Supplementary Online Content

Horn L, Wang Z, Wu G, et al. Ensartinib vs crizotinib for patients with anaplastic lymphoma kinase−positive non–small cell lung cancer: a randomized clinical trial. *JAMA Oncol.* Published online September 2, 2021.
doi:10.1001/jamaoncol.2021.3523

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Rates of Confirmed Objective Response by BIRC[a]

Variable	Ensartinib	Crizotinib
ITT population		
No. of patients	143	147
Objective response		
No. of patients	106	98
% (95% CI)	74 (66 - 81)	67 (58 - 74)
Complete response – no. (%)	17 (12)	8 (5)
Partial response – no. (%)	89 (62)	90 (61)
Duration of response[b]		
No. of patients	106	98
Median (95% CI) – mo	NR (22 - NR)	27 (13 - NR)
mITT population		
No. of patients	121	126
Objective response		
No. of patients	91	85
% (95% CI)	75 (67 - 83)	68 (59 - 76)
Complete response – no. (%)	17 (14)	7 (6)
Partial response – no. (%)	74 (61)	78 (62)
Duration of response[b]		
No. of patients	91	85
Median (95% CI) – mo	NR (22 - NR)	27 (11 - NR)

[a]Best response considered both systemic disease and CNS metastases (RECIST version 1.1 Combined Outcome). Best response assigned depended on the achievement of both measurement and confirmation criteria.
[b] Median duration of response in patients with confirmed response or partial response.
Abbreviations: CNS, central nervous system; ITT, intention to treat; mITT, modified intention to treat; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumors.

eTable 2. Treatment-Emergent Adverse Events in ≥10% of the Safety Population

Event n (%)	Ensartinib (N=143)				Crizotinib (N=146)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any AE	69 (48.3)	64 (44.8)	7 (4.9)	1 (0.7)	83 (56.8)	52 (35.6)	6 (4.1)	4 (2.7)
Rash (all)[a]	85 (59.4)	16 (11.2)	0	0	15 (10.3)	0	0	0
Alanine aminotransferase increased	66 (46.2)	6 (4.2)	0	0	58 (39.7)	11 (7.5)	0	0
Aspartate aminotransferase increased	53 (37.1)	1 (0.7)	0	0	53 (36.3)	4 (2.7)	0	0
Constipation	45 (31.5)	0	0	0	38 (26.0)	0	0	0
Cough	43 (30.1)	1 (0.7)	0	0	20 (13.7)	0	0	0
Pruritus (all)[b]	40 (28.0)	3 (2.1)	0	0	7 (4.8)	0	0	0
Nausea	38 (26.6)	2 (1.4)	0	0	41 (28.1)	3 (2.1)	0	0
Edema (all)[c]	36 (25.2)	3 (2.1)	0	0	38 (26.0)	3 (2.1)	0	0
Anemia	31 (21.7)	1 (0.7)	0	0	17 (11.6)	2 (1.4)	0	0
Blood alkaline phosphatase increased	29 (20.3)	1 (0.7)	0	0	24 (16.4)	1 (0.7)	0	0
Pyrexia	28 (19.6)	1 (0.7)	0	0	13 (8.9)	1 (0.7)	0	0
Blood creatinine increased	27 (18.9)	0	0	0	21 (14.4)	0	0	0
Vomiting	22 (15.4)	1 (0.7)	0	0	46 (31.5)	0	0	0
Decreased appetite	22 (15.4)	0	0	0	15 (10.3)	2 (1.4)	0	0
Gamma-glutamyltransferase increased	21 (14.7)	2 (1.4)	0	0	13 (8.9)	1 (0.7)	0	0
Back pain	20 (14.0)	0	0	0	10 (6.8)	0	0	0
Pain in extremity	18 (12.6)	0	0	0	12 (8.2)	0	0	0
Arthralgia	18 (12.6)	0	0	0	7 (4.8)	0	0	0
Hypoalbuminemia	17 (11.9)	0	0	0	20 (13.7)	1 (0.7)	0	0
Upper respiratory tract infection	17 (11.9)	1 (0.7)	0	0	15 (10.3)	0	0	0
Dizziness	17 (11.9)	0	0	0	14 (9.6)	1 (0.7)	0	0
Alopecia	16 (11.2)	0	0	0	7 (4.8)	0	0	0
Dysgeusia	15 (10.5)	0	0	0	16 (11.0)	0	0	0
Fatigue	15 (10.5)	1 (0.7)	0	0	10 (6.8)	2 (1.4)	0	0
Dry skin	14 (9.8)	1 (0.7)	0	0	1 (0.7)	0	0	0
Hyperuricemia	13 (9.1)	1 (0.7)	1 (0.7)	0	6 (4.1)	0	0	0

