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Depth of response and progression-free survival in patients with advanced *ALK*-positive non-small cell lung cancer treated with lorlatinib

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Background

- Lorlatinib is a brain-penetrant, third-generation ALK tyrosine kinase inhibitor indicated for the treatment of patients with *ALK*-positive metastatic NSCLC[1]
- Approval of lorlatinib in first line was based on the phase 3 CROWN study, which demonstrated significantly longer PFS and higher intracranial response with lorlatinib than crizotinib[2]
- After 5 years of follow-up, median PFS was not reached in the lorlatinib group, corresponding to the longest PFS for any single-agent molecular targeted treatment in advanced NSCLC[3]
- DepOR has been associated with survival outcomes in patients with metastatic NSCLC treated with targeted therapy[4]
- In this post hoc analysis of data from the CROWN study, the association between DepOR and PFS was assessed in the lorlatinib group

Methods

- The CROWN study (NCT03052608) is an ongoing, international, open-label, randomized, phase 3 trial comparing lorlatinib vs crizotinib in patients with previously untreated *ALK*-positive advanced NSCLC
  - Patients were randomized 1:1 to receive oral lorlatinib 100 mg once daily or crizotinib 250 mg twice daily
- DepOR is defined as the best percentage shrinkage in tumor size compared with baseline
- This post hoc analysis examined how DepOR is associated with demographics, baseline tumor characteristics, investigator-assessed PFS, and ctDNA–based biomarkers in the lorlatinib group
- Patients were evaluable for DepOR if they had target lesions at baseline and ≥1 adequate postbaseline assessment up to the time of progressive disease or new anticancer therapy
- Data cutoff for this analysis was October 31, 2023

Results

- In the lorlatinib group, 142 of 149 patients (95%) were evaluable for DepOR
  - The majority of patients (n=113 [80%]) experienced >50% shrinkage in target lesion (**Figure 1**)
    - 29 patients (20%) had 0% to 50% best target lesion shrinkage
    - 65 patients (46%) had >50% to 75% best target lesion shrinkage
    - 48 patients (34%) had >75% to 100% best target lesion shrinkage
- Demographics and baseline tumor characteristics were mostly similar across DepOR groups (**Table 1**); notably, a higher percentage of patients with baseline brain metastases was observed in the greater DepOR groups

Figure 1: Best target lesion shrinkage

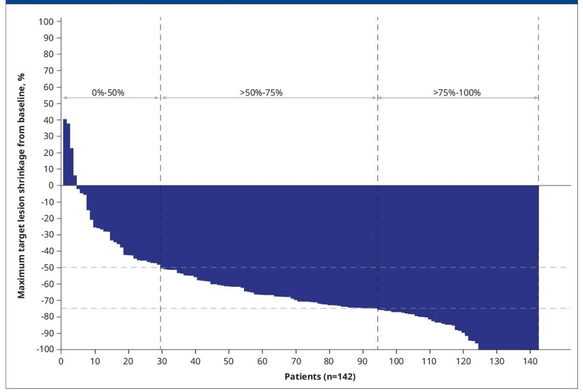


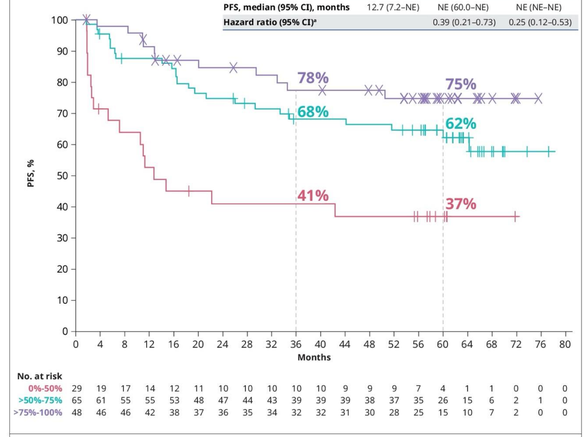
Table 1: Demographics and baseline clinical characteristics in DepOR groups

	0%-50% (n=29)	>50%-75% (n=65)	>75%-100% (n=48)
Age, median (range), years	66 (51-70)	61 (52-70)	59 (48-67)
Sex, n (%)			
Female	15 (52)	41 (63)	25 (52)
Male	14 (48)	24 (37)	23 (48)
Race, n %			
Asian	12 (41)	32 (49)	18 (38)
White	17 (59)	29 (45)	23 (48)
Not reported	0	4 (6)	7 (15)
ECOG PS, n (%)			
0	16 (55)	28 (43)	21 (44)
1	13 (45)	36 (55)	26 (54)
2	0	1 (2)	1 (2)
Brain metastases at baseline, n (%)	5 (17)	15 (23)	15 (31)
Other involved tumor sites at baseline, n (%)			
Lung	26 (90)	58 (89)	40 (83)
Lymph nodes, regional and distant	21 (72)	54 (83)	37 (77)
Bone	9 (31)	18 (28)	19 (40)
Pleura	9 (31)	18 (28)	15 (31)
Liver	5 (17)	9 (14)	9 (19)
Adrenal glands	5 (17)	4 (6)	3 (6)
Other	6 (21)	10 (15)	7 (15)

DepOR, depth of response; ECOG PS, Eastern Cooperative Oncology Group performance status.

