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Phase 3 Randomized Study of Ensartinib vs Crizotinib in Anaplastic Lymphoma Kinase (ALK)–Positive NSCLC Patients: eXalt3

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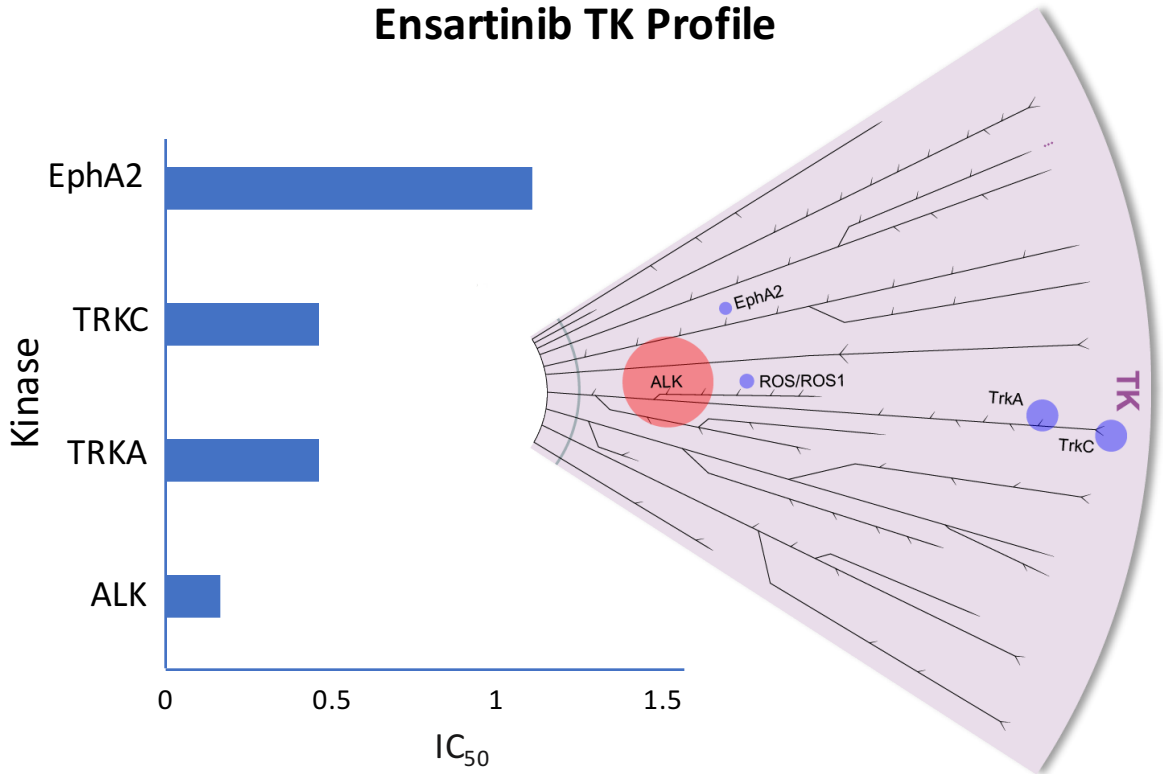
Disclosures

Commercial Interest	Relationship(s)
Consulting	Amgen, AstraZeneca, Bayer, EMD Serono, Incyte, Merck, Roche-Genentech, Pfizer, Xcovery
Research funding	Xcovery, Bristol Myers Squibb

Introduction

- Oncogenic rearrangements of the *ALK* gene occur in approximately 5%-7% of non-small-cell lung cancer (NSCLC) patients[1]
- Ensartinib is a potent, next-generation, once-daily oral ALK inhibitor, with broad preclinical activity against ALK resistance mutations[2]
  - Ensartinib potency is more than 10 times greater than that of crizotinib in enzymatic assays[2]
- In phase 1/2 trials, ensartinib has shown promising antitumor activity in patients with ALK TKI–naive, crizotinib-refractory, advanced ALK-positive NSCLC, including those with brain metastases[3-5]

Ensartinib TK Profile



1. Tsao AS, et al. *J Thorac Oncol.* 2016;11(5):613-638; 2. Lovly CM, et al. *Cancer Res.* 2011;71(14):4920-4931; 3. Horn L, et al. *Clin Cancer Res.* 2018;24(12):2771-2779; 4. Fang WF, et al. *J Clin Oncol.* 2018 Jun 1 [Epub ahead of print]. doi:10.1200/JCO.2018.36.15_suppl.e21122; 5. Yang Y, et al. *Lancet Respir Med.* 2020;8(1):45-53.

eXalt3: Global Phase 3, Open-Label, Randomized, Multicenter Study

- Stage IIIB/IV NSCLC
- ALK+ by local FDA-approved assays or central confimration by FISH by Abbott
- ECOG PS 0-2
- No prior ALK inhibitor
- ≤ 1 Prior chemotherapy regimen

NCT02767804

Randomized 1:1

Ensartinib 225 mg QD

Crizotinib 250 mg BID

Stratified by:
- Prior chemotherapy
- ECOG PS
- Asia Pacific vs ROW
- Brain metastases at BL

