(S138) LUVOMETINIB IN RECURRENT/REFRACTORY PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS: A PHASE 2 TRIAL

Topic: 04. Acute myeloid leukemia - Clinical

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Background

Pediatric recurrent/refractory Langerhans cell histiocytosis (LCH) represents a significant therapeutic challenge, with no approved targeted therapies despite the established role of MAPK pathway activation (e.g., BRAF V600E, MAP2K1 mutations) in its pathogenesis. Current salvage chemotherapies are associated with substantial toxicity. Luvometinib (FCN-159) is a highly potent and selective MEK1/2 inhibitor.

Aims

This phase 2 trial evaluated the efficacy and safety of luvometinib in pediatric patients with recurrent/refractory LCH irrespective of genotype. we have reported the preliminary efficacy and safety results of this study previously. Here we report the updated data with longer follow-up.

Methods

This was a single-arm, open-label, phase 2 trial conducted across 11 centers in China (NCT05997602). Eligible patients were aged 2-16 years with histologically confirmed, relapsed/refractory LCH after ≥1 prior systemic therapy. Patients received oral luvometinib at 5 mg/m² once daily in 28-day cycles until progression or unacceptable toxicity. The primary endpoint was the Independent Review Committee (IRC)-assessed objective response rate (ORR) per Positron Emission Tomography Response Criteria (PRC). Secondary endpoints included investigator-assessed ORR (per PRC and Histiocyte Society guidelines), disease control rate (DCR), progression-free survival (PFS), safety, and exploratory analyses of variant allele frequency (VAF) of MAPK pathway mutations in cell-free DNA (cfDNA) and health-related quality of life (HRQoL).

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Results

Between September 21, 2023 and February 19, 2025, 46 patients were enrolled (median age 7.0 years; 58.7% male). As of August 19, 2025, the median follow-up was 15.1 months. In the efficacy analysis set (n=42), the IRC-assessed ORR per PRC was 90.5% (95% CI: 77.4–97.3), with 69.0% achieving complete metabolic response (CMR). In the ITT analysis set(n=46), the investigator-assessed ORR and 12-month PFS rate per Histiocyte Society Evaluations and Treatment guidelines were 97.8% (95% CI, 88.5-99.9) and 97.8% (95% CI, 85.6-99.7) respectively. Responses were observed across various genotypes: the IRC-assessed ORR per PRC was 91.7% (22/24) in patients with *BRAF* mutations, 100% (4/4) in patients with *MAP2K1* mutations, and 92.3% (12/13) in those without detectable MAPK pathway mutations. VAF of MAPK pathway mutations in cfDNA was decreased to below detection (<0.1%) in 78.9% (15/19) of evaluable patients after six cycles of treatment. Treatment-related adverse events (TRAEs) of any grade occurred in 97.8% of patients, most commonly increased blood creatine phosphokinase (52.2%) and rash (50.0%). Grade ≥3 TRAEs occurred in 8.7% of patients; no TRAE led to treatment discontinuation. Patient- and parent-reported HRQoL showed consistent improvements from baseline.

Summary/Conclusion

Luvometinib demonstrated profound, genotype-agnostic efficacy and a manageable safety profile in recurrent/refractory pediatric LCH, supporting its potential as a novel salvage therapy.

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