

# Neurodegenerative Langerhans cell histiocytosis: long-term follow-up of 63 patients from the Italian Registry

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## Supplementary methods

### *Data collection*

Data on demographics, LCH presentation (organ involvement at diagnosis, lesional *BRAF* status, treatment, and reactivation), and ND-LCH characterization and follow-up (MRI, neurological, neurophysiological assessment treatment) were retrieved from the Registry or collected from clinical charts by local physicians. The *BRAF* mutational status was assessed on diagnostic fresh biopsies or Formalin-Fixed Paraffin-Embedded (FFPE) tissue biopsies by digital droplet PCR.

Treatments were administered according to the center expertise and included immunoglobulin (IVIG), *BRAF* inhibitors (BRAFi) such as vemurafenib or dabrafenib, MEK inhibitors (MEKi) such as cobimetinib and trametinib, and chemotherapy according to the LCH-IV protocol (NCT02205762) alone or in combination with other agents.

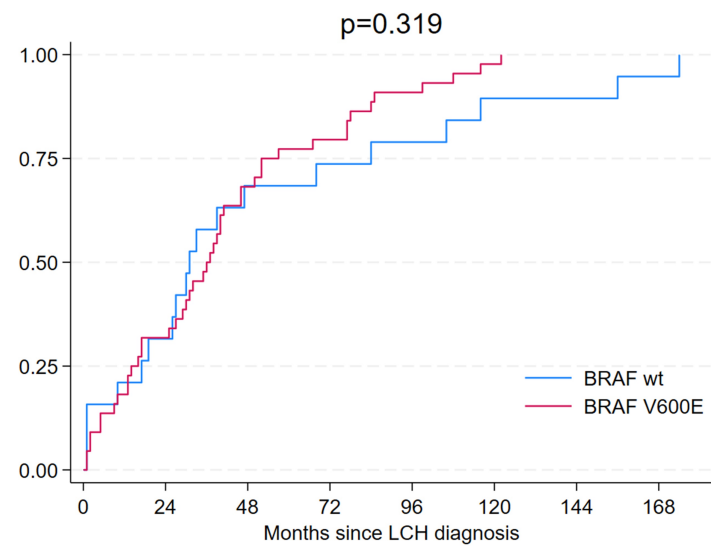
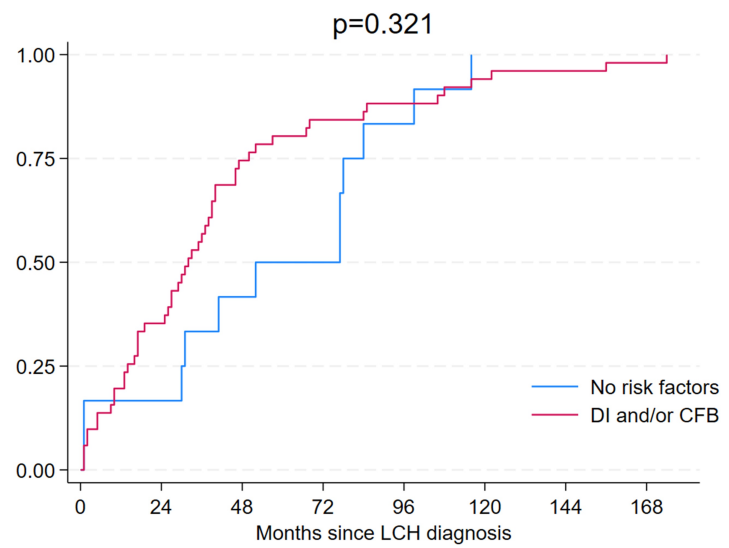
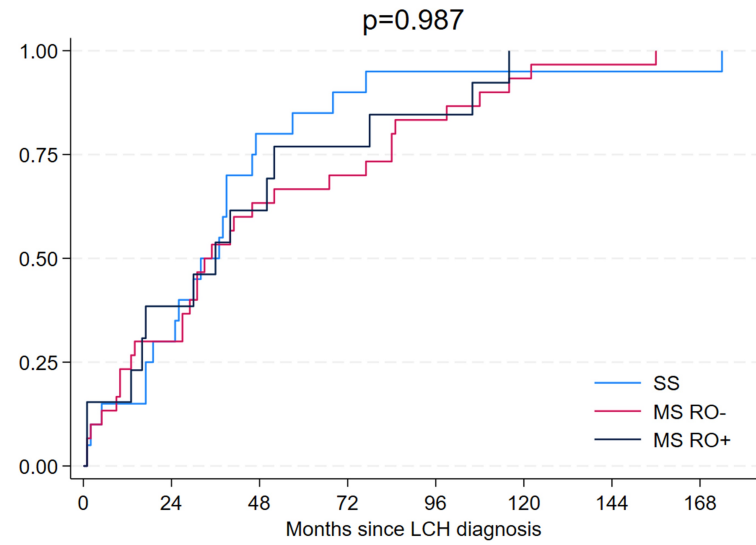
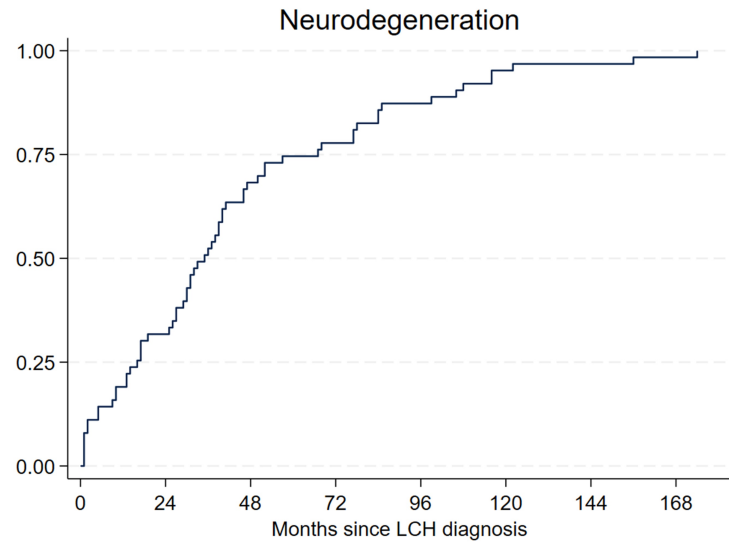
### *Statistical analysis*