[a] Rash (all) includes dermatitis acneiform, erythema, erythema multiforme, rash, rash erythematous, rash follicular, rash macular, rash maculopapular, rash pruritic, skin exfoliation, rash pustular, eczema, lichenoid keratosis/dermatitis, photosensitivity reaction, rash generalized or any preferred term that contains “rash.” [b] Pruritus (all) includes any preferred term that contains “pruritus.” [c] Edema (all) includes any preferred term that contains “edema.” Abbreviation: AE, adverse event;

eTable 3. List of Investigators

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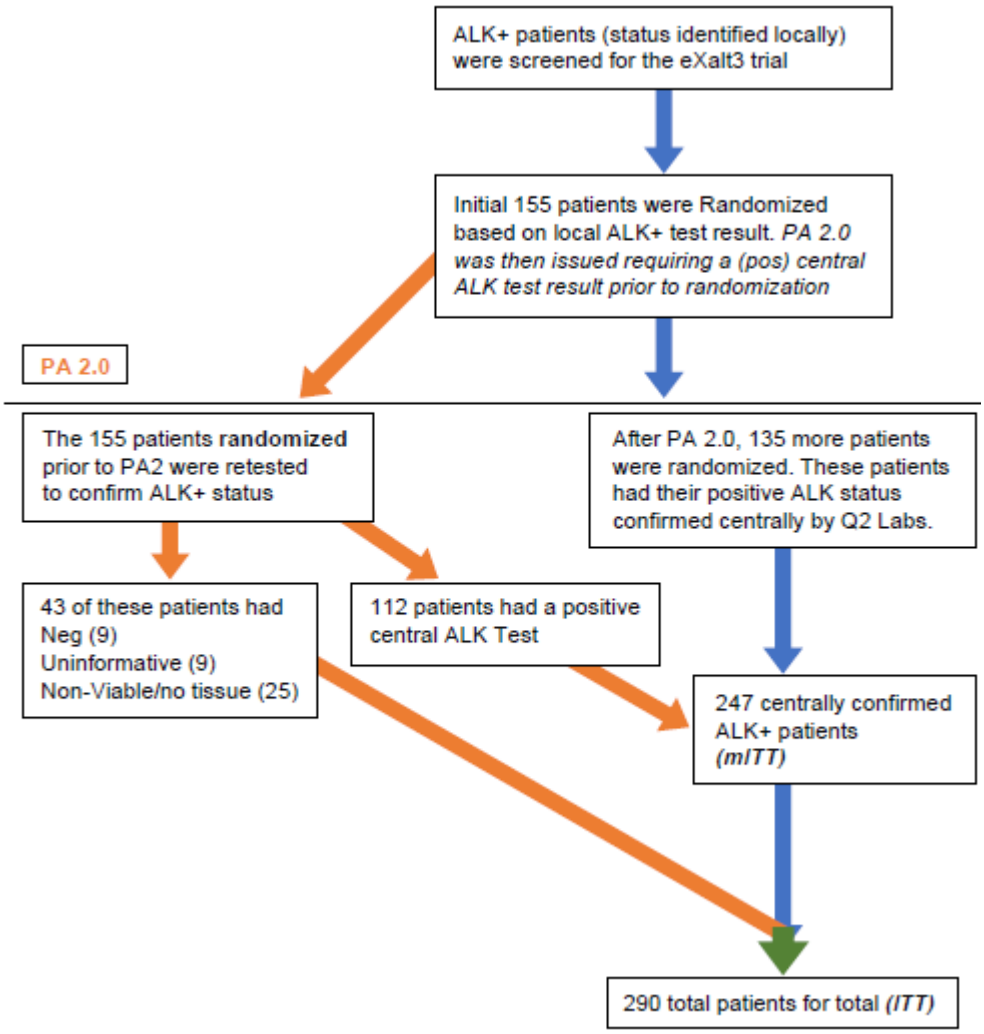
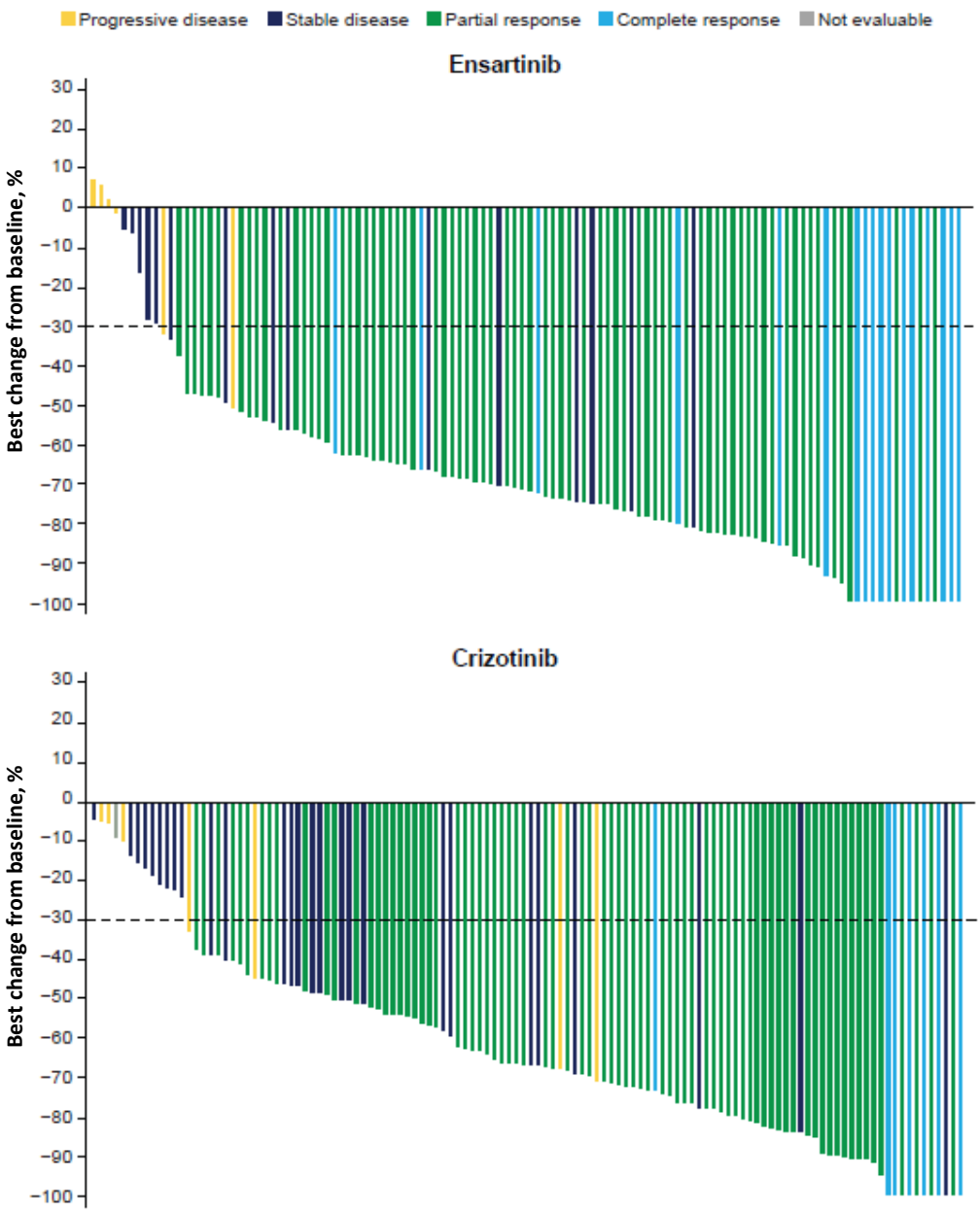
eFigure 1. Randomization Schema for ITT and mITT Populations