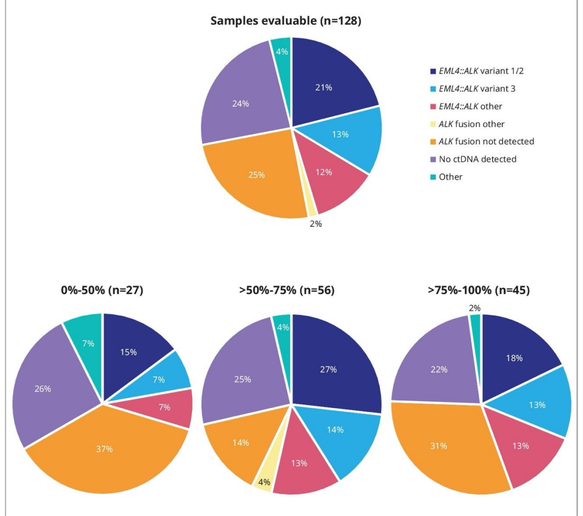
- Greater DepOR was associated with longer PFS (**Figure 2**)
  - In patients with 0% to 50% DepOR (n=29), median PFS was 12.7 months (95% CI, 7.2–not evaluable [NE])
  - In patients with >50% to 75% DepOR (n=65), median PFS was NE, with a hazard ratio (HR) of 0.39 (95% CI, 0.21–0.73) vs the 0%-50% group
  - In patients with >75% to 100% DepOR (n=48), median PFS was NE, with an HR of 0.25 (95% CI, 0.12–0.53) vs the 0%-50% group
- Of all plasma samples collected at screening (n=128), *EML4::ALK* long variant 1/2 was detected in 21%, and *EML4::ALK* short variant 3 was detected in 13%; *ALK* fusion was not detected in 25% of samples, and ctDNA was not detected in 24% (**Figure 3**)
- In the DepOR groups 0% to 50% (n=27), >50% to 75% (n=56), and >75% to 100% (n=45):
  - *EML4::ALK* variant 1/2 was detected in 15%, 27%, and 18% of samples, respectively
  - *EML4::ALK* variant 3 was detected in 7%, 14%, and 13% of samples, respectively
  - *ALK* fusion was not detected in 37%, 14%, and 31% of samples, respectively
  - ctDNA was not detected in 26%, 25%, and 22% of samples, respectively
- ctDNA dynamics at screening and cycle 2 day 1 (C2D1 or week 4) in DepOR groups 0% to 50% (n=22), >50% to 75% (n=53), and >75% to 100% (n=41) showed no association between DepOR and ctDNA clearance status (**Figure 4**)
  - ctDNA was not detected at either screening or C2D1 in 23%, 17%, and 15% of samples, respectively
  - ctDNA was detected at screening and not at C2D1 in 14%, 28%, and 32% of samples, respectively
  - ctDNA was not detected at screening and detected at C2D1 in 5%, 9%, and 10% of samples, respectively
  - ctDNA was detected at both screening and C2D1 in 59%, 45%, and 44% of samples, respectively

Figure 2: PFS by DepOR groups



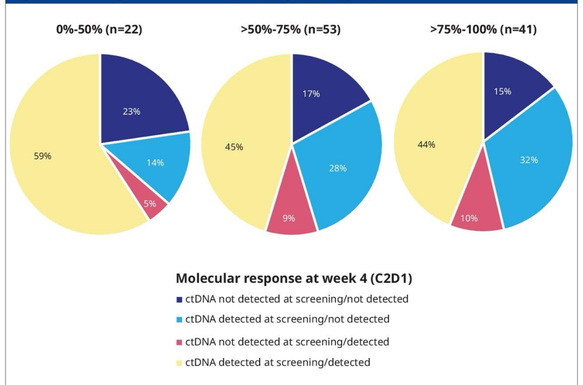
DepOR, depth of response; NE, not evaluable; PFS, progression-free survival.
[a]Unstratified analysis comparison vs 0%-50% group.

Figure 3: *ALK* fusion variants at screening by DepOR groups



ctDNA, circulating tumor DNA; DepOR, depth of response.

Figure 4: ctDNA dynamics at week 4 (C2D1) by DepOR groups



C2D1, cycle 2 day 1; ctDNA, circulating tumor DNA; DepOR, depth of response.

Conclusions

- With lorlatinib treatment, 80% of patients experienced >50% shrinkage in target lesion, and 34% had >75% shrinkage in target lesion
- Greater depth of response (DepOR) was associated with longer progression-free survival (PFS) in patients with advanced anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) treated with lorlatinib
  - The probability of remaining progression free at 5 years was 75% in patients with DepOR of >75%-100%, compared with 37% in patients with DepOR of 0%-50%
- No differences were observed in *ALK* fusion variants in the DepOR groups
- No association was observed between DepOR and circulating tumor DNA (ctDNA) clearance status

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