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Characterizing resistance mechanisms and predictors of early progression and long-term response to lorlatinib: Circulating tumor DNA (ctDNA) analyses from the CROWN study

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Background

In the phase 3 CROWN study (NCT03052608), lorlatinib showed unprecedented progression-free survival (PFS) benefit in patients (pts) with previously untreated advanced *ALK*+ NSCLC, with median PFS not reached after 7 y of follow-up. Despite durable outcomes, a minority of pts (~20%) experienced disease progression or death within 1 y of treatment. We analyzed ctDNA from pts in CROWN to identify potential resistance mechanisms and predictors of early progression and long-term response to lorlatinib.

Methods

296 pts were randomized 1:1 to lorlatinib 100 mg QD or crizotinib 250 mg BID. In the lorlatinib arm (n=149), blood samples collected at baseline (BL; n=120) and end of treatment from pts with progression (EOT; n=18) were used for ctDNA analyses (Guardant Infinity). Early progressors (EPs) are pts with PFS events at ≤1 y; long-term responders (LTRs) are pts without PFS events at 7 y. Analyses included characterization of resistance mechanisms at EOT; comparisons of BL genomic alterations in EPs and LTRs, and between pts with and without intracranial (IC) progression; and efficacy analyses by longitudinal assessment of methylation-based tumor fraction (TF).

Results

Analyses of paired BL and EOT ctDNA samples (n=17) revealed no new *ALK* resistance mutations and showed that bypass (RTK/RAS/MAPK) and other cancer-related pathways, eg, inflammatory response and angiogenesis pathway, may lead to resistance to lorlatinib. BL ctDNA analyses showed more genomic alterations in EPs than LTRs (median 10 vs 6). *FGFR4*, *DICER1*, and *ARAF* genomic alterations were more frequent in pts with vs without IC progression (25-38% vs ≤3%). BL TF level was prognostic for PFS. On-treatment decrease in TF at wk 4 and wk 24 was associated with longer PFS. Additional pathway analyses in EPs will be presented.

Conclusions

ctDNA analyses from CROWN suggest lorlatinib resistance is primarily mediated through bypass pathway and other potential tumorigenic inflammatory and angiogenic mechanisms rather than on-target *ALK* mutations. BL genomic complexity and on-treatment changes in methylation-based TF may help identify pts at risk of early progression.

Clinical trial identification

NCT03052608.

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Legal entity responsible for the study

Pfizer.

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Disclosure

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