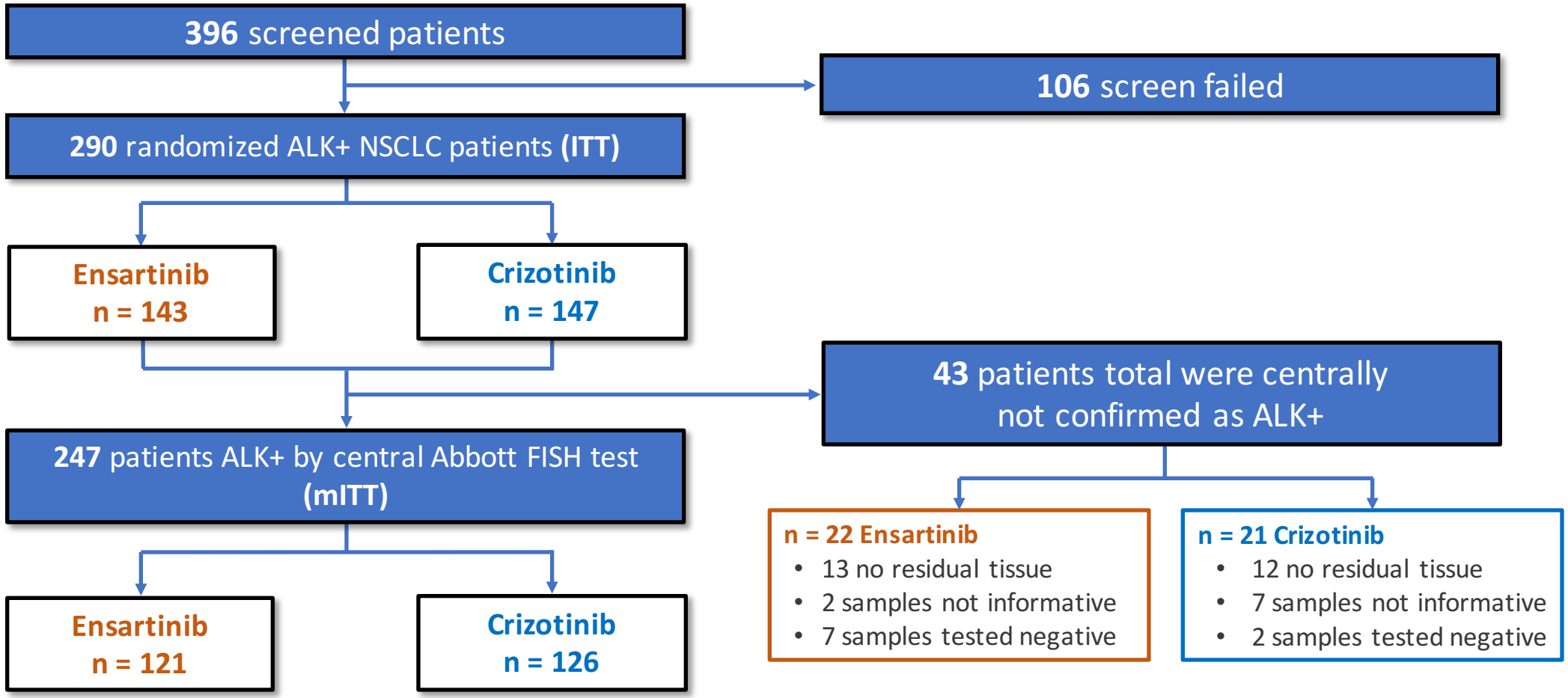
- **No crossover allowed**
- **Trial fully accrued as of Nov 2018**

Primary endpoint: blinded independent review committee (BIRC)–assessed median PFS (mPFS) per RECIST v1.1 in ITT population
Key secondary endpoints: OS, ORR/DOR (overall and brain), and TTF in the brain

BL, baseline; DOR, duration of response; ITT, intent to treat; ROW, rest of world; TTF, time to treatment failure.

