Poster 992P

Updated analyses from the CROWN study of first-line lorlatinib vs crizotinib in Asian patients with *ALK*-positive non-small cell lung cancer

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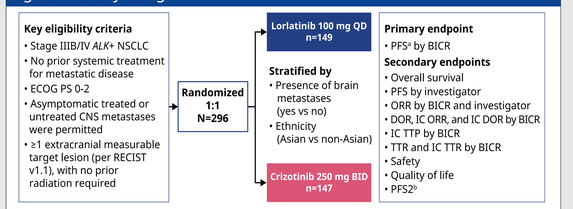
Background

- Lorlatinib is a brain-penetrant, third-generation ALK tyrosine kinase inhibitor (TKI) with antitumor activity in patients with *ALK*-positive NSCLC[1,2]
- An interim analysis from the phase 3 CROWN study (NCT03052608) of lorlatinib vs crizotinib showed that lorlatinib improved PFS and demonstrated IC activity in patients with untreated advanced *ALK*-positive NSCLC[2]
  - At a median of 18.3 months of follow-up in the lorlatinib arm, median PFS was not reached (NR; 95% CI, NR-NR) with lorlatinib and was 9.3 months (95% CI, 7.6-11.1) with crizotinib (hazard ratio [HR], 0.28; 95% CI, 0.19-0.41; *P*<.001)
  - In patients with measurable baseline brain metastases, the frequency of confirmed IC response was greater with lorlatinib (82%) than crizotinib (23%)
- Based on the results of this study, lorlatinib has been approved in many countries for first-line treatment in patients with metastatic *ALK*-positive NSCLC[2-5]
- We report updated results in the Asian subgroup from the phase 3 CROWN study after 36 months of follow-up

Methods

- The phase 3 CROWN study is an ongoing, international, randomized, phase 3 trial comparing lorlatinib with crizotinib in patients with previously untreated *ALK*-positive NSCLC (**Figure 1**)
- Efficacy endpoints were analyzed using unstratified analyses in the Asian subgroup; safety data were summarized descriptively

Figure 1: Study design

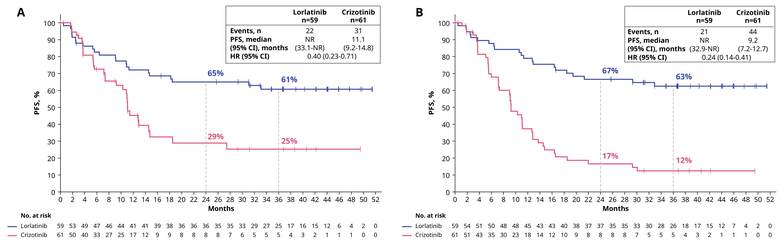


BICR, blinded independent central review; BID, twice daily; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression; TTR, time to tumor response.
[a] Defined as the time from randomization to RECIST-defined progression as assessed by the independent radiologist or death due to any cause, whichever occurred first.
[b] Defined as the time from randomization to the date of progression of disease with first subsequent systemic anticancer therapy or death due to any cause, whichever occurred first.

Results (data cutoff: September 20, 2021)

- In the Asian subgroup, 120 patients were randomized to receive lorlatinib (n=59) or crizotinib (n=61)
- In the lorlatinib and crizotinib arms, 11 (19%) and 15 (25%) patients, respectively, had brain metastases
- Median PFS by BICR was NR in the lorlatinib arm and 11.1 months (95% CI, 9.2-14.8) in the crizotinib arm (HR, 0.40; 95% CI, 0.230-0.710; **Figure 2A**)
- Per investigator, median PFS was NR in the lorlatinib arm and 9.2 months (95% CI, 7.2-12.7) in the crizotinib arm (HR, 0.24; 95% CI, 0.139-0.406; **Figure 2B**)
- Per BICR, 80% of lorlatinib-treated patients and 29% of crizotinib-treated patients had a response that lasted ≥12 months
- Clinically meaningful improvements in ORR and IC ORR were observed with lorlatinib vs crizotinib (**Table 1**)
- Median IC TTP was NR in the lorlatinib arm and 16.6 months (95% CI, 11.0-NR) in the crizotinib arm (HR, 0.03; 95% CI, 0.004-0.200; **Figure 3**)
- Grade 3/4 all-cause adverse events (AEs) occurred in 80% of patients in the lorlatinib arm and 62% in the crizotinib arm (**Table 2**)
  - The incidence of grade 3/4 AEs in the lorlatinib arm was largely due to the frequent occurrence of altered levels of lipids such as hypercholesterolemia and hypertriglyceridemia (**Figure 4**)
- All-cause AEs leading to permanent treatment discontinuation were reported in 8% of patients in the lorlatinib arm and 13% in the crizotinib arm

Figure 2: PFS[a] by (A) BICR and (B) investigator



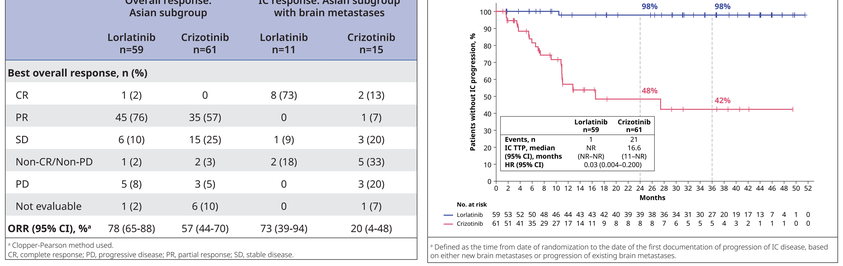
[a] Defined as the time from randomization to RECIST-defined progression as assessed by the independent radiologist (A) or investigator (B) or death due to any cause, whichever occurred first.

