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Efficacy and safety of lorlatinib in patients with *ALK*+ metastatic non-small cell lung cancer previously treated with an ALK inhibitor: results from a phase 4 study

Alessandra Bearz,[1] Serena Ricciardi,[2] Nirmal Vivek Raut,[3] Manuel Cobo Dols,[4] Satheesh Chiradoni Thungappa,[5] Paola Claudia Sacco,[6] Holger Thurm,[7] Dmitri Pavlov,[7] Francesca Toffalorio,[8] Enriqueta Felip[9]

[1]CRO National Cancer Institute, Aviano, Italy; [2]San Camillo-Forlanini Hospital, Rome, Italy; [3]Jupiter Hospital, Pune, India; [4]Hospital Regional Universitario de Málaga, Málaga, Spain; [5]HCG Oncology, Bengaluru, India; [6]S.G. Moscati Hospital, Avellino, Italy; [7]Pfizer, San Diego, CA, USA; [8]Pfizer, Milan, Italy; [9]Vall d'Hebron Institute of Oncology, Barcelona, Spain

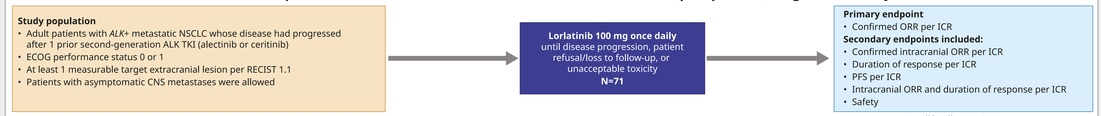
Background

- Lorlatinib is a brain-penetrant, third-generation ALK TKI with overall and intracranial activity in both treatment-naive and previously treated patients with *ALK*+ metastatic NSCLC[1-3]
- Based on the pivotal phase 1/2 study (NCT01970865), lorlatinib was approved by the European Commission for the treatment of patients with *ALK*+ metastatic NSCLC whose disease had progressed after[2,4]:
  - Alectinib or ceritinib as the first ALK TKI therapy or
  - Crizotinib and at least 1 other ALK TKI
- Due to the limited number of patients (n=28) who were included in the pivotal study and received lorlatinib after progression with just 1 second-generation ALK TKI,[2] this postapproval study was conducted to confirm the efficacy of lorlatinib in this setting

Methods

- In this phase 4 open-label study (NCT04362072), adult patients with *ALK*+ metastatic NSCLC that progressed on first-line alectinib or ceritinib were treated with lorlatinib 100 mg once daily (**Figure 1**)
- Tumor assessments were done at every 6 weeks ±1 week up to approximately 24 months (cycle 35)
- The primary endpoint was confirmed ORR by ICR
  - The goal was to demonstrate lorlatinib's superiority over the historical control ORR of 30% with platinum-based doublet chemotherapy

Figure 1: Study design



ECOG, Eastern Cooperative Oncology Group; **RECIST**, Response Evaluation Criteria in Solid Tumors.
[a]All efficacy endpoints were assessed by RECIST 1.1 .
[b]This poster presents safety data that have been updated from those described in the abstract, which had a data cutoff of May 29, 2024.

Results

- A total of 85 patients were screened, and 71 were treated with lorlatinib
- As of study completion on October 23, 2024, all patients had discontinued treatment, most commonly due to progressive disease and other reasons (27 each [38%]) ; of the 27 patients who discontinued treatment due to other reasons, 13 switched to commercial lorlatinib and 11 entered a continuation study
- Baseline characteristics are shown in **Table 1**
- The median duration of lorlatinib treatment was 9.7 months (range, 0.3-42.8 months)
- The study met its primary endpoint, with a confirmed ORR of 42% (95% CI, 31%-55%) (**Table 2** and **Figure 2**)
- After an 18.0-month median duration-of-response follow-up, the median duration of response was not reached (NR; 95% CI, 8.6 months-not evaluable [NE]), with a 65% probability of patients remaining in response for ≥12 months

Table 1: Demographics and clinical characteristics

	Lorlatinib N=71
Age, median (range), years	59 (26-87)
Male, n (%)	41 (58)
Race, n %	
White	54 (76)
Asian	15 (21)
Not reported	2 (3)
ECOG performance status, n (%)	
0	37 (52)
1	34 (48)
Prior anticancer drug regimens, n (%)	
1	59 (83)
2	11 (15)
3	0
≥4	1 (1)
Prior ALK TKI therapy, n (%)	
Alectinib[a]	60 (85)
Ceritinib	11 (15)

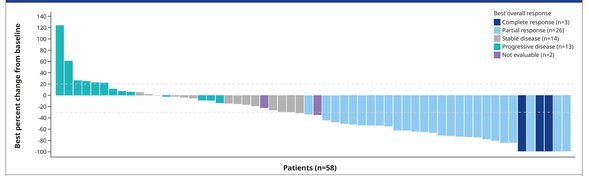
[a]One patient received crizotinib and then switched to alectinib.

Table 2: Best overall response per ICR

	Lorlatinib N=71
Objective response rate, n (%)	30 (42)
95% CI	31-55
Best overall response, n %	
Complete response	4 (6)
Partial response	26 (37)
Stable disease	14 (20)
Non-CR/non-PD	6 (8)
Progressive disease	13 (18)
Not evaluable	8 (11)
Reason for not evaluable, n (%)	
No postbaseline assessments due to early death	3 (4)
No postbaseline assessments due to other reasons	3 (4)
Stable disease <6 weeks after treatment start	2 (3)
Duration of response, median (95% CI), months	NR (8.6-NE)

Data cutoff: May 29, 2024.
CR, complete response; PD, progressive disease.

