1197P

First-line Lorlatinib Versus Crizotinib in *ALK*-Positive Non-Small Cell Lung Cancer: Asian Subgroup Analysis of CROWN

Qing Zhou,[1]* Hye Ryun Kim,[2]* Ross A. Soo,[3] Gee-Chen Chang,[4] Chao-Hua Chiu,[5] Hidetoshi Hayashi,[6] Sang-We Kim,[7] Shunsuke Teraoka,[8] Yasushi Goto,[9] Jianying Zhou,[10] Victor Ho-Fun Lee,[11] Baohui Han,[12] James Chung Man Ho,[11] Dong-Wan Kim,[13] Chia-Chi Lin,[14] Shun Lu,[12] Anna Polli,[15] Anna Maria Calella,[15] Tony Mok,[16] Yi-Long Wu[1]

[1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; [2]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]National University Cancer Institute, Singapore; [4]Division of Pulmonary Medicine, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan; School of Medicine and Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan; Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [5]Taipei Veterans General Hospital, Taipei, Taiwan; [6]Kindai University Faculty of Medicine, Osaka, Japan; [7]University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]Wakayama Medical University, Wakayama, Japan; [9]National Cancer Center Hospital, Tokyo, Japan; [10]First Affiliated Hospital of Zhejiang University, Hangzhou, China; [11]University of Hong Kong, Hong Kong; [12]Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [13]Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [14]National Taiwan University Hospital, Taipei, Taiwan; [15]Pfizer, Milan, Italy; [16]State Key Laboratory of Translational Oncology and Chinese University of Hong Kong, Hong Kong
*Co-first authors

Objective: This analysis investigated the efficacy and safety results in Asian patients with untreated *ALK*-positive NSCLC in CROWN

Conclusions: A consistent and clinically meaningful improvement in PFS was observed for lorlatinib versus crizotinib in the Asian subgroup of CROWN, and the overall efficacy and safety were consistent with results observed in the overall population

Presenting author: Qing Zhou

Email for more information

@PfizerOncMed #ESMO21

Click or scan this quick response (QR) code to download this poster along with associated material.

Plain Language Summary
Please scan this QR code with your smartphone app to view a plain language summary.

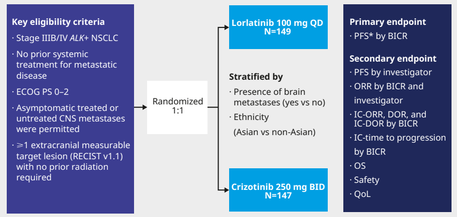
Background

- Lorlatinib is a potent, third-generation inhibitor of anaplastic lymphoma kinase (ALK)
- In the Phase 3 CROWN trial (NCT03052608), lorlatinib significantly prolonged progression-free survival (PFS) versus crizotinib in patients with untreated *ALK*-positive non-small cell lung cancer (NSCLC) (hazard ratio [HR], 0.28; 95% confidence interval [CI], 0.19–0.41; P<0.001)[1]
  - Overall and intracranial response rates were also higher with lorlatinib versus crizotinib
- Adverse events (AEs) that were more common with lorlatinib than with crizotinib (with ⩾10% difference) included hypercholesterolemia, hypertriglyceridemia, edema, increased weight, peripheral neuropathy, and cognitive effects[1]
- Despite a higher incidence of grade 3–4 AEs with lorlatinib (72% vs 56% with crizotinib), discontinuations due to AEs were similar (7% lorlatinib, 9% crizotinib)[1]
- The safety profile of lorlatinib in the CROWN study was consistent with a previous Phase 1/2 study[2,3]
- Here we report efficacy and safety results from the Asian subgroup of CROWN

Methods

- The CROWN trial design is shown in Figure 1
- Patients were randomized (1:1) to receive oral lorlatinib 100 mg once daily or oral crizotinib 250 mg twice daily, stratified by the presence of brain metastases (yes/no) and ethnicity (Asian/non-Asian)
- The primary endpoint and key secondary endpoint analyses were conducted for the Asian subgroup using a data cutoff date of March 20, 2020, consistent with the primary interim analysis[1]
- Analyses were conducted, as per in the overall population, within the Asian subgroup and the emphasis was on estimation of treatment effect rather than hypothesis testing
- Overall survival (OS) was analyzed using a hierarchical testing procedure and no adjustments for multiplicity were performed on other analyses
- Given the limited sample size in the Asian subgroup, the subgroup analyses focused on unstratified analyses

Figure 1. CROWN Study Design



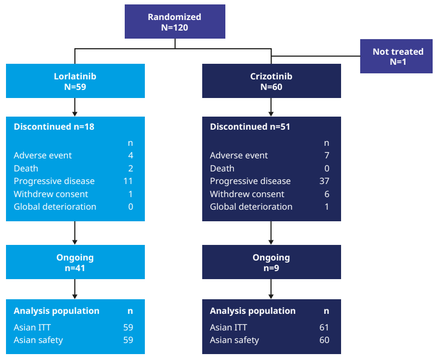
Abbreviations: ALK=anaplastic lymphoma kinase; BICR=blinded independent central review; BID=twice daily; CNS=central nervous system; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; IC=intracranial; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QD=once daily; QoL=quality of life; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1.
*Defined as the time from randomization to RECIST-defined progression or death due to any cause.