eXalt3: Statistical Considerations

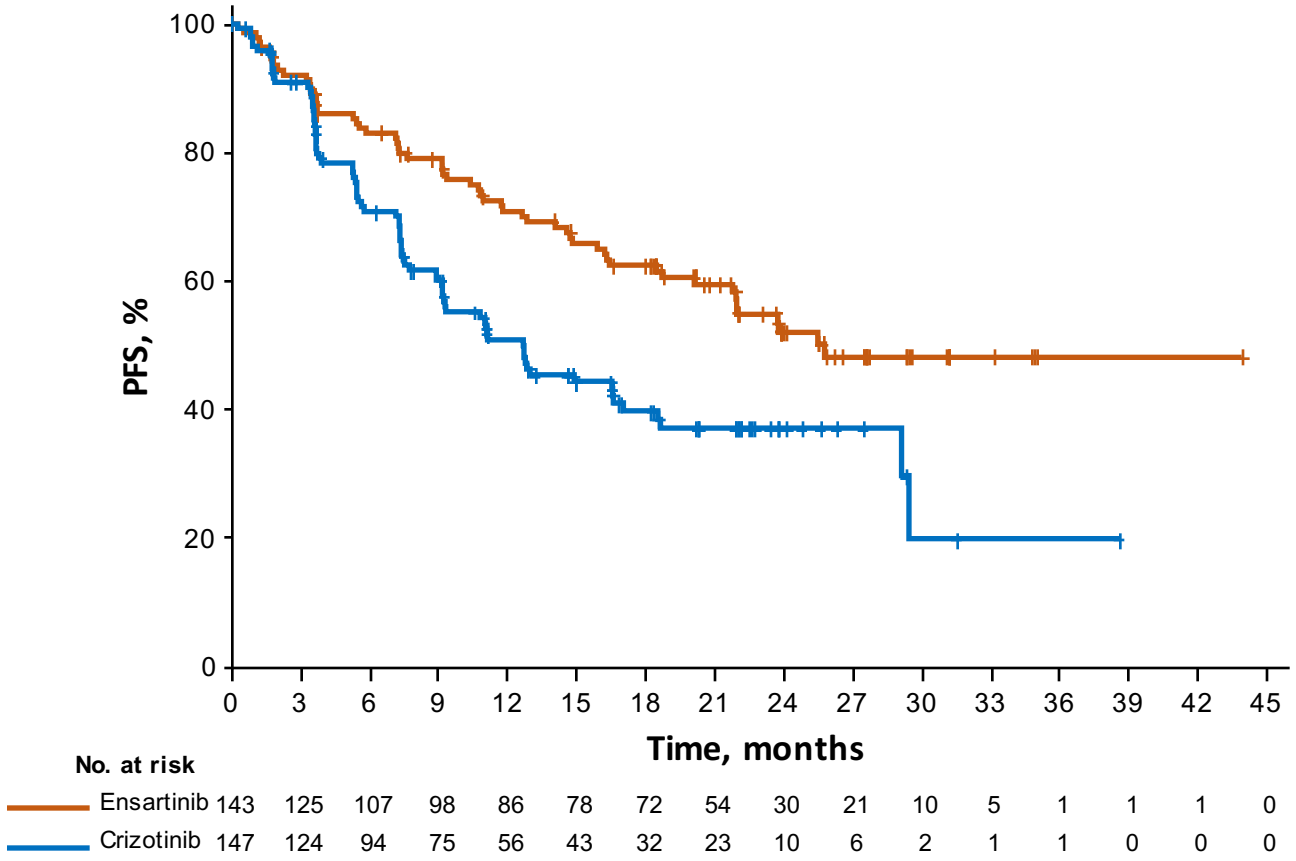
- Only 1 interim analysis was planned at ≈ 75% of mPFS events by BIRC in the ITT population (143/190 events)
  - mPFS was tested at a 2-sided α level of **0.019** (based on O'Brien-Fleming group sequential design)
- Per protocol, **3** prespecified randomized populations were included in the analysis:
  - **ITT**: patients with locally determined ALK+ NSCLC
  - **Modified ITT (mITT)**: patients with centrally confirmed ALK+ by Abbott FISH test as required by FDA for CDx
  - **Safety**: patients who received ≥ 1 dose of either study drug
- As of July 1, 2020 data cutoff:
  - Treatment was ongoing in 64 ensartinib patients (45%) and 25 crizotinib patients (17%)
  - 139 BIRC-assessed mPFS events (73%) occurred in the **ITT** population
  - 119 BIRC-assessed mPFS events (63%) occurred in the **mITT** population


396 screened patients
106 screen failed
290 randomized ALK+ NSCLC patients (ITT)
Ensartinib
n = 143
Crizotinib
n = 147
43 patients total were centrally not confirmed as ALK+
247 patients ALK+ by central Abbott FISH test (mITT)
n = 22 Ensartinib
• 13 no residual tissue
• 2 samples not informative
• 7 samples tested negative
n = 21 Crizotinib
• 12 no residual tissue
• 7 samples not informative
• 2 samples tested negative
Ensartinib
n = 121
Crizotinib
n = 126

Demographics and Baseline Characteristics (ITT)

	Ensartinib (n = 143)	Crizotinib (n = 147)
Median age (range), years	54 (25, 86)	53 (26, 90)
Age > 65 years, n (%)	24 (17)	23 (16)
Male, n (%)	72 (50)	77 (52)
Race, n (%)		
Asian	77 (54)	84 (57)
Non-Asian	66 (46)	63 (43)
ECOG performance status, n (%)		
0-1	136 (95)	139 (95)
Tobacco use at study entry, n (%)		
Never	85 (59)	94 (64)
Current/former	58 (41)	53 (36)
Prior radiotherapy to the brain, n (%)	7 (5)	7 (5)
Brain metastases by BIRC at baseline, n (%)	47 (33)	57 (39)
Prior chemotherapy, n (%)	34 (24)	42 (29)

BIRC-Assessed mPFS (ITT)

