

Long-term Survival and Safety Analysis of eXalt3 Study: Ensartinib vs Crizotinib as First-line Regimen in ALK+ NSCLC Patients

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BACKGROUND

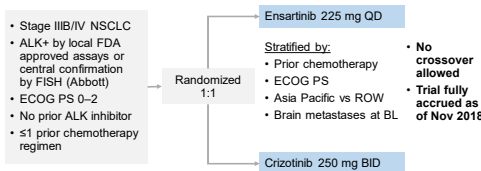
- Ensartinib is a second-generation small molecule that inhibits anaplastic lymphoma kinase (ALK).¹
- Results from eXalt3 (NCT0267804), a phase III randomized study, led to the approval of ensartinib by United States Food and Drug Administration based on the interim analysis (blinded independent review committee [BIRC]-assessed progression-free survival [PFS] with ensartinib vs crizotinib in the intent-to-treat [ITT] population: median, 25.8 mos. vs 12.7 mos.).^{2,3}
- Here, we report mature overall survival (OS), and updated PFS, duration of response (DOR), and safety data from the eXalt3 trial (data cutoff: April 1, 2025).

METHODS

Study Design

- Eligible patients with advanced ALK-positive non-small cell lung cancer (NSCLC) who were ALK tyrosine kinase inhibitor-naïve (up to one prior chemotherapy regimen) were randomized to receive ensartinib (225 mg; once daily) or crizotinib (250 mg; twice daily) until disease progression, unacceptable toxicity, or withdrawal of consent (Figure 1).

Figure 1: Study Design



ALK, anaplastic lymphoma kinase; BID, twice daily; BL, baseline; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, US Food and Drug Administration; FISH, fluorescence in situ hybridization; NSCLC, non-small cell lung cancer; QD, once daily; ROW, rest of world.

Analytical Plan

- Efficacy endpoints were defined as follows:
 - OS: time from randomization to death due to any cause.
 - PFS: time from randomization to the first date of progression or death due to any cause.
 - DOR: time from the first recorded, confirmed objective response (complete or partial response) to the first date of documented disease progression.
- Median OS, PFS, and DOR, with corresponding 95% confidence intervals (CIs), were estimated using Kaplan-Meier methods. Hazard ratios (HRs) with 95% CIs were estimated using the Cox proportional hazards regression model.
- Efficacy results are presented for the prespecified modified ITT (mITT) population consisting of patients with central laboratory-confirmed ALK-positive NSCLC by fluorescence in situ hybridization.
- Safety outcomes were evaluated in the safety population (ie, patients who received at least one dose of either study drug).

RESULTS

- In total, 290 patients were randomized (ensartinib, n=143; crizotinib, n=147) with 247 patients in mITT population (ensartinib, n=121; crizotinib, n=126).
- Overall median age was 54.0 years, 24.7% of patients had prior chemotherapy, and 36.8% of patients had baseline central nervous system metastases (4.5% had prior brain radiotherapy) in the mITT population (Table 1).

Table 1: Baseline Patient Characteristics (mITT Population)

Characteristic	Ensartinib (n=121)	Crizotinib (n=126)
Age, median (range), y	54.0 (25–86)	53.0 (26–90)
>65 y, n (%)	15 (12.4)	18 (14.3)
Sex, n (%)		
Female	60 (49.6)	62 (49.2)
Race, n (%) ^a		
Non-Asian ^b	49 (40.5)	49 (38.9)
Asian	73 (60.3)	78 (61.9)
ECOG performance status at baseline, n (%)		
0 or 1	115 (95.0)	119 (94.4)
2	6 (5.0)	7 (5.6)
Stage of disease, n (%)		
IIIB	9 (7.4)	9 (7.1)
IV	112 (92.6)	117 (92.9)
CNS metastases at baseline ^c , n (%)	41 (33.9)	50 (39.7)
Previous radiotherapy to brain, n (%)	5 (4.1)	6 (4.8)
One previous chemotherapy regimen, n (%)	26 (21.5)	35 (27.8)

^aMore than one race can be selected for a patient. ^bNon-Asian patients included White (ensartinib, 45 [37.2%]; crizotinib, 43 [34.1%]), Black or African American (ensartinib, 1 [0.8%]; crizotinib, 3 [2.4%]), Native Hawaiian or other Pacific Islander (ensartinib, 0 [0%]; crizotinib, 1 [0.8%]), and other (ensartinib, 3 [2.5%]; crizotinib, 2 [1.6%]). ^cThe presence of brain metastases was assessed by an independent review committee. CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; n, sample size; y, year.

- At the April 1, 2025 data cutoff, the median follow-up in the mITT population was 77.2 mos.
- The median OS in the mITT population was 74.0 mos. (95% CI, 50.9–not estimable [NE]) in the ensartinib arm and 55.7 mos. (95% CI, 38.0–NE) in the crizotinib arm (HR, 0.89; 95% CI, 0.63–1.26) (Figure 2).
- Five-year OS rates were 55.2% and 46.7%, respectively.
- OS findings were consistent across key subgroups (Figure 3).
- At the conclusion of PFS assessments by BIRC (July 2022), the PFS in the mITT population was 31.3 mos. for ensartinib and HR was 0.47 (95% CI 0.32–0.68).
- At the April 1, 2025 data cutoff, investigator-assessed median PFS in the mITT population was 29.7 mos. (95% CI, 18.3–39.6) for ensartinib and 12.9 mos. (95% CI, 11.0–15.0) for crizotinib (HR, 0.47; 95% CI, 0.34–0.63; log-rank P<0.0001) (Figure 4).