Results

PATIENTS

- In the Asian subgroup, 120 patients were randomized (59 to lorlatinib, 61 to crizotinib [1 not treated]) (Figure 2); 48 in Japan, 21 in the Republic of Korea, 20 in mainland China, 16 in Taiwan, 8 in Singapore, and 7 in Hong Kong
- Patient demographics and disease characteristics were well balanced between the treatment groups except for a slight imbalance in female patients, with a lower proportion in the lorlatinib group compared with the crizotinib group (Table 1)

Figure 2. Participant Disposition (Treatment Phase; Asian ITT Population)



Abbreviations: ITT=intent-to-treat.

EFFICACY

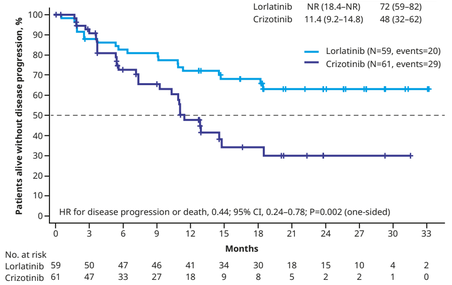
- Of the 120 patients in the Asian intent-to-treat (ITT) population, 20 of 59 patients (34%) in the lorlatinib group, and 29 of 61 (48%) in the crizotinib group had had disease progression or died by the time of the data cutoff (March 20, 2020)
- The percentage of patients alive without disease progression at 12 months was 72% (95% CI, 59–82) in the lorlatinib group and 48% (95% CI, 32–62) in the crizotinib group (HR for disease progression or death, 0.44; 95% CI, 0.24–0.78; P=0.002) (Figure 3)
  - Median PFS was not reached (NR) (95% CI, 18.4–NR) in the lorlatinib group and 11.4 months (95% CI, 9.2–14.8) in the crizotinib group

Table 1. Baseline Characteristics (Asian ITT Population)

Characteristic	Lorlatinib (N=59)	Crizotinib (N=61)
Age, median (range), y	61 (30–83)	55 (26–84)
Sex, female, no. (%)	27 (46)	37 (61)
ECOG Performance Status, no. (%)		
0	21 (36)	22 (36)
1	37 (63)	37 (61)
2	1 (2)	2 (3)
Use of previous anticancer drug therapy,* no. (%)	7 (12)	6 (10)
Brain metastasis at baseline,† no. (%)	11 (19)	16 (26)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat.
*According to the protocol, previous adjuvant or neoadjuvant anticancer therapy was allowed if it had been completed more than 12 months before randomization.
†Per independent central neuroradiological review.

Figure 3. PFS by BICR (Asian ITT Population)



Abbreviations: BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; NR=not reached; PFS=progression-free survival.

- Among all patients in the Asian subgroup, significantly higher objective response rate (as assessed by blinded independent central review [BICR]) was observed in the lorlatinib group compared with the crizotinib group (76% [95% CI, 63–86] vs 57% [95% CI, 44–70]) (Table 2)
- The duration of response was ⩾12 months in 73% of patients in the lorlatinib group and 26% of patients in the crizotinib group
- Among the patients with measurable or non-measurable brain metastases at baseline (11 and 16 patients in the lorlatinib and crizotinib groups, respectively), a significantly higher objective intracranial response rate (assessed by BICR) was observed in the lorlatinib group compared with the crizotinib group (73% [95% CI, 39–94] vs 25% [95% CI, 7–52]) (Table 2)
- The duration of intracranial response was at ⩾12 months in 88% of patients in the lorlatinib group and 0% of patients in the crizotinib group
- At the time of data cutoff, overall survival data were immature, with deaths having occurred in 10 patients (17%) in the lorlatinib group and 9 patients (15%) in the crizotinib group
- The HR for death was 0.99 (95% CI, 0.40–2.45)

