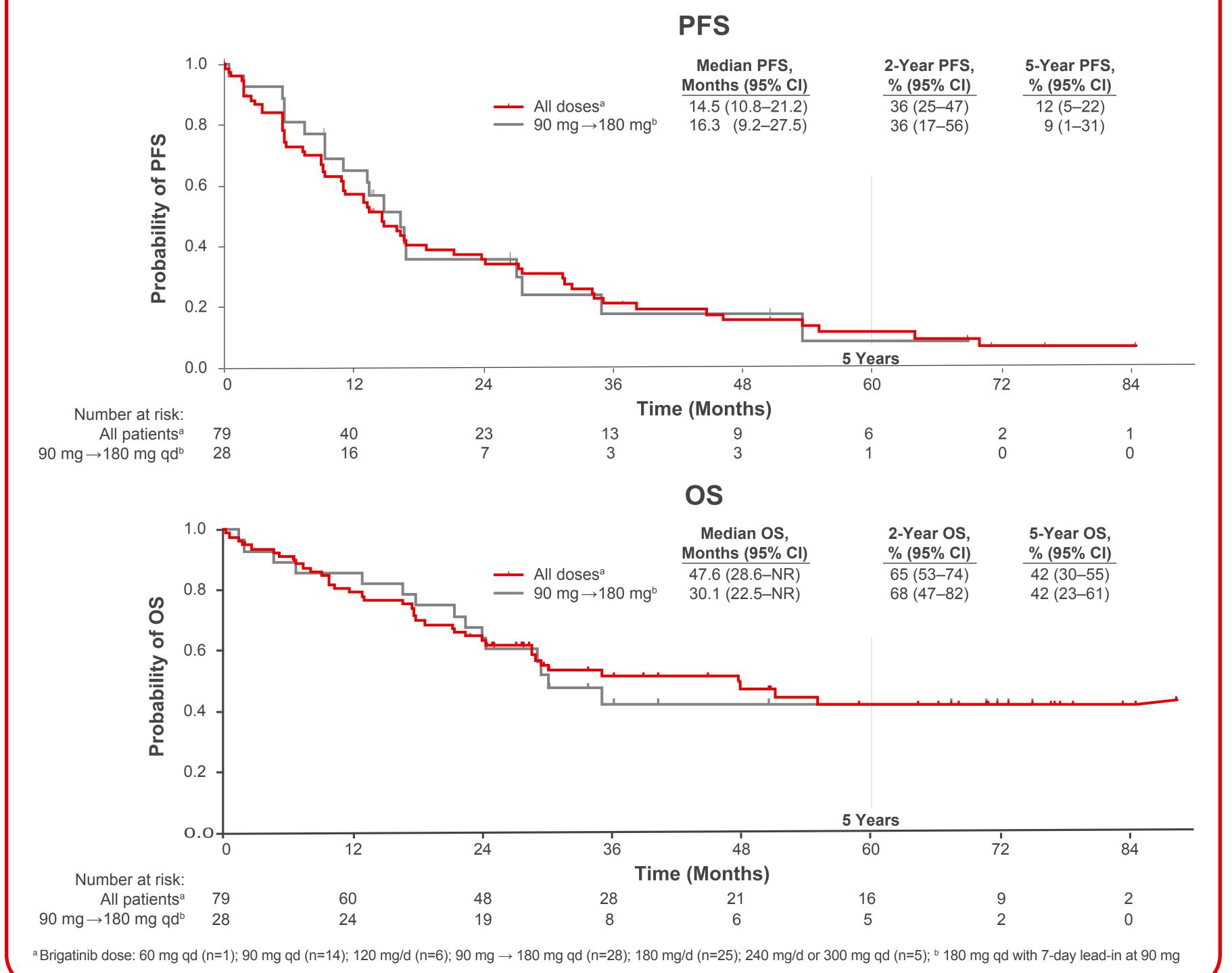
90 mg bid or 180 mg qd; "Kaplan-Meler methods were used to estimate Dof



responders, mo (95% CI)