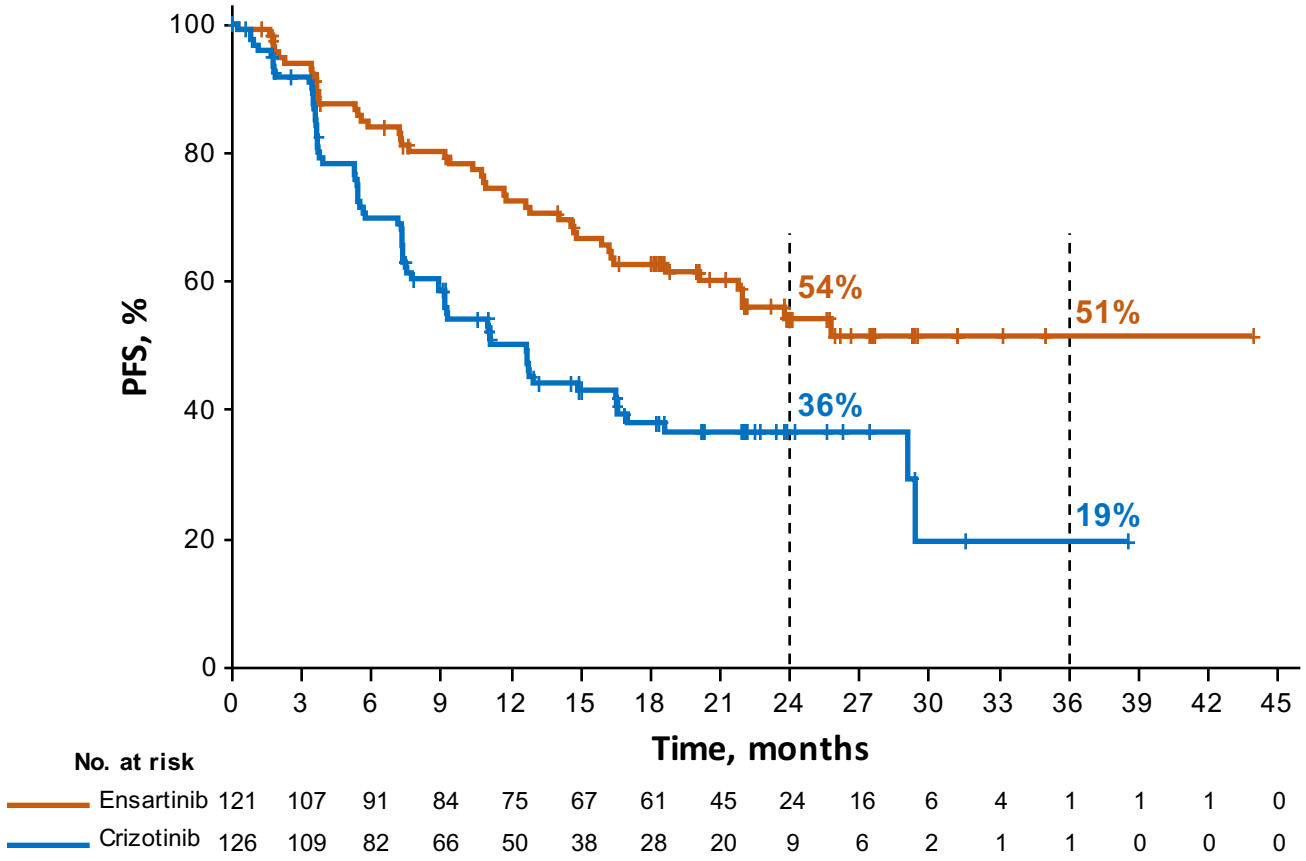


NR, not reached.

	Ensartinib (n = 143)	Crizotinib (n = 147)
mPFS (95% CI), mo	**25.8** (21.8-NR)	**12.7** (9.2-6.6)
Hazard ratio (95% CI)	**0.51** (0.35-0.72)	
P value (log-rank test)	**.0001**	

	Median follow-up (range), mo
Ensartinib	23.8 (0-44)
Crizotinib	20.2 (0-38)

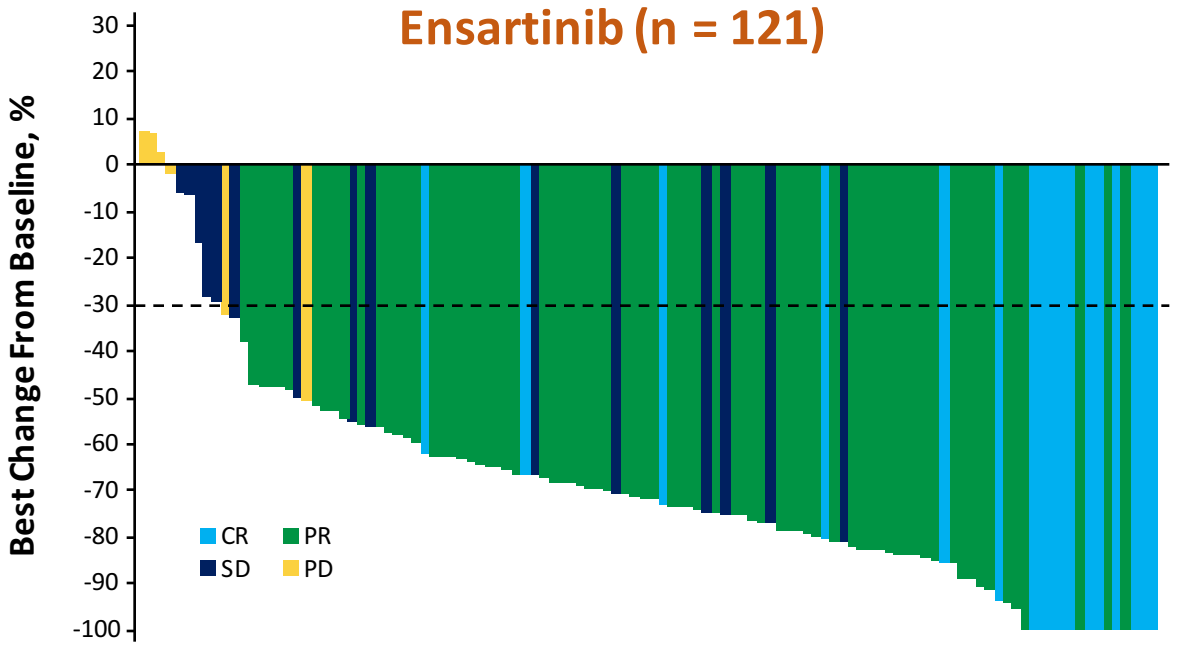
BIRC-Assessed mPFS (mITT)