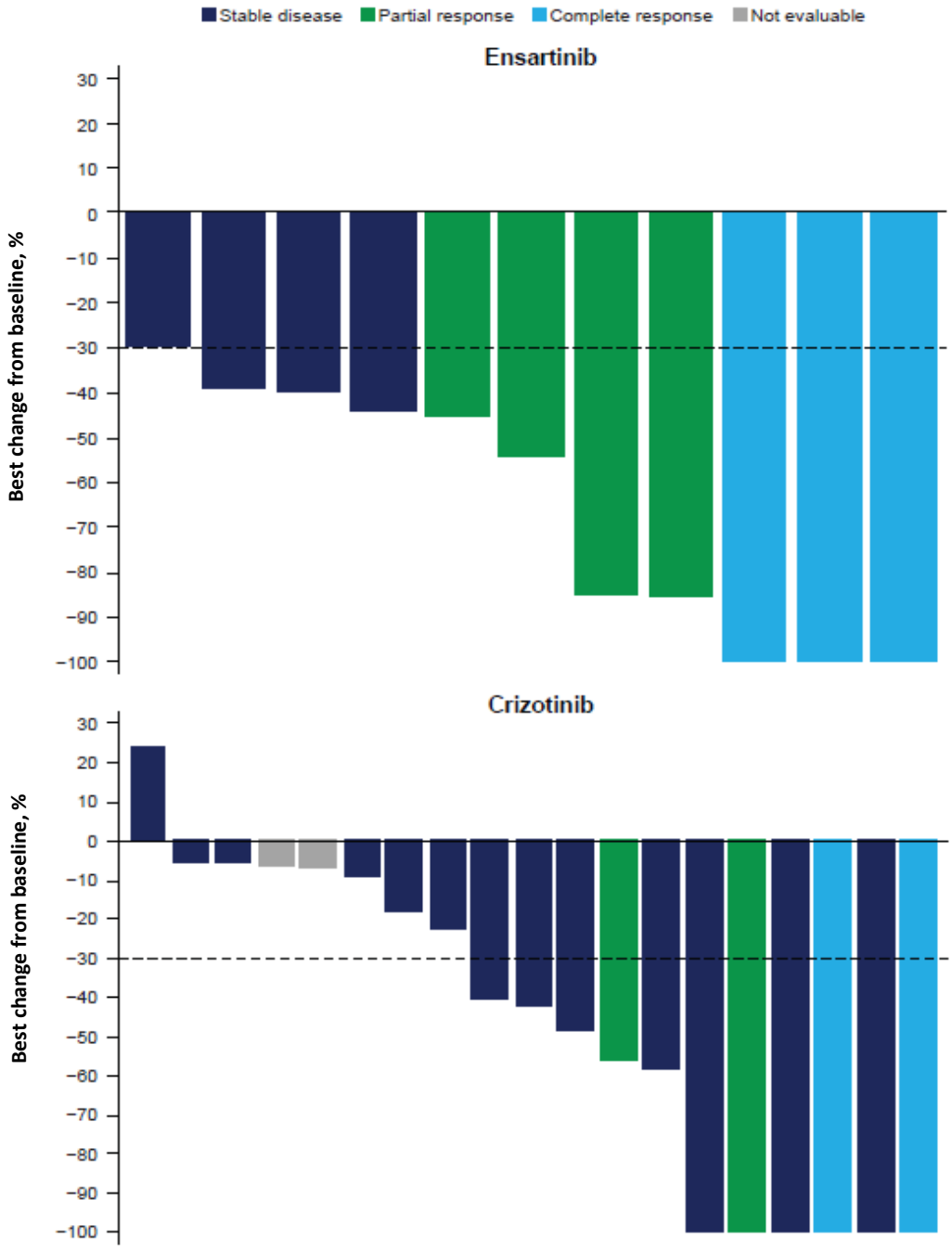
Patients were initially randomized into the trial based on a local test for ALK. After PA 2.0, ALK testing confirmed by a central laboratory analysis was required. The ITT population consisted of all patients randomized into the trial. The mITT population included patients who were randomized into the trial based on positive local testing with additional central confirmation or were randomized into the trial based on positive central testing. Abbreviations: ALK, anaplastic lymphoma kinase; ITT, intention to treat; mITT, modified intention to treat; PA 2.0, protocol amendment 2.0.