Table 1: Summary of overall and IC response by BICR

	Overall response: Asian subgroup		IC response: Asian subgroup with brain metastases	
	Lorlatinib n=59	Crizotinib n=61	Lorlatinib n=11	Crizotinib n=15
Best overall response, n (%)				
CR	1 (2)	0	8 (73)	2 (13)
PR	45 (76)	35 (57)	0	1 (7)
SD	6 (10)	15 (25)	1 (9)	3 (20)
Non-CR/Non-PD	1 (2)	2 (3)	2 (18)	5 (33)
PD	5 (8)	3 (5)	0	3 (20)
Not evaluable	1 (2)	6 (10)	0	1 (7)
ORR (95% CI), %[a]	78 (65-88)	57 (44-70)	73 (39-94)	20 (4-48)

[a] Clopper-Pearson method used.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3: IC TTP[a] by BICR



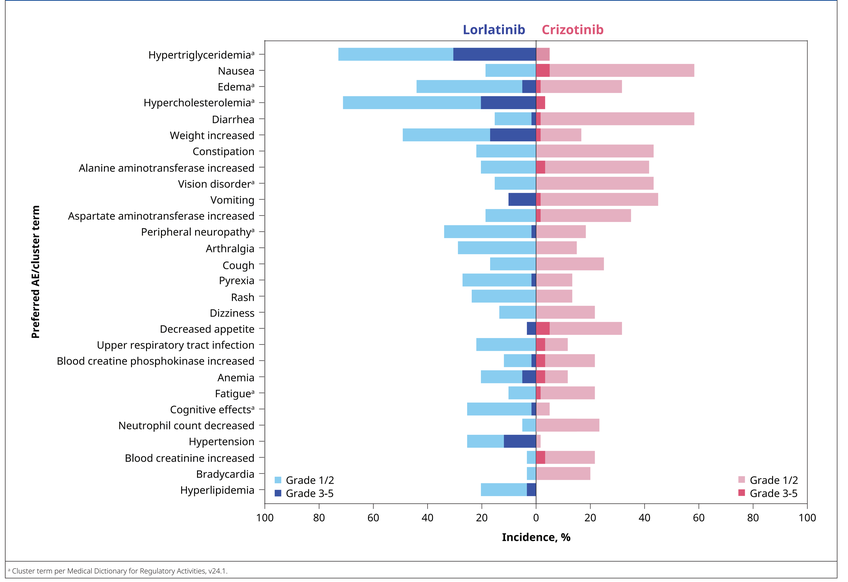
[a] Defined as the time from date of randomization to the date of the first documentation of progression of IC disease, based on either new brain metastases or progression of existing brain metastases.

Table 2: Summary of all-cause AEs[a]

	Lorlatinib n=59	Crizotinib n=60
AEs	59 (100)	60 (100)
Serious AEs	27 (46)	18 (30)
Grade 3/4 AEs	47 (80)	37 (62)
Discontinuation of study treatment due to AEs	5 (8)	8 (13)

[a] Data are n (%).

Figure 4: All-cause AEs in ≥20% of patients in either treatment arm



[a] Cluster term per Medical Dictionary for Regulatory Activities, v24.1.

Conclusions

- Efficacy results in the Asian subgroup of patients with anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) were consistent with those in the overall population in the phase 3 CROWN study
  - Lorlatinib showed improved overall and intracranial (IC) efficacy compared with crizotinib as measured by progression-free survival (PFS) and objective response rate (ORR)
  - Efficacy benefit in the lorlatinib arm was observed in both patients with and those without baseline brain metastases
- No new safety signals were observed in the Asian subgroup, and the safety profile was consistent with that observed in the overall population of the phase 3 CROWN study
- Our data support the use of lorlatinib as a first-line treatment option in Asian patients with *ALK*-positive NSCLC with or without baseline brain metastases

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Acknowledgments: The authors would like to thank the participating patients and their families, investigators, subinvestigators, research nurses, study coordinators, and operations staff. Editorial and medical writing support was provided by Eleanor Porteous, MSc, of ClinicalThinking, Inc, which was funded by Pfizer.