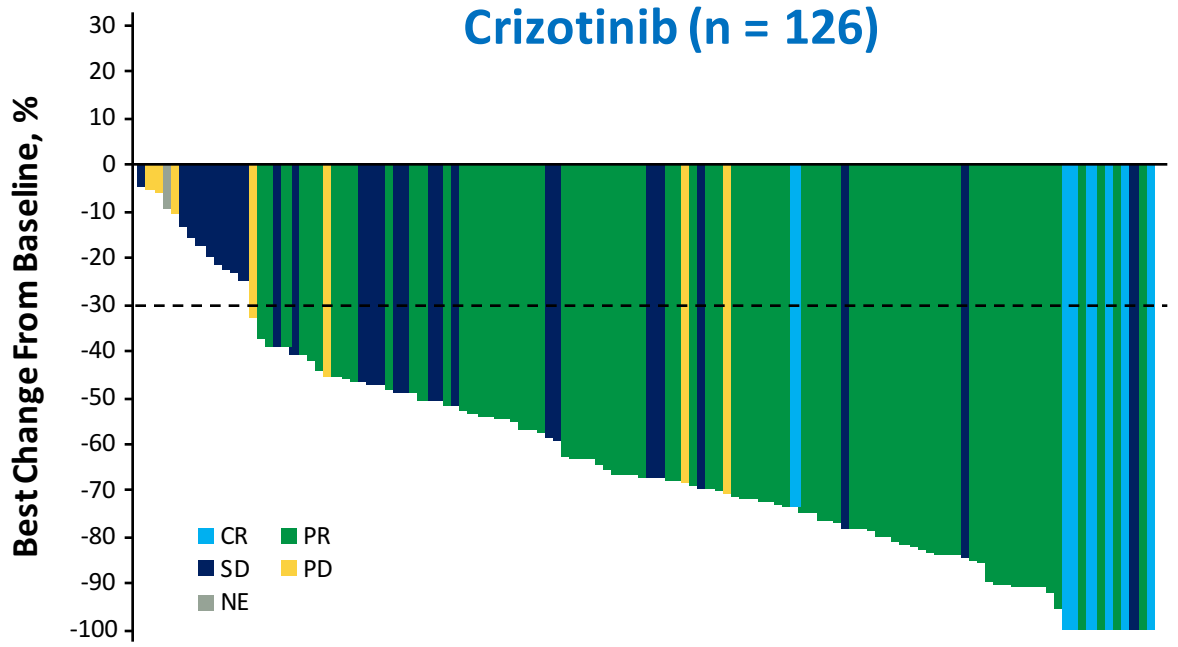


	Ensartinib (n = 121)	Crizotinib (n = 126)
mPFS (95% CI), mo	NR (20.2-NR)	12.7 (8.9-16.6)
Hazard ratio (95% CI)	**0.45** (0.30-0.66)	
P value (stratified log-rank test)	**< .0001**	

	Median follow-up (range), mo
Ensartinib	23.7 (0-44)
Crizotinib	20.2 (0-38)

BIRC-Assessed Best Systemic Change From Baseline (mITT)