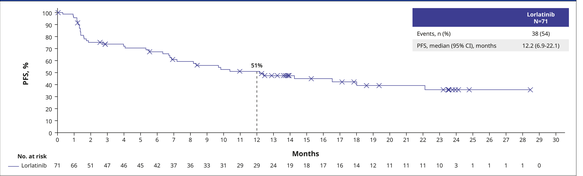
Figure 2: Best percent change from baseline in sum of diameters of target lesion



Data cutoff: May 29, 2024.
Only includes patients with measurable lesions at baseline and at least 1 adequate postbaseline percent assessment up to time of PD or new anticancer therapy.
One patient who achieved a CR had only nonmeasurable disease at baseline per IRC and is not included in this plot.

- Median PFS was 12.2 months (95% CI, 6.9-22.1 months), with a 51% probability of patients being progression free at 12 months (**Figure 3**)
- In patients with baseline CNS metastases (n=30), the intracranial ORR was 47% (95% CI, 28%-66%) (**Table 3**)
- Median duration of intracranial response was NR (range, 2.9-22.6 months), with all patients remaining in response at the last assessment
- Among the 60 patients who received alectinib as the prior ALK TKI, the ORR was 42% (95% CI, 29%-55%)
- Among the 11 patients who received ceritinib as the prior ALK TKI, the ORR was 46% (95% CI, 17%-77%)

Figure 3: PFS per ICR assessment



Data cutoff: May 29, 2024.

Table 3: Intracranial best overall response per ICR in patients with baseline CNS metastases

	Lorlatinib N=30
Objective response rate, n (%)	14 (47)
95% CI	28-66
Best overall response, n %	
Complete response	10 (33)
Partial response	4 (13)
Stable disease	1 (3)
Non-CR/non-PD	10 (33)
Progressive disease	2 (7)
Not evaluable	3 (10)
Reason for not evaluable, n (%)	
No postbaseline assessments due to other reasons	2 (7)
Stable disease <6 weeks after treatment start	1 (3)
Duration of response, median (range), months	NR (2.9-22.6)

Data cutoff: May 29, 2024.

- Any-grade treatment-emergent AEs (TEAEs) occurred in 97% of patients; grade 3/4 TEAEs occurred in 39% (**Table 4**)
- The most frequently reported (≥20% of patients) all-cause TEAEs were hypercholesterolemia (59%), hypertriglyceridemia (56%), edema (46%), fatigue (27%), and peripheral neuropathy (21%) (**Table 5**)
- Any-grade treatment-related TEAEs occurred in 90% of patients; grade 3/4 treatment-related TEAEs occurred in 27%
- The most frequently reported (≥20% of patients) treatment-related TEAEs were hypercholesterolemia (55%), hypertriglyceridemia (55%), and edema (37%)
- TEAEs led to dose interruption in 22 patients (31%), dose reduction in 11 (15%), and permanent treatment discontinuation in 9 (13%); no patients discontinued due to treatment-related TEAEs

Table 4: Safety summary

	Lorlatinib N=71
TEAEs, n (%)	
Any grade	69 (97)
Grade 3/4	28 (39)
Grade 5	10 (14)
Serious TEAEs	23 (32)
Dose interruption	22 (31)
Dose reduction	11 (15)
Permanent treatment discontinuation	9 (13)
Treatment-related TEAEs, n (%)	
Any grade	64 (90)
Grade 3/4	19 (27)
Grade 5	0
Serious TEAEs	1 (1)
Dose interruption	10 (14)
Dose reduction	7 (10)
Permanent treatment discontinuation	0

Data cutoff: October 23, 2024.

Table 5: Treatment-emergent adverse events (any grade ≥10%)

Cluster	Lorlatinib N=71	
	Any Grade	Grade 3/4
Any, n (%)	69 (97)	28 (39)
Hypercholesterolemia	42 (59)	6 (8)
Hypertriglyceridemia	40 (56)	9 (13)
Edema	33 (46)	3 (4)
Fatigue	19 (27)	0
Peripheral neuropathy	15 (21)	1 (1)
Dyspnea	14 (20)	4 (6)
Diarrhea	13 (18)	1 (1)
Anemia	12 (17)	1 (1)
Hyperlipidemia	12 (17)	0
Pyrexia	12 (17)	0
Arthralgia	9 (13)	0
COVID-19	9 (13)	1 (1)
Mood effects	9 (13)	0
Pain in extremity	9 (13)	1 (1)
Cough	8 (11)	0
Weight increased	7 (10)	1 (1)

Data cutoff: October 23, 2024.

Conclusions

- In this phase 4 study, lorlatinib provided clinically meaningful benefits in patients with anaplastic lymphoma kinase (*ALK*)–positive metastatic non-small cell lung cancer (NSCLC) whose disease had progressed on alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy
- The study met its primary endpoint, with the lower limit of the 95% CI for objective response rate (ORR) exceeding 30%, surpassing the historical ORR with platinum-based doublet chemotherapy; the confirmed ORR was 42% (95% CI, 31%-55%)
- Median progression-free survival (PFS) was 12.2 months per independent central review (ICR) assessment
- Lorlatinib showed intracranial clinical benefit in patients with baseline central nervous system (CNS) metastases, with a confirmed intracranial ORR of 47% per ICR assessment
- Treatment was generally tolerable, with adverse events (AEs) that were manageable through temporary discontinuation, dose reduction, and/or standard supportive medical therapy; no new safety signals were identified
- Efficacy and safety results from this study of lorlatinib were consistent with the pivotal phase 1/2 study and the known safety profile[1,2]

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Correspondence: Alessandra Bearz, Alessandra.Bearz@cro.it

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