Continuous variables were presented as medians and interquartile range (IQR) while categorical variables as absolute numbers and percentages. Comparisons between groups were made using the chi-square or Fisher's exact tests for categorical variables, and the Mann-Whitney test for continuous variables. Predictors of overt clinical ND-LCH were investigated through an univariable logistic regression model. Odds ratios (ORs) were expressed by  $\exp(B)$  values and reported with their respective 95% confidence intervals (95% CIs). In the multivariable Cox regression model, variables were entered using a forward selection method, after checking for multicollinearity. For time-to-event analysis we designed Kaplan-Meier curves with the log-rank test. Two-sided  $p$ -value  $< 0.05$  was considered statistically significant. Statistical analyses were performed using Stata, version 17.

## **Supplementary figures**

**Figure S1 – Kaplan-Meier time to ND-LCH diagnosis:** LCH: Langerhans Cell Histiocytosis; ND-LCH: neurodegenerative Langerhans Cell Histiocytosis; DI: diabetes insipidus; CBL: craniofacial bone lesion; SS: single-system; MS: multi-system; RO: risk organ.

**Figure S2 - Kaplan-Meier time to brain MRI abnormalities worsening:** LCH: Langerhans Cell Histiocytosis; ND-LCH: neurodegenerative Langerhans Cell Histiocytosis; MRI: magnetic resonance imaging.



### MRI worsening