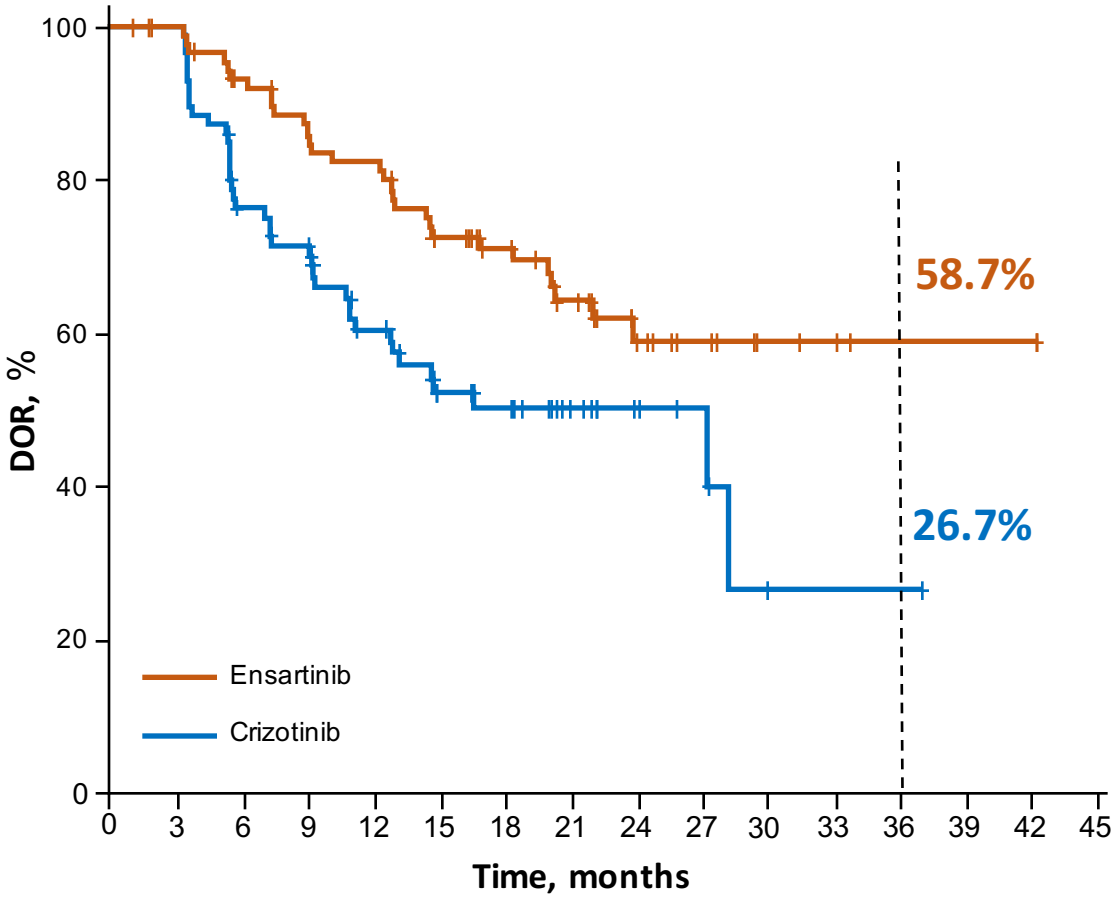


BIRC-assessed confirmed systemic ORR: ensartinib = 75%; crizotinib = 67%

CR rates: ensartinib = 14%; crizotinib = 6%

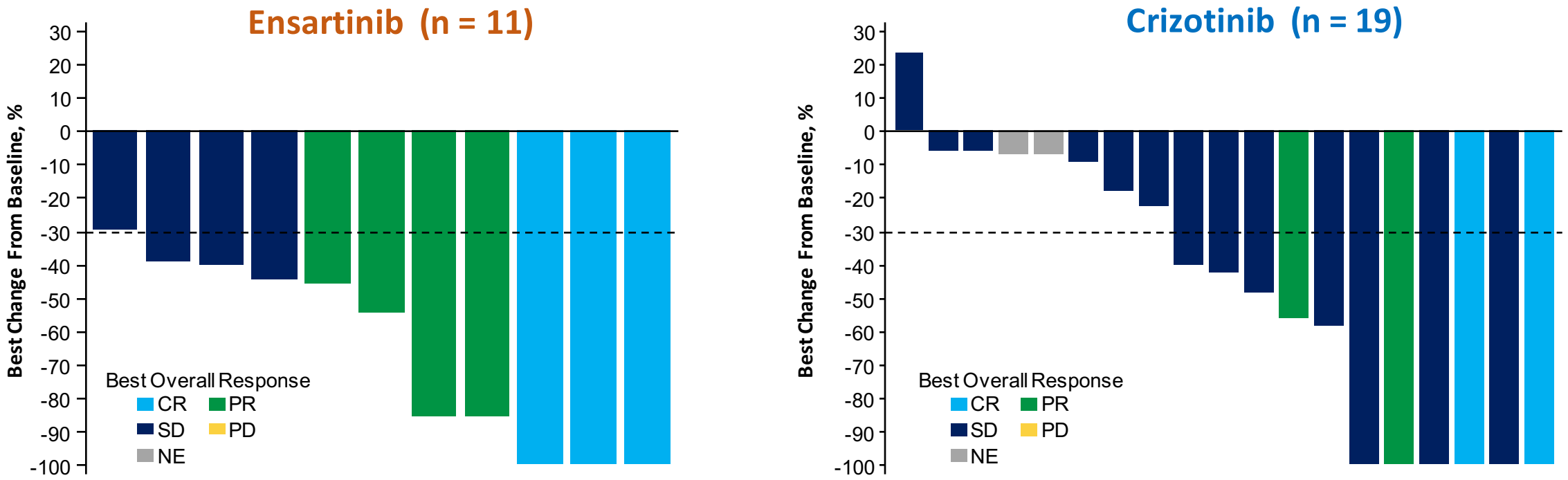
NE, not evaluable

BIRC-Assessed Systemic Duration of Response (mITT)



	Ensartinib (n = 91)	Crizotinib (n = 85)
Median DOR (95% CI), mo	NR (22.05-NR)	27.3 (11.27-NR)
At 24-mo (95% CI), %	58.7 (45.24-69.90)	50.0 (37.80-61.09)
At 36-mo (95% CI), %	58.7 (45.24-69.90)	26.7 (6.75-52.34)

BIRC-Assessed Intracranial Best Change From Baseline in Patients With Measurable Brain Metastases (mITT)