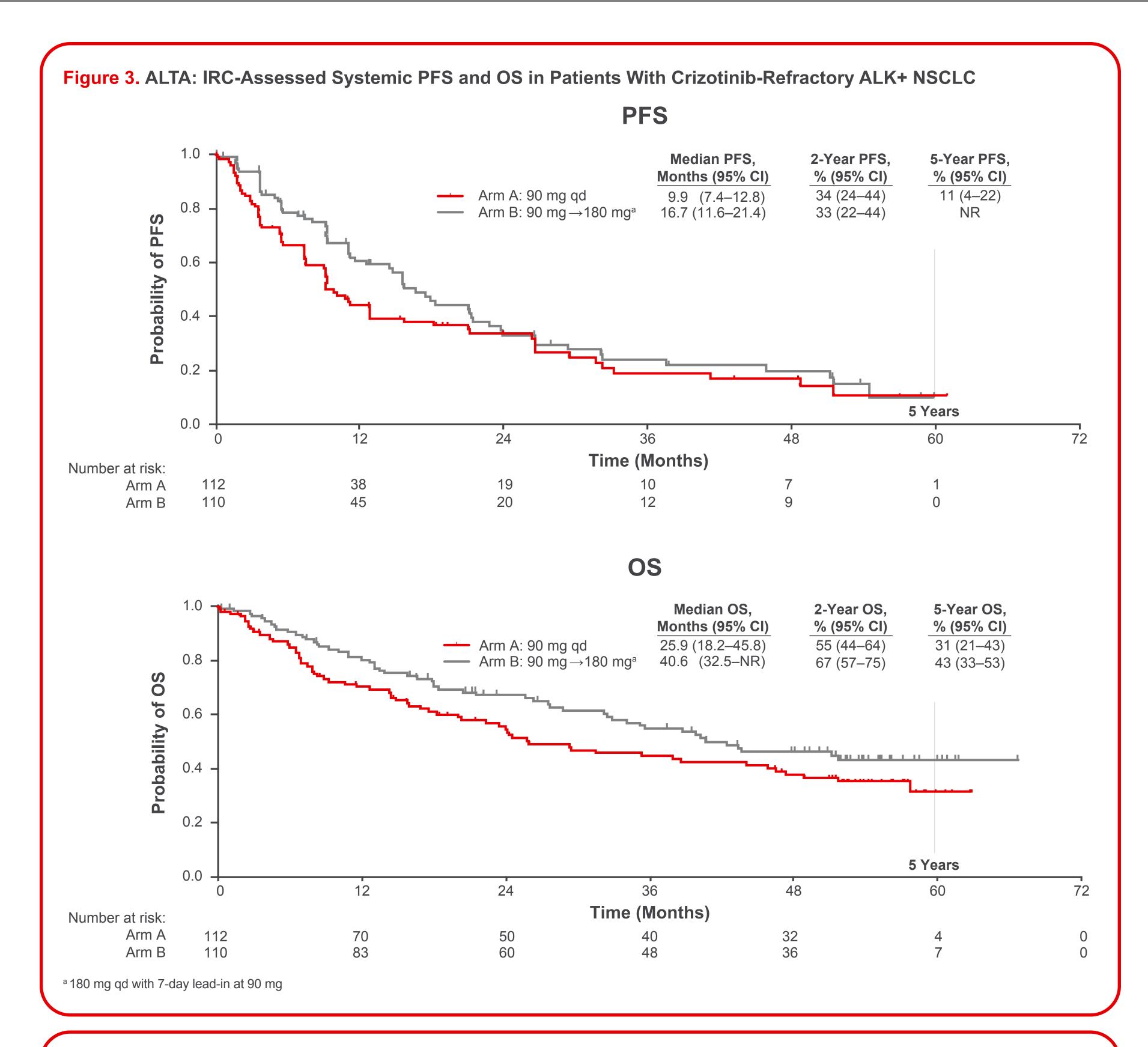
180 mg gd with 7-day lead-in at 90 mg; ^bKaplan-Meier methods were used to estimate DoR

Figure 2. Phase 1/2 Study: Investigator-Assessed Systemic PFS and OS in Patients With ALK+ NSCLC