Figure 2: KM Plot for OS (mITT Population)

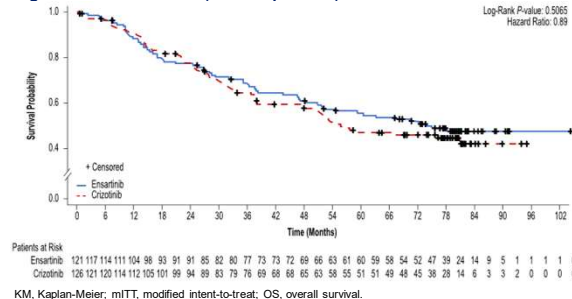


Figure 3: OS by Subgroups (mITT Population)

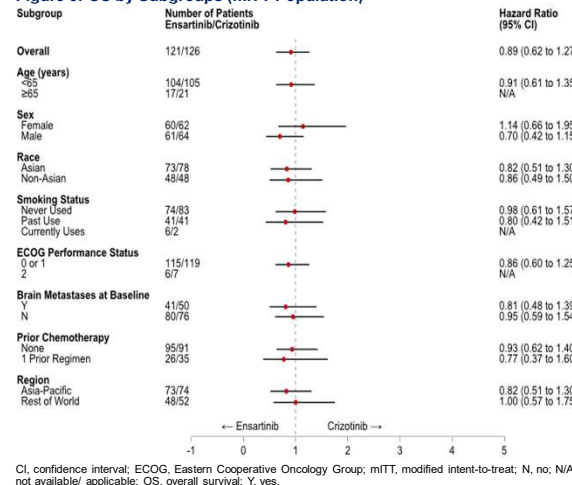
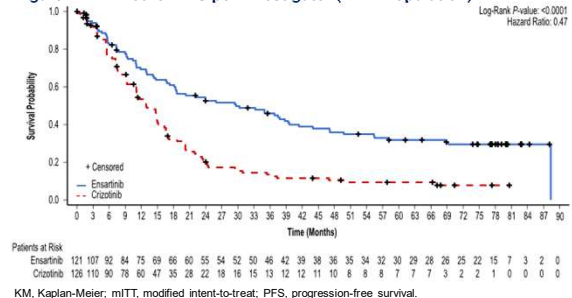
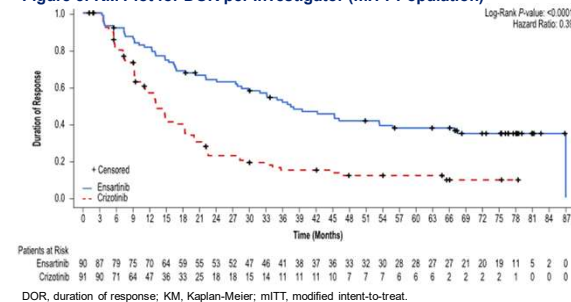


Figure 4: KM Plot for PFS per Investigator (mITT Population)



- Among responders, the median DOR was 37.45 mos. (95% CI, 27.83–53.45) in the ensartinib arm (n=90) and 13.14 mos. (95% CI, 10.84–16.69) in the crizotinib arm (n=91) (HR 0.39, 95% CI, [0.28–0.57]; log-rank P<0.0001) (Figure 5).
- The 12-month time to treatment failure in the brain rate was 4% vs 25%, respectively (HR 0.34).

Figure 5: KM Plot for DOR per Investigator (mITT Population)



- No new safety signals were detected (Table 2). Rash and elevated transaminases continued to be the most common AEs of ensartinib, mostly Grades 1–2. These AEs are reversible through measures such as dose reduction or discontinuation.

Table 2: Safety Summary (Safety Population)

	Ensartinib (n=143)	Crizotinib (n=146)
Median treatment duration, mos.	24.3	11.7
TRAE all grades, n (%)	138 (96.5)	137 (93.8)
Grade 3–5, n (%)	79 (55.3)	66 (45.2)
Grade 5, n (%)	1 (0.7)	4 (2.7)
Treatment-related SAE, n (%)	13 (9.1)	9 (6.2)
TRAE leading to dose reduction, n (%)	36 (25.2)	30 (20.5)
TRAE leading to treatment discontinuation, n (%)	16 (11.2)	11 (7.5)

SAE, serious adverse event; TRAE, treatment-emergent adverse event.

CONCLUSIONS

Long-term follow-up demonstrated a sustained OS benefit with ensartinib, further reinforcing its superior efficacy versus crizotinib. No new safety signals were identified. These findings support ensartinib as a first-line treatment option for patients with ALK-positive NSCLC, expanding available treatment options and facilitating individualized care.

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