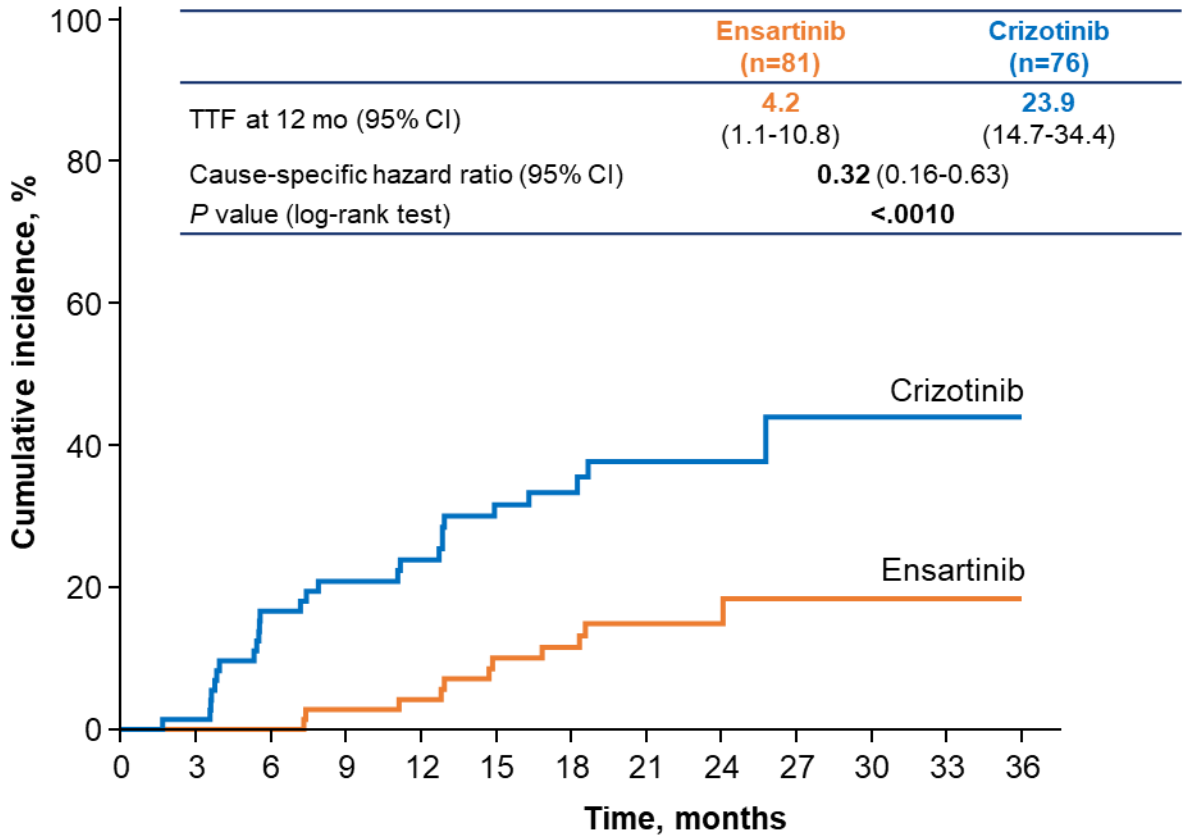
eFigure 2. BIRC-Assessed Best Systemic Change from Baseline in the mITT Population. Abbreviations: BIRC, blinded independent review committee; mITT, modified intention to treat.



eFigure 3. BIRC-Assessed Intracranial Best Change from Baseline in Patients with Measurable and Evaluable Brain Metastases in the mITT Population. Abbreviations: BIRC, blinded independent review committee; mITT, modified intention to treat.



eFigure 4. BIRC-Assessed Time to Progression in the Brain in Patients Without Brain Metastases at Baseline in the Modified Intention-to-Treat Population.
Competing risks analysis was per IRR. BIRC, blinded independent review committee; IRR, TTF, time to treatment failure.



eFigure 5. Median Progression-Free Survival (mPFS) in Patients with Brain Metastases at Baseline in mITT

Abbreviations: mPFS, median progression-free survival; NR, not reached.