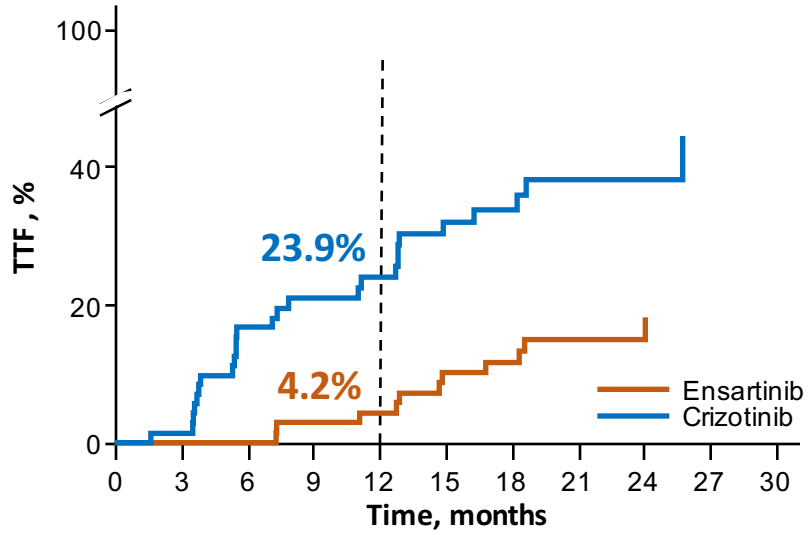


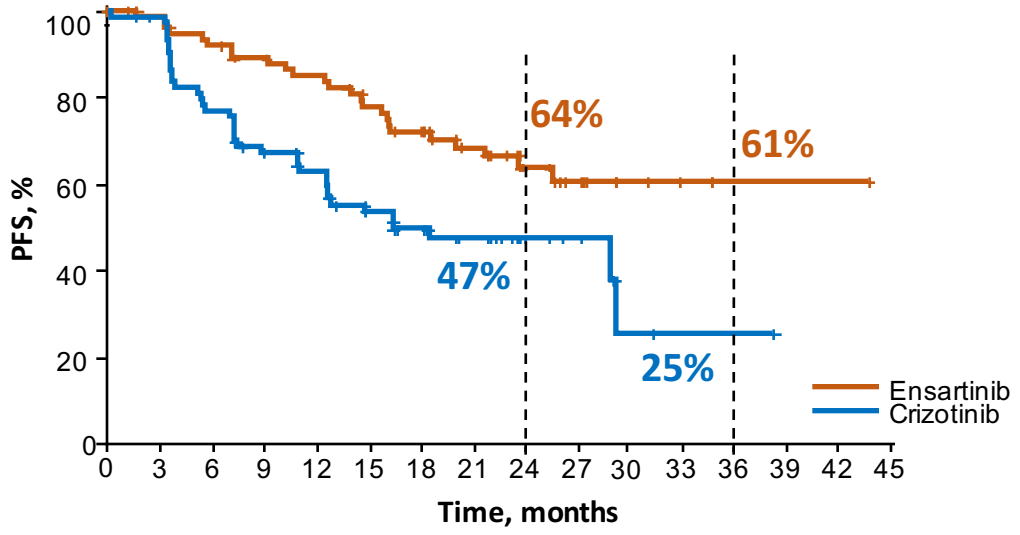
BIRC-assessed intracranial confirmed ORR: ensartinib = 64%; crizotinib = 21%

BIRC-Assessed TTF and mPFS in Patients Without Brain Metastases (mITT)

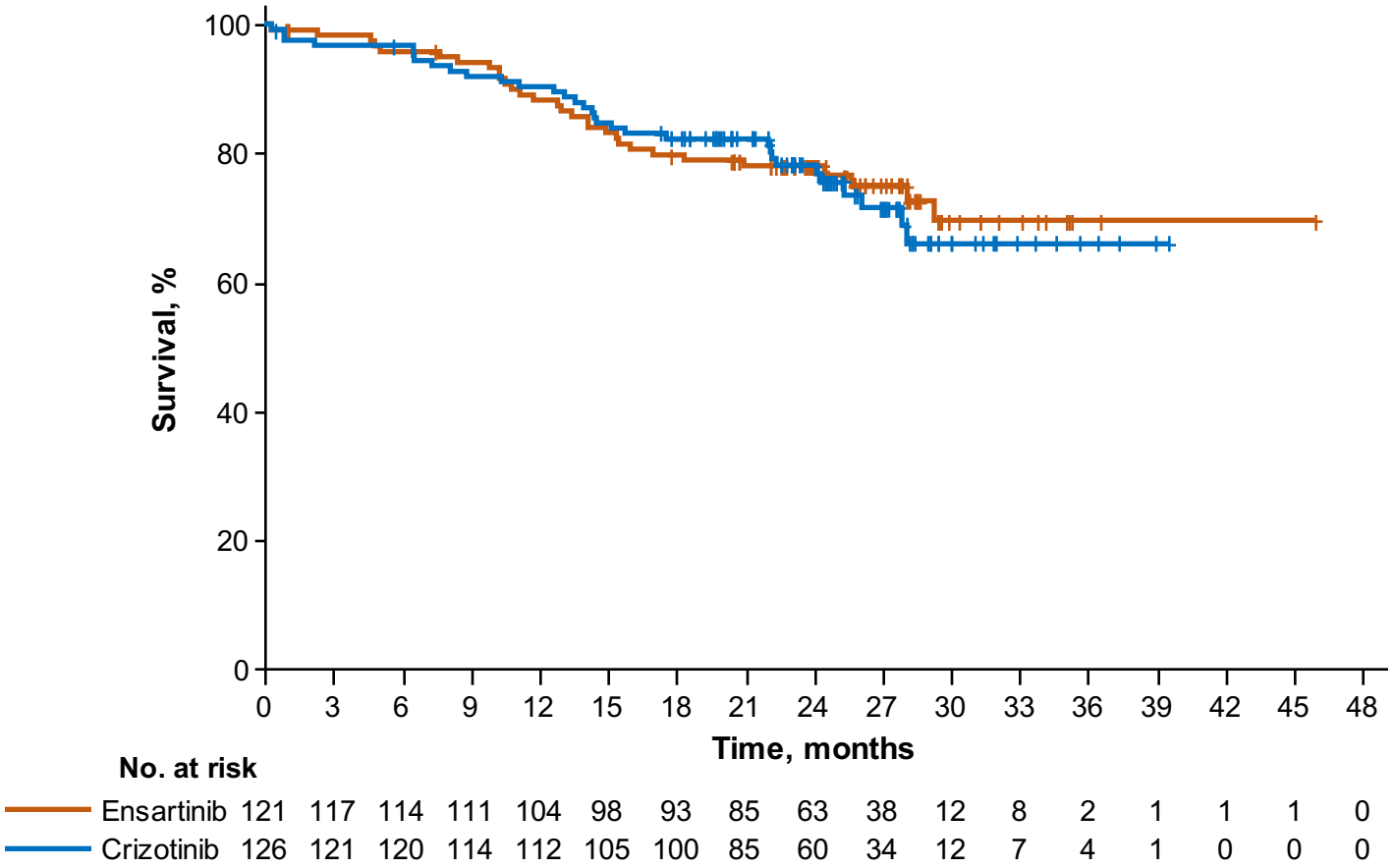
	Ensartinib (n = 81)	Crizotinib (n = 76)
TTF at 12-mo (95% CI), %	4.2 (1.4-12.8)	23.9 (15.8-36.2)
Hazard ratio (95% CI)	**0.32** (0.15-0.64)	
P value	**.0011**	