SAFETY

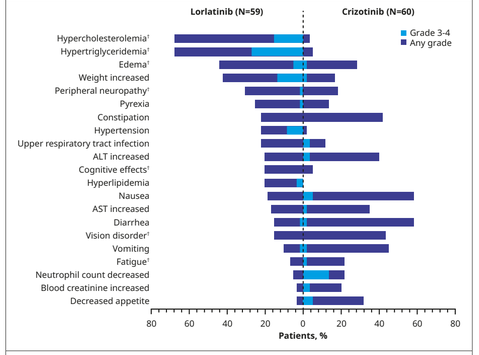
- Adverse events (AEs) that were more common with lorlatinib than with crizotinib (with ⩾10% difference) included hypercholesterolemia (68% vs 3%), hypertriglyceridemia (68% vs 5%), edema (44% vs 28%), increased weight (42% vs 17%), peripheral neuropathy (31% vs 18%), pyrexia (25% vs 13%), hypertension (22% vs 2%), upper respiratory tract infection (22% vs 12%), cognitive effects (20% vs 5%), and hyperlipidemia (20% vs 0%) (Figure 4)
- Grade 3–4 AEs were reported by 78% (lorlatinib) versus 60% (crizotinib)
  - The most common grade 3–4 AEs (in ⩾10% of patients) with lorlatinib were hypertriglyceridemia (27%), hypercholesterolemia (15%), and weight increased (14%), and with crizotinib was neutrophil count decreased (13%)
- Serious AEs occurred in 42% and 25% of patients in the lorlatinib and crizotinib group, respectively
- Fatal AEs occurred in 3 patients (5%) in the lorlatinib group and none in the crizotinib group
- AEs leading to dose interruption or dose reduction, respectively, were reported in 54% and 31% of patients in the lorlatinib group and 55% and 30% in the crizotinib group
- Fewer patients had AEs leading to permanent treatment discontinuation in the lorlatinib group (7%) than the crizotinib group (12%)

Table 2. Objective Response by BICR in All Patients and Intracranial Objective Response by BICR Among Patients With Brain Metastases at Baseline (Asian Population)

	Lorlatinib	Crizotinib
ITT population		
No. of patients	59	61
Confirmed objective response		
No. of patients	45	35
% (95% CI)*	76 (63–86)	57 (44–70)
Odds ratio (95% CI)	2.39 (1.02–5.70)	
Complete response, no. (%)	1 (2)	0
Partial response, no. (%)	44 (75)	35 (57)
Stable disease	7 (12)	15 (25)
Neither complete response nor progressive disease	1 (2)	2 (3)
Progressive disease	5 (8)	3 (5)
Not evaluable	1 (2)	6 (10)
Duration of response		
No. of events	11	14
No. censored	34	21
Median (95% CI),† months	NR (NR–NR)	12.8 (9.4–NR)
Median time to tumor response (IQR), months	1.8 (1.7–1.9)	1.8 (1.7–1.9)
Patients with brain metastases at baseline		
No. of patients	11	16
Confirmed intracranial response‡		
No. of patients	8	4
% (95% CI)*	73 (39–94)	25 (7–52)
Duration of intracranial response		
No. of events	0	1
No. censored	8	3
Median (95% CI),† months	NR (NR–NR)	9.4 (NR–NR)

Abbreviations: BICR=blinded independent central review; CI=confidence interval; IQR=interquartile range; ITT=intent-to-treat; NR=not reached.
*Clopper-Pearson method.
†Brookmeyer and Crowley method.
‡Intracranial assessment was performed by independent central neuroradiological review.

Figure 4. All Causality AEs* With ⩾10% Difference in Frequency (Asian Safety Population)



Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase.
*Incidence of ⩾20% in either group.
†Cluster term.

Conclusions

- In the Asian subgroup of CROWN, a consistent and clinically meaningful improvement in PFS was observed for lorlatinib versus crizotinib
- Baseline characteristics were similar to the overall population,[1] except for a slightly greater gender imbalance between treatments in the Asian subgroup
- The efficacy and safety of lorlatinib versus crizotinib in the Asian subgroup of CROWN was consistent with the overall population[1]

References: 1. Shaw AT, et al. *N Engl J Med*. 2020;383:2018-2029. **2.** Shaw AT, et al. *Lancet Oncol*. 2017;18:1590-1599. **3.** Solomon BJ, et al. *Lancet Oncol*. 2018;19:1654-1667.

Disclosures: Qing Zhou declares honoraria from AstraZeneca and Roche.

Acknowledgments: This study was sponsored by Pfizer. Medical writing support, funded by Pfizer, was provided by Annette Smith, PhD, of CMC AFFINITY, McCann Health Medical Communications.

Presented at the 2021 Virtual ESMO Congress • September 16–21, 2021