Disclosures: **QZ** has been an invited speaker for AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, MSD, Pfizer, Roche, and Sanofi. **HRK** reports advisory services for AstraZeneca, MSD, and grants from AstraZeneca, Bristol Myers Squibb, Ono, and Roche, outside the submitted work. **RS** has served on an advisory board for Amgen, AstraZeneca, Bayer, BMS, Eli Lilly, Merck, Novartis, Pfizer, Roche, Takeda, and Yuhan; has been an invited speaker for Boehringer Ingelheim; received instruction research grants from AstraZeneca and Boehringer Ingelheim; and reports other for Taiho. **C-HC** has been an invited speaker and principal investigator and served on an advisory board for Taipei Veterans General Hospital. **HH** has been an invited speaker for Ono Pharmaceutical, Bristol Myers Squibb, AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceutical, Eli Lilly Japan, Merck, MSD K.K., Novartis, Pfizer, Takeda, and Janssen; served on advisory boards for Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly Japan, Shanghai Pharmaceuticals, Pfizer, and AstraZeneca; received funding and research grants from AstraZeneca; has been a principal investigator for Ono Pharmaceutical; and is a member of West Japan Oncology Group. **S-WK** has nothing to report. **ST** has been an invited speaker for AstraZeneca, Boehringer Ingelheim, Chugai, Eli Lilly Japan, Novartis, Ono, and Taiho; and served on an advisory board for Pfizer R&D. **D-WK** has been an invited speaker for Korean Association for Lung Cancer, Korean Cancer Association, Korean Society of Medical Oncology, Taiwan Lung Cancer Society, and Asian Thoracic Oncology Research Group; received medical writing assistance fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chong Keun Dang, Daiichi Sankyo, GSK, Pfizer, MSD, Merck, Novartis, Roche, Takeda, and Yuhan; served on advisory board for Amgen, AstraZeneca, BMS/ONO Pharmaceuticals, Daiichi Sankyo, GSK, Janssen, Merck, MSD, Pfizer, Sk Biopharm, and Takeda; served as a member of the board of directors for Asian Thoracic Oncology Research Group, Korean Association for Lung Cancer, Korean Cancer Association, and Korean Society of Medical Oncology; received institutional research grants from Alpha Biopharma, Amgen, AstraZeneca/Medimmune, Boehringer Ingelheim, BMS, Bridge BioTherapeutics, Chong Keun Dang, Daiichi Sankyo, GSK, Hanmi, Janssen, Merck, Merus, Mirati Therapeutics, MSD, Novartis, ONO Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, and Yuhan; served as a principle investigator for Chong Keun Dang; served as a scientific advisor for Health Insurance Review and Assessment Service, Korea; and received travel support from Amgen, Daiichi Sankyo, International Association for the Study of Lung Cancer, Asian Thoracic Oncology Research Group, and Taiwan Lung Cancer Society. **HZhan** is an employee of Pfizer Inc. **HZhao** is an employee of Pfizer Inc. **HL** is an employee of Pfizer Inc. **TM** has been an invited speaker for AbbVie, ACEA Pharmaceuticals, Alpha Bio, Amgen, Amoy Diagnostics, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Daiichi Sankyo, Fishawack, InMed Medical Communication, Lunit USA, Merck Serono, MSD, Roche, MD Health, Medscape, PeerVoice, P. Permanyer SL, Prime Oncology, Research to Practice, Touch Medical Media, Sanofi, Takeda, PER, AstraZeneca, HUTCHMED, Aurora Tele-Oncology, and Sanomics; served on advisory boards for AbbVie, ACEA Pharmaceuticals, Alpha Bio, Amgen, Amoy Diagnostics, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Blueprint Medicines, Berry Oncology, Cstone Pharmaceuticals, Daiichi Sankyo, Fishawack, Eisai, Gritstone, Guardant, G1 Therapeutics, Hengrui, Ignyta, IQVIA, Incyte, Innovia, Janssen, Loxo Oncology, Qiming Development, Lunit USA, Merck Serono, MSD, Roche, Mirati Therapeutics, MorehealthNovartis, OrigiMed, Puma BioTechnology, Sanofi, Takeda, Virtus Medical Group, Yuhan, and Curio Science; served in an advisory role for geneDx and AstraZeneca; has stocks/shares in Sanomics, HUTCHMED, BioMics Limited, Loxo Oncology, OrigiMed, Virtus Medical, Lunit USA, and Aurora Tele-Oncology; received institutional funding for clinical trials from AstraZeneca, BMS, Merck Serono, MSD, Novartis, Pfizer, Roche, SFJ Pharmaceuticals, Xcovery, Takeda, G1 Therapeutics, and Clovis Oncology; and served in a leadership role for American Society of Clinical Oncology, Asia Thoracic Oncology Research Group, Chinese Lung Cancer Research Fund, Chinese Society of Clinical Oncology, Hong Kong Society of Medical Oncology, Hong Kong Thoracic Society, International Association for the Study of Lung Cancer, and St Stephen's College. **Y-LW** has been an invited speaker for AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Hengrui, Merck, MSD, Pfizer, Roche, Sanofi, and Yuhan; has served on advisory boards for AstraZeneca, MSD, and Takeda; served in a leadership role for Chinese Thoracic Oncology Research Group and Chinese Society of Clinical Oncology; and was the conference president for International Association for the Study of Lung Cancer 2020 World Conference on Lung Cancer.

Presented at the ESMO Congress 2022; September 9-13, 2022; Paris, France