	Ensartinib (n = 81)	Crizotinib (n = 76)
mPFS (95% CI), mo	NR (25.8-NR)	16.6 (12.7-29.5)
Hazard ratio (95% CI)	**0.40** (0.23-0.70)	
P value	**.0009**	



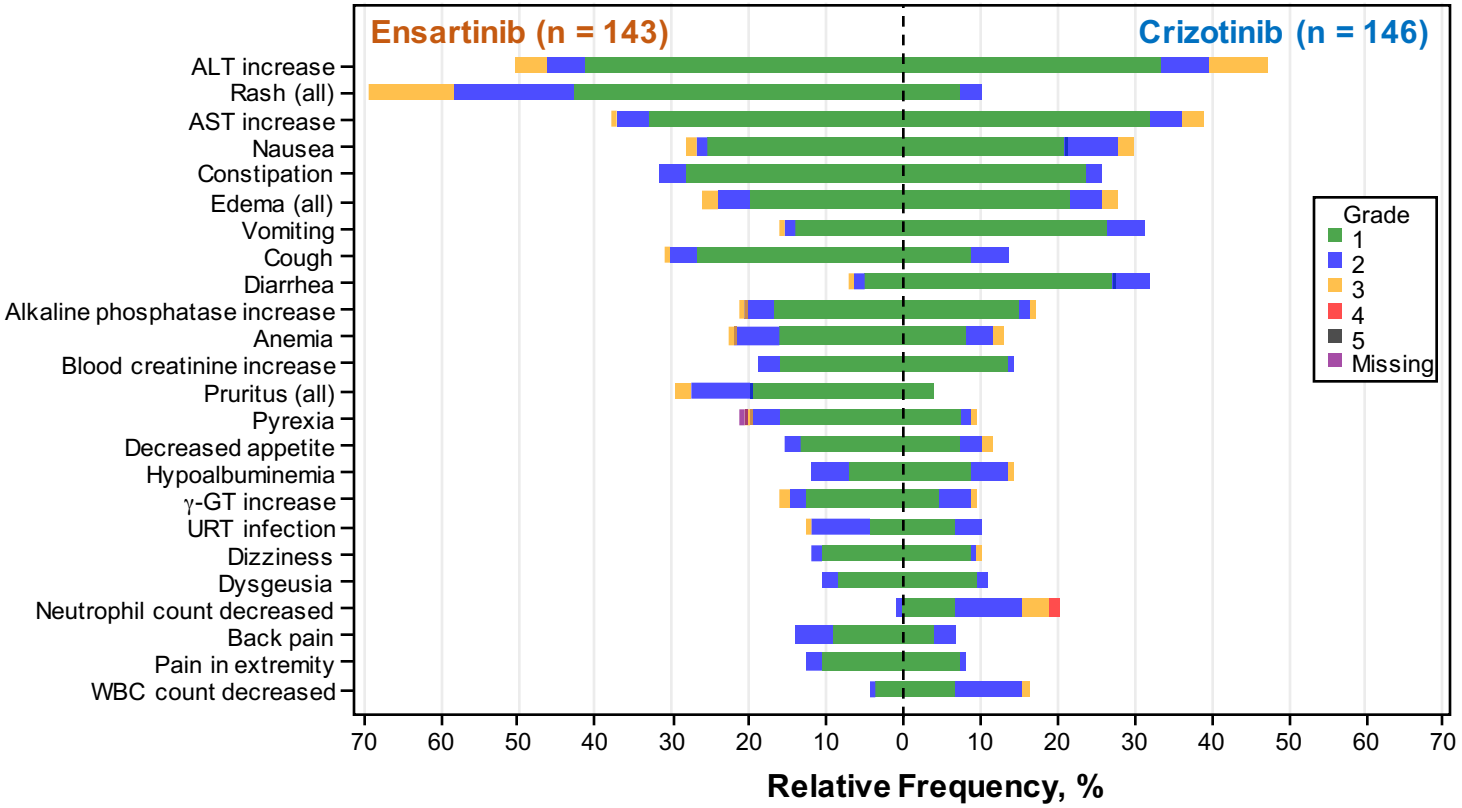


Overall Survival (mITT)



	Ensartinib (n = 121)	Crizotinib (n = 126)
Median OS (95% CI), mo	NR (NR-NR)	NR (NR-NR)
Hazard ratio (95% CI)	**0.88** (0.52-1.50)	
P value (log-rank test)	**.6470**	
24-mo OS (95% CI), %	78 (69-84)	78 (69-84)

TRAEs Reported in ≥ 10% all patients (Safety Population, N = 289)



	Ensartinib (n = 143)	Crizotinib (n = 146)
Serious TRAE, n (%)	11 (8)	9 (6)
TRAEs leading to dose reduction, n (%)	34 (24)	29 (20)
TRAE leading to drug discontinuation, n (%)	13 (9)	10 (7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GT glutamyl transferase; TRAE, treatment related adverse event; URT, upper respiratory infection; WBC, white blood cell count.

Conclusions

- Ensartinib achieved 25.8 months mPFS in the ITT population and NR (HR = 0.45) in the mITT population as assessed by the BIRC in this preplanned interim analysis
- With longer follow-up, ensartinib is trending toward further improved mPFS overall and in patients without brain metastases at baseline
- Ensartinib showed superior efficacy in the brain over crizotinib
- Ensartinib showed a favorable safety profile with low-grade rash and transaminitis as the most frequent treatment-related AEs
- Ensartinib represents a new first-line treatment option for patients with ALK+ NSCLC

Acknowledgments

eXalt3 Study

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