• Among the 71 patients with ALK+ NSCLC previously treated with crizotinib, median PFS was 13.4 months (95% CI: 9.2–16.7), median OS was 30.1 months (95% CI: 21.4–55.0), and 5-year probability of OS was 35%

For the 8 patients with crizotinib-naive ALK+ NSCLC (90 mg qd, n=1; 90 mg \rightarrow 180 qd, n=3; other doses, n=4), all of whom had confirmed objective responses on brigatinib, median PFS was 34.2 months (95% CI: 7.4–63.9) and all 8 patients were alive 2 years after the first dose



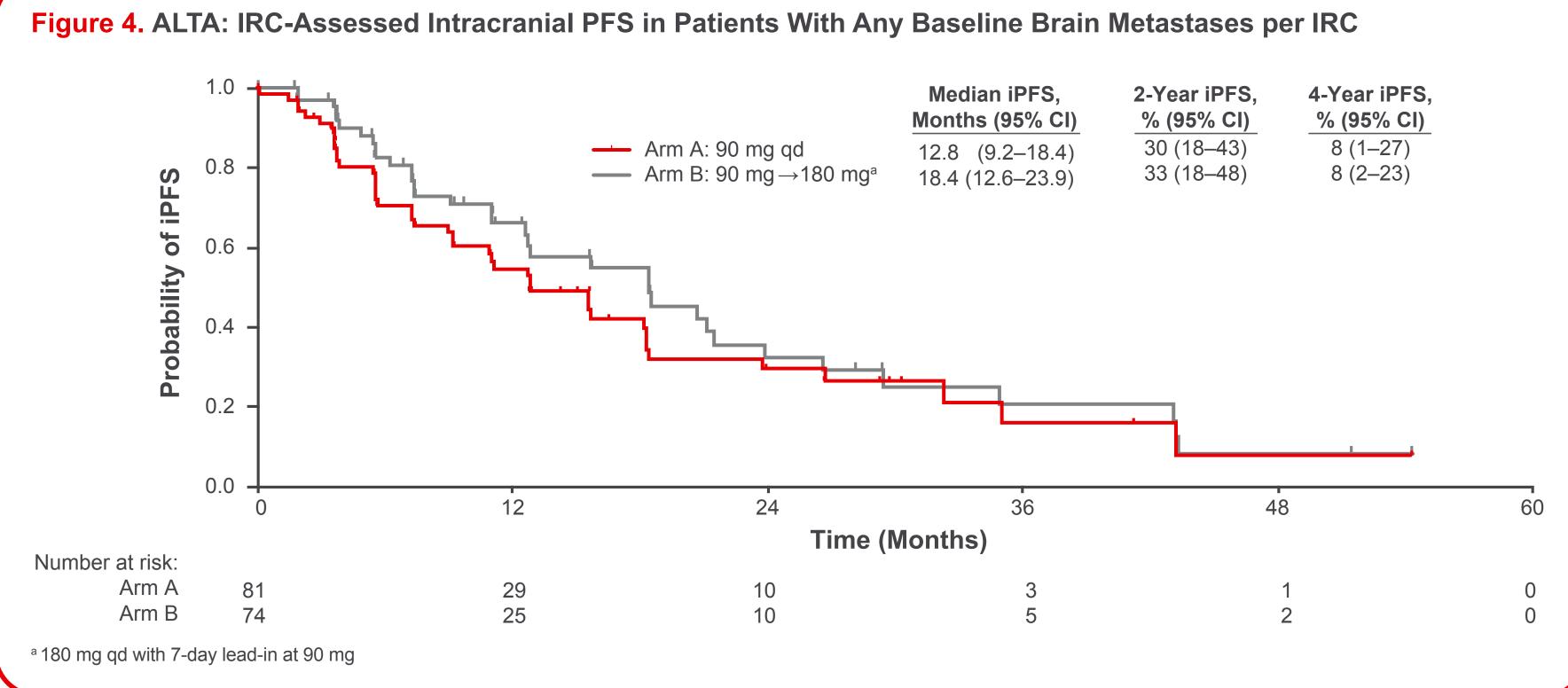


Table 4. Most Common Treatment-Related Adverse Events

	Phase 1/2 Study		ALTA				
TRAEs of Any Grade in ≥15% or Grade ≥3 in >3% of Patients	Patients With ALK+ NSCLC ^a (n=79)		Arm A: 90 mg qd (n=109)		Arm B: 90 mg→180 mg qd ^ь (n=110)		
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %	
Diarrhea	48	1	17	0	35	0	
Nausea	51	1	26	0	34	1	
Increased blood CPK	16	5	17	6	34	14	
Fatigue	39	3	12	1	20	0	
Vomiting	20	0	15	0	19	0	
Increased lipase	30	18	11	6	18	8	
Muscle spasms	19	0	9	0	19	0	
Increased AST	28	3	11	0	18	3	
Hypertension	16	8	7	5	18	6	
Increased amylase	27	5	12	2	16	2	
Increased ALT	18	3	11	0	13	4	
Cough	15	1	3	0	10	0	
Dyspnea	15	3	7	0	7	0	
Increased blood insulin	15	0	0	0	1	0	
Hypophosphatemia	15	5	0	0	1	1	

	Phase 1/2 Study		ALTA
	Patients With ALK+ NSCLC ^a (n=79)	Arm A: 90 mg qd (n=109)	Arm B: 90 mg→180 mg qd ^ь (n=110)
Dose reduction due to any AE, n (%)	10 (13)	9 (8)	36 (33)
Dose interruption due to any AE, n (%)	47 (59)	53 (49)	67 (61)
Discontinuation due to any AE, n (%)	8 (10)	4 (4)	14 (13)
Median dose intensity, mg/d	174	90	169

• Deaths occurring within 30 days of last dose of brigatinib:

- Phase 1/2 study: 15 patients with ALK+ NSCLC
- 2 deaths possibly related to brigatinib treatment (unexpected death on day 568; sepsis on day 541)
- ALTA: 36 patients (22 in arm A; 14 in arm B)
- One death possibly related to brigatinib treatment (sudden death on day 3 in arm B)

) **Summary**

- Brigatinib showed sustained long-term activity and PFS in the final analyses of the phase 1/2 and phase 2 (ALTA) trials
