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Post-Ensartinib Outcomes in Refractory Anaplastic Lymphoma Kinase (ALK)–Rearranged Non-Small Cell Lung Cancer (NSCLC)

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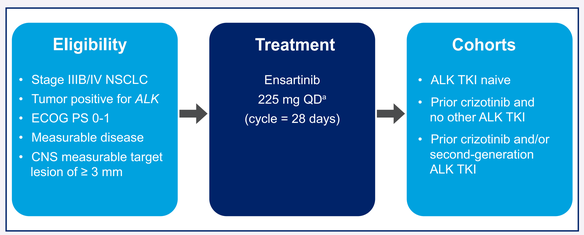
INTRODUCTION

- ALK tyrosine kinase inhibitors (TKIs) are the standard-of-care therapy for patients with *ALK*-rearranged NSCLC tumors; however, tumors inevitably relapse because of acquired resistance[1,2]
- Ensartinib is a potent small-molecule ALK TKI[3] that demonstrated clinical activity and durable disease control in patients with *ALK*-positive (*ALK*+) NSCLC, including patients who were ALK TKI naive or previously had received ALK TKIs and those with central nervous system (CNS) metastases[4]
- In the open-label, multicenter, phase 1/2 eXalt2 trial, the response rate was 60% among the *ALK*+ evaluable patients treated at ≥ 200 mg (n = 60), with most patients (80%) experiencing tumor regression[4]
  - Intracranial responses occurred in 64% of patients (9/14) with baseline intracranial lesions. The response rate in patients who had previously received crizotinib as their only prior ALK TKI was 69.0% (20/29)
  - Ensartinib was well tolerated, with a low (5%) rate of discontinuation due to treatment-related adverse events (AEs)[4]
  - The most common toxicity associated with ensartinib was rash (any Grade, 56%; Grade 3, 12%; Grade 4, 0%), which was generally managed with the use of topical medications, and for more severe toxicity, by holding the dose until improvement[4]
- Here, we report the response and survival outcomes in 4 patients with advanced, *ALK*+ NSCLC from the eXalt2 trial who were crizotinib resistant and received sequential ALK inhibitor therapy at our institution

METHODS

Figure 1. eXalt2 Study Design (expansion portion)[2]



ECOG PS, Eastern Cooperative Oncology Group performance status; **QD,** per day.
[a] Prior dose-escalation cohorts established 225 mg as the recommended dose for phase 2.

- Patients received ensartinib until progressive disease (PD), unacceptable toxicity, or investigator discretion
- The primary endpoints were safety and tolerability, and the secondary endpoints were pharmacokinetics and preliminary biological activity
- Tumor assessments were performed locally every 8 weeks
- Patients with asymptomatic brain metastases at baseline were allowed to enroll
- Plasma samples were collected on the first day of each cycle. Next-generation sequencing on circulating tumor DNA (ctDNA) was performed at Resolution BioScience (Redmond, WA, USA)

RESULTS

- Patients had a median age of 52 years (range, 40-58 years), and all had brain metastases at baseline (**Table 1**)

Table 1. Baseline Characteristics

Patient Characteristics	N = 4
Age, mean years	**50.5**
Sex (female/male)	**3/1**
Ethnicity	
Asian	1
White	2
Unknown	1
Smoking status: never	**4**
***MET* positive**	**2**
Prior chemotherapy	**4**
Prior crizotinib treatment	**4**
Brain metastases	
Nontarget only	1
Target and nontarget	4

Efficacy and Safety with Ensartinib

- Response to ensartinib is shown in **Table 2**
- All 4 patients achieved an objective partial response (PR) to ensartinib, including 1 patient with an acquired *ALK* F1174V crizotinib resistance mutation
- The most common AEs observed with ensartinib were mild rash, diarrhea, and fatigue and did not require dose reduction

Table 2. Response to Ensartinib

Patient Characteristics	N = 4
ORR	
PR	4
Intracranial response	
CR[a]	1
PR	1
SD	2
Tumor reduction from baseline, median, %	**43**
Range	39-56

ORR, overall response rate; **CR,** complete response; **SD,** stable disease.
[a] Nontarget lesion.

- Patient responses after ensartinib are shown in **Figures 2-5**

Figure 2.

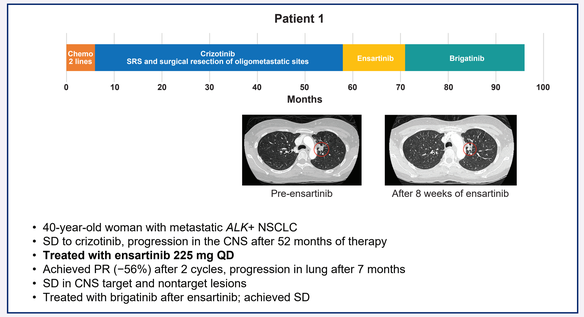


Figure 3.

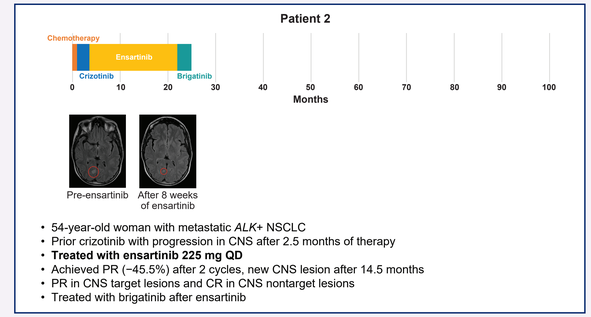


Figure 4.

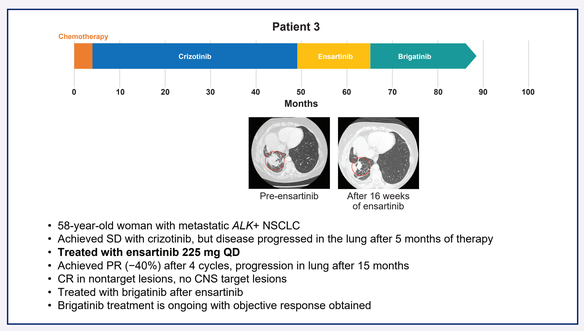
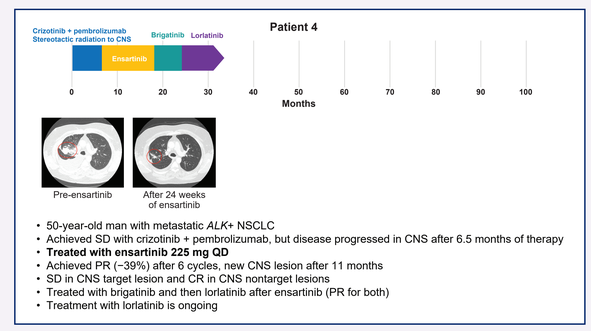


Figure 5.



- After ensartinib therapy:
  - No new somatic alterations were identified in the patient who received post-ensartinib ctDNA sequencing
  - Overall survival was > 20 months
    - 2 patients remain alive 27 and 95 months after first anticancer therapy

CONCLUSIONS

- In eXalt2, ensartinib demonstrated clinical activity in patients with advanced, *ALK*+ NSCLC and brain metastases after crizotinib treatment
- All 4 patients had response to ensartinib after crizotinib
- No new somatic alterations were identified in the patient who received post-ensartinib ctDNA sequencing
- Interestingly, durable responses were still achieved after ensartinib with sequential, second-generation ALK TKI(s)
- Our experience supports the role of sequential ALK TKI therapy to achieve long-term survival in patients with *ALK*+ NSCLC

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