- Among the 79 ALK+ NSCLC patients in the phase 1/2 study, with median follow-up of 28 months and 5.6 years since the last patient enrolled, the confirmed ORR per investigators was 67%, with median DoR of 14.9 months – Median PFS was 14.5 months in all patients and 34.2 months in crizotinib-naive patients; median OS was
- 47.6 months in all patients, with 5-year OS probability of 42%
- 10 patients were still receiving brigatinib up to study end
- In ALTA, the approved dosing regimen (180 mg qd with 7-day lead-in at 90 mg; arm B) was associated with numerically higher ORR, PFS, and OS than the 90-mg daily dose (arm A)
- With median follow-up of 28.3 months and 4.4 years after the last patient enrolled, the approved dosing regimen (arm B) demonstrated a confirmed ORR by IRC of 56%, with median DoR of 15.7 months, median IRC-assessed PFS of 16.7 months, median OS of 40.6 months, and 5-year OS probability of 43%
- 10 patients in arm A and 17 patients in arm B were still on brigatinib up to study end
- Brigatinib intracranial activity was maintained in patients with baseline brain metastases - The intracranial ORR by IRC was 67% in patients with measurable CNS lesions, with median intracranial DoR of 16.6 months; median intracranial PFS was 18.4 months in patients with any baseline brain metastases
- The safety profile of brigatinib was consistent with previous reports, with no new safety concerns noted

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Abbreviations

AE, adverse event; ALK, anaplastic lymphoma kinase; ALK+, ALK gene rearranged; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; CI, confidence interval; CNS, central nervous system; CPK, creatine phosphokinase; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; iPFS, intracranial progression-free survival; IRC, independent review committee; KM, Kaplan-Meier; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TRAE, treatment-related adverse event; TKI, tyrosine kinase inhibitor

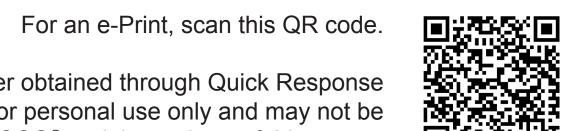
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